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Effect of plant-derived extracts and compounds on human intestinal bacteria and cells *in vitro*

DOCTORAL THESIS

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Declaration

I, Tomáš Kudera, hereby declare that this thesis entitled “Effect of tropical plant-derived products on human intestinal microbiota and cells *in vitro*” was written independently, all texts in this thesis are original, and all the sources have been quoted and acknowledged by means of complete references and according to Citation rules of the FTA.

In Prague, March 23, 2024

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Abstract

The development of chronic bacterial dysbiosis has become a known risk resulting from inappropriate antimicrobial therapy of infectious diarrhoea. Moreover, direct association between such microbial disturbances and onset of gastrointestinal carcinogenesis has been increasingly discussed. Diarrheal diseases and intestinal cancers are both serious health problems that substantially contribute to mortalities worldwide. New therapeutic approaches based on agents with dual antibacterial and anticancer effect that is less disruptive for human microbial ecology are therefore needed. In many tropical countries, there is still a rich tradition of the use of local plants for the treatment of gastrointestinal disorders, whereas several phytochemicals have already been employed in the development of internationally available pharmaceuticals and dietary supplements used for digestive ailments. However, many of these plant-derived products have not been systematically studied for their selective biological activities against intestinal bacteria and cell lines. Therefore, in this thesis, *in vitro* inhibitory activities of 35 ethanolic extracts obtained from 13 Cambodian and 19 Philippine antidiarrheal medicinal plants together with 10 phytochemicals and their synthetic analogues were determined by broth microdilution method against 12 diarrheagenic bacteria. Furthermore, their toxicity to two intestinal cancer cell lines (Caco-2 and HT-29) using thiazolyl blue tetrazolium bromide cytotoxicity assay and safety to minimum of six probiotic intestinal bacteria (mainly bifidobacteria and lactobacilli) and one intestinal non-cancer cell line (FHs 74 Int) were determined. In addition, the literature analysis focused on quantitative structure-property relationship analysis of the most effective compounds and their chemotaxonomic distribution in relation to ethnobotanical profile was performed. The extracts of *Ancistrocladus tectorius*, *Artocarpus blancoi*, and *Pentacme siamensis* produced significant growth-inhibitory effects against diarrheagenic bacteria at the concentrations nontoxic to intestinal non-cancer cell lines. Moreover, the extract of *P. siamensis* was relatively safe to probiotic bacteria. Three phytochemical synthetic analogues, namely chloroxine, nitroxoline, and zinc pyrithione, exhibited selective antibacterial actions with lesser effects on probiotic bacteria. However, their antimicrobially active concentrations were toxic to intestinal non-cancer cell lines. Plant extracts of *A. blancoi*, *Ehretia microphylla*, *Lagerstroemia cochinchinensis*, *Melastoma saigonense*, and *P. siamensis* as well as phytochemicals 8-hydroxyquinoline and sanguinarine produced selective

antiproliferative activities against intestinal cancer cell lines. Based on results of laboratory experiments, quinoline and isoquinoline alkaloids were identified as the classes of plant constituents to be subjected to broader literature analysis focused on their structure-activity relationship, chemotaxonomic distribution, and utilization of their biological properties in ethnobotanical practices. Benzophenanthridines, indolo(iso)quinolines, furoquinolines, Amaryllidaceae isoquinolines, simple quinolines, and protoberberines were found as the most prospective structural subclasses of these alkaloids. Investigation of their chemotaxonomic distribution in relation to ethnobotanical profile then identified several genera belonging to Rutaceae, Papaveraceae and other mainly Ranunculales families involving a large proportion of medicinally important antidiarrheal and anticancer plant species. This dissertation study identifies structural classes of phytochemicals and plant taxa that are worth further research focused on development of a new efficient and safer antibacterial and anticancer drugs employed in the treatment of diarrhoea and associated intestinal cancer diseases.

Key words: antibacterial; anticancer; microbiota; diarrhoea; selectivity; medicinal plants

Abstrakt

Rozvoj chronické bakteriální dysbiózy je jedním ze známých rizik vyplívající z nevhodné antimikrobiální léčby infekčních průjmů. V poslední době byla tato mikrobiální nerovnováha navíc dávána do přímé souvislosti s rizikem gastrointestinální karcinogenese. Průjmová onemocnění spolu s rakovinovým onemocněním střev významně přispívají k úmrtnosti po celém světě a představují tak závažný problém. Jedním z možných řešení je zavedení léčebné strategie založené na použití látek kombinující antibakteriální a protirakovinný účinek bez negativního vlivu na rovnováhu lidského střevního mikrobiomu. Již celá řada rostlinných látek přispěla k vývoji mezinárodně dostupných léčiv a doplňků stravy doporučených pro léčbu zažívacích potíží a to na základě přetrvávajících tradic používání rostlin k léčbě onemocnění gastrointestinálního charakteru, zejména v tropických zemích. Nicméně u mnoha z těchto produktů rostlinného původu nebyly systematicky studovány jejich selektivní biologické účinky na střevní baktérie a buňky. Z tohoto důvodu se tato dizertační práce zabývala stanovením *in vitro* inhibičních účinků 35 ethanolových extraktů získaných ze 13 kambodžských a 19 filipínských protiprůjmových léčivých rostlin spolu s 10 rostlinnými látkami či jejich syntetickými analogy proti 12 druhům průjmových bakteriím pomocí mikrodiluční bujónové metody. S použitím takzvané „thiazolyl blue tetrazolium bromide cytotoxicity" eseje byl dále byl stanoven jejich protirakovinný účinek proti dvěma střevním rakovinným buněčným liniím (Caco-2 a HT-29). Stejným způsobem byla testována jejich potenciální toxicita proti alespoň šesti druhům probiotických střevních bakterií (převážně bifidobakterie a laktobacily) a jedné normální střevní buněčné linii (FHs 74 Int). Kromě toho byla provedena také analýza literatury zaměřená na kvantitativní analýzu vztahů mezi strukturou a vlastnostmi nejúčinnějších sloučenin a jejich chemotaxonomickou distribuci v závislosti na etnobotanickém využití. Výsledky testů ukázaly, že extrakty druhů *Ancistrocladus tectorius, Artocarpus blancoi* a *Pentacme siamensis* mají významné inhibiční účinky proti průjmovým bakterií v koncentracích, které nebyly toxické pro normální střevní buňky. Tyto antimikrobiální účinky byly v případě extraktu z *P. siamensis* také relativně bezpečné pro probiotické bakterie. Mezi testovanými látkami, tři syntetické analogy, jmenovitě kloroxin, nitroxolin a pyrithion zinečnatý, vykázaly selektivní antibakteriální účinky se sníženou toxicitou na prospěšné bakterie. Nicméně, při těchto koncentracích byly látky toxické vůči normálním střevním

buňkám. Dále, extrakty z *A. blancoi*, *Ehretia microphylla*, *Lagerstroemia cochinchinensis*, *Melastoma saigonense* a *P. siamensis* stejně jako rostlinné látky 8-hydroxychinolin a sanguinarin vykázaly selektivní antiproliferativní účinky proti střevním rakovinným liniím. Na základě stanovených vlastností *in vitro* pro testované látky a indikací vyplívajících z předchozích fytochemických screeningů nejvýznamnějších rostlinných druhů byly identifikovány chinolinové a isochinolinové alkaloidy jako skupina rostlinných látek, které mají statisticky největší tendenci vykazovat kýženou kombinaci bioaktivních účinků. Z následné literární rešerše vyplynulo, že nejslibnější strukturní podtřídy těchto alkaloidů jsou benzofenanthridiny, indolo(iso)chinoliny, furochinoliny, isochinoliny z čeledi Amaryllidaceae, jednoduché chinoliny a protoberberiny. Z chemotaxonomického hlediska dále vzešlo, že hlavními zdroji těchto látek jsou rody patřící do čeledí routovité, makovité a dalších zejména spadajících do řádu pryskyřníkotvaré. Tyto taxony zahrnují významné množství druhů využívaných pro jejich protiprůjmové a protirakovinné účinky. Tato disertační studie tedy identifikuje strukturní třídy rostlinných látek a rostlinné taxony, které by mohly být předmětem dalšího výzkumu zaměřeného na vývoj nových účinných a bezpečnějších antibakteriálních a protirakovinných léčiv používaných při léčbě průjmových onemocnění a souvisejících střevních nádorů.

Klíčová slova: Antibakteriální; protirakovinné; mikrobiota; průjem; selektivita; léčivé rostliny

Contents

List of tables

List of figures

1. Introduction

The intestinal tract of healthy humans hosts a high and diverse number of different microorganisms dominated by bacterial phyla *Bacteroidetes*, *Firmicutes*, *Actinobacteria* and *Proteobacteria* (Hermsen and de Goffau 2016). Depending on the specific composition of these microbial species accumulated over a lifetime, such indigenous microbiota provides many crucial functions to their hosts and plays a fundamental role in their health. For example, it contributes to the digestion and nutrient uptake, to the metabolism of xenobiotics, and to the development of human immune system (Shen et al 2012). Besides the most profound lactobacilli and bifidobacteria, the following bacterial genera have been recognized to serve these probiotic functions: *Bacillus*, *Enterococcus*, *Escherichia*, *Leuconostoc*, *Pediococcus*, *Saccharomyces*, and *Streptococcus* (Fijan 2014). Despite that microbiota employs diverse mechanisms to maintain homeostasis and symbiotic coexistence with the host, there are circumstances under which either facultative or obligate bacterial pathogens utilize certain strategies to disrupt the balance and establish dysbiotic infection (McKenney and Kendall 2016). The strains of *Campylobacter jejuni*, *Clostridium* spp., *Escherichia coli*, *Salmonella* spp., *Shigella* spp., *Vibrio cholerae*, and *Yersinia enterocolitica* belong to the major causes of intestinal infections (Tejan et al 2018). Due to the severe acute forms of such infections, these so-called diarrhoeal diseases prevail the third leading cause of death among all communicable diseases in the world, particularly affecting under-five children in developing countries (WHO 2020b). Since the risk of antibiotic-associated gut dysbiosis complicates empiric antimicrobial treatment of diarrhoea, new therapeutic approaches based on highly selective antibacterial agents that are less disruptive for human microbial ecology should be adopted on top of the standard probiotics supplementations (Garrett 2014; Behnsen et al. 2013). In addition to infectious diarrhoea, it has also been reported that gut dysbiosis significantly increases wthe risk for many other diseases. Among conditions such as allergies, cardiovascular disease, and obesity (Li et al. 2021), the contribution to the pro-inflammatory processes that eventually lead to intestinal carcinogenesis has been increasingly discussed in the recent years (Li et al. 2021; Garrett 2014; Veziant et al. 2021). In 2020, colorectal cancer was third most diagnosed malignancy in the world following breast and lung cancers, and second leading cause of

cancer death after the lung cancer (WHO 2020a). Regarding that colon cancer tends to be diagnosed in rather advanced stages due to the initial oligosymptomatic character, the treatment of infectious diarrhoea by antibiotic drugs possessing additional bioactive properties allowing suppression of abnormally proliferating cells might lower the risk of the development or quick progression of potentially associated carcinogenesis.

Over the last decades, plant-derived products have become a mainstay in providing novel chemical scaffolds for the development of drugs with anti-infective and anticancer effects (Kokoska et al., 2019). There are already several over-the-counter pharmaceuticals, dietary supplements, and herbal medicines recommended for the support and maintenance of gastrointestinal health, containing phytochemicals and synthetic phytochemical analogues with properties against diarrheagenic bacteria and intestinal cancer cells. Berberine (*Hydrastis canadensis*), chloroxine derived from 8-hydroxyquinoline (*Microstachys corniculata*), and achyranthine (*Achyranthes aspera*) are examples of alkaloids and alkaloid-related compounds present in commercially available products (Rathee et al. 2016; Kokoska et al. 2019; Esmeeta et al. 2022; Sui et al. 2016). The *in vitro* selective antibacterial and anticancer effects of plant-derived products have also been reported. For example, Chan et al. (2018) reported that the phenolic-rich extracts from various dietary spices and medicinal herbs (e.g., *Cinnamomum burmannii*, *Reynoutria japonica*, and *Syzygium aromaticum*) exerted *in vitro* growth-inhibitory effects against selected foodborne pathogenic bacteria but not against lactic-acid bacteria. Then, the study of Doskocil et al. (2015) showed that Amaryllidaceae alkaloids from *Zephyranthes robusta* exert selective antiproliferative effect on intestinal cancer cells. Since antidiarrheal species still constitute a large proportion of medicinal plants employed in traditional herbal systems around the world, products such as extracts and compounds derived from such species are worth for phytochemical and pharmacological investigations (Palombo 2016).

This study examines and reviews various plant-derived products such as extracts, compounds, and their derivatives as a potential scaffolds for agents involved in the development of a new therapeutic drugs used for the treatment of infectious diarrhoea and associated intestinal cancer diseases possessing dual antibacterial and anticancer effect that is less disruptive for human intestinal environment and microbial ecology. Since both international and local markets already provide multiple over-the-counter

pharmaceuticals, dietary supplements, and herbal medicines recommended for the support and maintenance of gastrointestinal health containing significantly bioactive plant compounds and their derivatives, it initially focuses on examination and identification of those that appear to be most prominent. Therefore, a number of plant compounds, their analogues, and structurally related chemicals from various phytochemical classes are tested for their selective inhibitory effects on intestinal bacteria and cells *in vitro*. For appropriate comparison of these features to the currently used therapeutic drugs, several standard antidiarrheal antibiotics are also included in the tests. Considering that majority of useful drugs derived from plants have been discovered by follow-up of ethnomedical use and that examination of plants traditionally used for the treatment of gastrointestinal complaints has led to the discovery of several bioactive compounds including those tested in the first part of this study (Fabricant and Farnsworth 2001), it subsequently focuses on assessing the same *in vitro* dual and selective properties of extracts of ethnobotanically important but pharmacologically unrecognized antidiarrheal medicinal plants from Southeast Asia, namely Cambodia and the Philippines.

The results of laboratory experiments indicated that quinoline and isoquinoline alkaloids are classes of plant constituents that tend to attain a needed combination of bioactive properties. For that reason, the last part of this dissertation is dedicated to the broad review analysis of literature dealing with 258 (iso)quinolines previously tested for their bioactive properties against intestinal diarrheagenic/probiotic bacteria and/or cancer/non-cancer cells *in vitro*. The review analyses quantitative structure-property relationship of (iso)quinolines and evaluates their potentials to produce combination of bioactivities suitable for the treatment of bacterial diarrhoea and dysbiosis-associated intestinal cancers. Based on analysis of relationship between chemotaxonomic distribution and ethnobotanical profile, it also identifies plant taxa that are prospective for further phytochemical and pharmacological research.

In summary, this dissertation identifies structural classes of phytochemicals and plant taxa that are worth further research focused on development of a new efficient and safer antibacterial and anticancer drugs employed in antidiarrheal and anticancer therapies. Apart from providing some of the missing *in vitro* data for phytochemicals and antibiotics already used for treatment of bacterial diarrhoea , the study reports for first

time the antibacterial and anticancer properties of certain Cambodian and Philippine medicinal plants. Generally, this dissertation can be used by life science researches, especially those working in the areas of pharmacy, pharmacology, and medicinal and natural product chemistry. With the support of findings obtained from the literature analysis, it could also assist to scientific community to build up an improved research concept combining ethnobotanical and chemotaxonomic approaches to identify a new pharmacologically important plant species.

2. Literature review

2.1 Infectious and cancer diseases associated with intestinal dysbacteriosis

2.1.1 Intestinal microbiota

The human gastrointestinal tract is home to an enormous and complex community of commensal bacteria particularly consisting of the divisions *Firmicutes*, *Bacteroides*, *Proteobacteria*, *Fusobacteria*, *Verrucomicrobia*, *Cyanobacteria*, and *Actinobacteria*. This gut microbial community known as microbiota has co-evolved with its host over millennia and provides benefits in several ways (Wu and Wu 2012). Generally, there are three main functions that microbiota has in the human gastrointestinal tract. First, there is the metabolic function that includes the production of vitamins, amino acid synthesis and release, and bile acid biotransformation. This includes the fermentation of nondigestible substrates and endogenous mucus which stimulates their growth and produces short-chain fatty acids such as acetate, propionate, and butyrate that is the preferred energy source for the epithelial cells. Second, there is the protective function of these commensal organisms that prevent pathogenic colonization by competing for attachment sites, nutrients, and through the production of antimicrobial substances. Finally, there is the structural and histological function as these communities contribute to epithelial cells' growth, the mucus layer creation, and the tight junctions strengthening. All the three functions are together essential for the development and regulation of immune system. They contribute to lymphatic system stimmulation, B- and T-cells development, and the barrier fortification (Prakash et al. 2011). Although microbiota consists of large number of different bacterial species, certain strains are particularly known to confer such health benefit on the host. These probiotic functions have mainly been demonstrated for some species of the following genera: *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Enterococcus*, *Streptococcus*, *Pediococcus*, *Leuconostoc*, *Bacillus*, and *Escherichia* (Fijan 2014).

Despite the ability of microbiota to restrict pathogen invasion and maintain homeostasis by keeping symbiotic coexistence with the host, pathogens have evolved

mechanisms to overcome challenges posed by the commensal bacteria. Generally, the changes in host environment, diet and use of antibiotics can cause reorganization of the community that allows pathogenic bacteria and pathobionts to promote dysbiosis and establish intestinal infection (McKenney and Kendall 2016). The following are the main genera of enteric bacteria, of which some strains of the following genera are responsible for infectious diseases: *Escherichia*, *Shigella*, *Salmonella*, *Campylobacter*, *Clostridium*, and *Aeromonas* (Li et al 2021). One strategy employed by these harmful strains is to use specific nutrients that are not primarily metabolized by commensal bacteria. For example, unlike the commensal strains of *E. coli*, the enterohemorrhagic types can utilise galactose, hexuronates, mannose, ribose and ethanolamine. Another strategy is that they induce inflammation by their virulence factors. For instance, infection caused by *Salmonella enterica* ssp. *enterica* serovar Typhimurium results in the production of reactive oxygen species by neutrophils, which facilitates the conversion of endogenous thiosulphate into tetrathionate, thereby selectively promoting its growth. Then, certain Gram-negative enteric pathogens such *Serratia marcescens*, an opportunistic enteric pathogen responsible for a significant proportion of hospital-acquired infections, can directly kill their commensal competitors through the expression of the type VI secretion system (Kamada et al. 2013, Murdoch et al. 2011).

The association between dysbiotic changes in gut microbiome composition and inflammatory processes leading to intestinal carcinogenesis has been increasingly discussed (Garrett 2014; Veziant et al. 2021). Generally, malignant transformation of intestinal epithelial cells and the development of colorectal cancer includes at least three relevant steps, namely (i) the induction of oncogenic mutations within the Lgr5+ intestinal stem cells, (ii) an altered β-catenin/Wnt signalling, and (iii) proinflammatory cascades such as TNFα-NFκB and IL6-STAT3 that catalyse colorectal cancer development. There is emerging evidence regarding a causal role of certain bacteria in colorectal cancer evolution, especially *Fusobacterium nucleatum*, colibactin-producing *E. coli* and toxigenic *Bacteroidis fragilis* (Gorkiewicz and Moschen 2017). Other bacteria with suggested oncogenic role in the human intestines are *Alistipes* spp., *Bilophila wadsworthia*, *Enterococcus faecalis*, *Parvimonas* spp., and *Streptococcus gallolyticus* (Veziant et al. 2021; Gorkiewicz and Moschen 2017). In case of *F. nucleatum*, the FadA antigen is a ligand for E-cadherin on intestinal epithelial cells that activates the β-catenin signalling pathway, thereby promoting uncontrolled cell growth, acquisition of a stem

cell-like phenotype of epithelia and loss of cell polarity. Regarding *E. coli* oncogenic strains, the genomic polyketide synthase island encodes the genotoxin colibactin that is capable of inducing DNA damage and mutations in epithelial cells (Gorkiewicz and Moschen 2017). Studies also indicate that probiotic intestinal bacteria can reveal anticancer activity on colorectal cancer cells through down-regulation and up-regulation of anti-apoptotic and pro-apoptotic genes. For example, in the study of Kuugbee et al. (2016), administration of lactobacilli and bifidobacteria altered the gut microbiota and decreased colon cancer development by decreasing tumour incidence, multiplicity/count, and volume in a rat model. Another study showed that *Lacticaseibacillus rhamnosus* prevents colorectal cancer as it suppresses expressions of inflammatory and angiogenesis genes, and upregulates the apoptotic gene expression (Huang et al. 2021). The anti-inflammatory and cancer-preventive effects have been broadly discussed in the cases of other intestinal bacteria, especially *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* (Dikeocha et al. 2022; Hou et al. 2021).

2.1.2 Epidemiology

2.1.2.1 Bacterial gut infections

All types of infections of gastrointestinal tract substantially contribute to the complex of health conditions known as diarrhoeal diseases. From the epidemiological point of view, infectious diarrhoea prevails the third leading cause of death among all communicable diseases in the world, particularly affecting under-five children in lower income countries (WHO 2020b). Although all-cause gastroenteritis has declined substantially due to the introduction of rotavirus vaccines, in less developed world, bacterial pathogens remain a major cause of medically attended diarrhoea with *Aeromonas*, *Shigella*, *Campylobacter*, and enterotoxigenic *E. coli* predominating. Moreover, multidrug-resistant strains of *Shigella*, and *Campylobacter* have emerged globally (Kotloff 2022). As indicated earlier, other bacterial strains that has been notably contributing to diarrhoeal diseases are *Bacillus cereus, Clostridium difficile, Clostridium perfringens, Salmonella* spp., *Enterococcus faecalis*, *Listeria monocytogenes, Vibrio cholerae*, *Vibrio parahaemolyticus* and *Yersinia enterocolitica* (Tejan et al. 2018). Some of these species cause infections that predominate in the developed countries. For example, antibiotic-associated *C. difficile* diarrhoea is a significant contributor to the

morbidity and mortality of healthcare-associated infections in the USA, resulting in over 400,000 infections and nearly 29,000 fatalities per year (Al Sharaby et al. 2022). The cases of human gastroenteritis caused by *Y. enterocolitica* also predominate in developed countries of temperate zones (Riahi et al. 2021).

2.1.2.2 Intestinal cancers

Although malignancy can occur in nearly every part of the digestive system including oesophagus, stomach, small bowel, liver, pancreas, and gallbladder, the highest frequency of cases is observed in the large intestine and rectum (Zhu et al. 2021). Colorectal cancer is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related deaths in the world (WHO 2020a). The developed countries are at the highest risk, however the incidence of these cancers in developing nations is steadily increasing (Rawla et al., 2019). Over the last 40 years, both the incidence and mortality rate for colorectal cancer have declined for adults over age 50, but the incidence in 20- to 49-year-olds has been on the rise (Radcliff et al. 2023). In fact, the global burden of colorectal cancer is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030 (Arnold et al. 2017). Although genetic predisposition has been identified as one of the key risk factors in the development of this malignancy (Rebuzzi et al. 2023), more than half of all cases and deaths are attributable to risk factors such as smoking, unhealthy diet, high alcohol consumption, physical inactivity, and excess body weight (Siegel et al. 2023). In relation to that, dysbiotic microbiome commonly observed in colorectal cancer patients has also been linked to lifestyles and environmental conditions (Hoang et al. 2023). It has been hypothesised that factors negatively affecting gut microbiota such as antibiotic overuse, C-section deliveries, limited breast-feeding, and diets poor in fibre and microbes is associated with the rise of noncommunicable diseases in the developed countries including colorectal cancer (Puntillo et al. 2022).

2.1.3 Treatment

2.1.3.1 Antibiotic therapy

It is important to note that vast majority of diarrhoeal cases have a self-limiting course that do not require medical attention. Regarding the life-threatening acute types

particularly affecting under-5 children, primary therapy consists of oral rehydration with solutions containing sugar and salt (WHO 2017). Generally, empirical antibiotic therapy has been found rather counterproductive in acute diarrhoea (Zollner-Schwetz and Krause 2015). In addition to the common side effects, the disturbances in the ecological equilibrium between the host and the normal microbiota associated with the long-term persistence of antibiotic resistance genes have been the negative consequences of empirical antimicrobial treatment. Due to that, such administration of antibiotics is frequently followed by antibiotic-associated diarrhoea and fungal overgrowth particularly caused by *C. difficile* and *Candida* species, respectively. On the other hand, using antibiotics with a narrow spectrum of action does not severely impair colonization resistance and the risk that resistant bacterial strains develop and get transferred between patients is reduced (Jernberg et al. 2010). For that reason, evaluation of stool specimen for bacterial agents (mainly *Escherichia*, *Clostridium*, *Salmonella*, *Campylobacter*, and *Shigella*) is recommended to be performed in severely ill patients with significant dehydration, fever, bloody diarrhoea, underlying immune deficiency, recent use of antibiotics, advanced age, and significant comorbidities (Zollner-Schwetz and Krause 2015). In case of campylobacteriosis, salmonellosis, shigellosis, and yersiniosis, the antibiotic agents such as ciprofloxacin, ampicillin, azithromycin, and cefotaxime are usually used. The infections caused by diarrheagenic *E. coli* is recommended to be treated with rifaximin, ciprofloxacin, or azithromycin. Then, ampicillin and gentamicin are drugs of choice in the treatment of listeriosis. Due to the increasing resistance of *V. cholerae* to standard treatment with co-trimoxazole, tetracycline, or doxycycline, the use of ciprofloxacin and azithromycin have lately been preferred. Finally, clostridial diarrhoea caused by *C. difficile* is usually treated by administration of metronidazole and vancomycin. Although fluoroquinolones and macrolides remain the most important cornerstones of antibiotic therapy of intestinal bacterial infections, slow rise in extreme resistance must be considered (Lubbert 2015). In parallel to the ongoing growth of international travel, the annual rates of resistant diarrheagenic microorganisms increase dramatically (Riddle 2020). Since the stool examination is impossible to perform for every diarrhoeal patient for whom antimicrobial therapy is recommended (Diniz-Santos et al. 2006), a proper choice of drugs allowing maximized effect on broad spectrum of possible pathogens with limited risks for side-effects is important (Lubbert 2015). With most of the drugs currently used, even short exposures can disrupt the gut microbiome up

to a year or more and repeated exposures appear to attenuate recovery from ever occurring. The bacterial phylum that commonly increases in the gut after antibiotic treatment are the *Proteobacteria* including *Enterobacteriaceae* that are pro-inflammatory and often carry antibiotic resistance genes (McDonald 2017). Therefore, seeking for effective but also highly selective antimicrobial agents that are less disruptive for human microbial ecology is becoming a strategy preferred by researchers working in the areas of pharmacy and pharmacology (Garrett 2019).

2.1.3.2 Anticancer therapy

Currently, the treatment plan for colorectal cancer is mainly combined with surgery, radiotherapy, and chemotherapy (Ma et al. 2020). The principal chemotherapeutic regimen known as FOLFOX include 5-fluorouracil, oxaliplatin and/or folinic acid. In metastatic colorectal cancer, another regimen named FOLFIRI is usually applied and consists of folinic acid concurrently taken with irinotecan and followed by 5-fluorouracil (Gupta et al. 2019). Other anticancer drugs and regimens used in the chemotherapy of bowel cancers are aflibercept, bevacizumab, capecitabine, cetuximab, panitumumab, regorafenib, FOLFOXIRI (folinic acid + 5-fluorouracil + oxaliplatin + irinotecan), XELOX (capecitabine + oxaliplatin), and XELIRI (capecitabine + irinotecan). Referring to the mechanisms of anticancer actions, these drugs either mis-incorporate the fluoro nucleotide into RNA and DNA of the cells while inhibiting the enzyme thymidylate synthase, or they act as inhibitors of vascular endothelial growth factor, epidermal growth factor receptor, and oral multi-kinase. The inhibitors of cyclooxygenase-2 and poly (ADP-ribose) polymerase or transition metal complexes are chemotherapeutics of newly emerging anticancer treatments, namely celecoxib, olaparib, and ruthenium (McQuade et al. 2017). Due to implementation of a new targeted drugs and treatment regimens, the length of median survival of patients with advanced colorectal cancer had increased between 1970 and 2010 from 4–5 to 22–24 months (Glimelius and Cavalli-Bjorkman 2012). Despite these advancements, response rates of patients with disseminated colorectal cancer treated with chemotherapy do not exceed 50% and the palliative systemic therapy without biological agents remains a therapeutic standard for about 75% of the overall patients, especially those from developing countries. One of the main issues of intestinal cancers is their oligosymptomatic character that usually does not allow the diagnoses in early stages at which the chances for positive

therapeutic outcomes are significantly higher (Rogowski and Sulzyc-Bielicka 2016). Therefore, improvements in early diagnosis through regular medical examinations based on identifying specific disease markers are necessary (Lech 2016). In the context of intestinal carcinogenesis derived from bacterial diarrhoea and dysbiosis, the disease progression could potentially be prevented if agents possessing additional bioactive properties that allow suppression of abnormally proliferating cells are chosen for the antibiotic therapy. For instance, the ability to reveal *in vitro* antiproliferative activity against colon cancer cells has previously been reported in case of derivatives of antidiarrheal antibiotics ciprofloxacin and tetracycline (Bourikas et al. 2009; Onoda et al. 2005). Antimicrobial agents such as antibiotics and plant alkaloids have already been incorporated into adjuvant and neoadjuvant chemotherapy of colorectal cancers regimens and resulted in an improvement in both 5- and 10-year survival rates (McQuade et al. 2017).

2.2 Antibacterial and anticancer plant-derived products

Over the last decades, plant-derived products have become a mainstay in providing novel chemical scaffolds for the development of pharmaceutical drugs with various therapeutic applications including antimicrobial and anticancer agents (Kokoska et al. 2019; Iqbal et al. 2017). Mainstream medicine is increasingly receptive to the use of drugs derived from plants as traditional chemotherapeutics become ineffective and as new diseases remain intractable to these types of drugs (Cowan 1999; Iqbal et al. 2017). Regarding that medicinal plants have been used as traditional treatments for numerous human diseases for thousands of years in many parts of the world, they are generally accepted as a source of effective and relatively safe medicines (Palombo 2006). In rural areas of developing countries, medicinal system is still primarily dependent on plants and traditional uses and applications of herbal products continue to be involved in the daily practices (Kim 2005). There have been numerous reports of the use of traditional plants for the maintenance of digestive health and treatment of diverse gastrointestinal conditions. Traditional herbal antidiarrheal medicines have been recorded in African, American, Asian, European and other indigenous medicinal systems (Palombo 2006). Therefore, it is not a surprise there are already several over-the-counter pharmaceuticals, dietary supplements, and herbal medicines recommended for the support and

maintenance of gastrointestinal health, containing phytochemicals and synthetic phytochemical analogues with recorded *in vitro* effects on diarrheagenic bacteria and intestinal cancer cells (Kokoska et al. 2019; Iqbal et al. 2017).

2.2.1 Pharmaceutical and food products

2.2.1.1 Alkaloids

Among the bioactive secondary metabolites synthetised by plants, alkaloids represent an important group of phytochemical compounds employed in the development of pharmaceutical and food products that are commonly used for a health care of the human digestive system. Alkaloids are a group of nitrogen-containing compounds that may consist of one or more nitrogen atoms usually within the heterocyclic ring. Generally, higher plants belonging to families such as Ranunculaceae, Leguminosae, Papaveraceae, Menispermaceae, and Loganiaceae are the main sources of these substances. Alkaloid-containing products marketed as medicines for gastrointestinal complaints are particularly valued for their strong antibacterial, antitumor, and/or anti-inflammatory properties (Debnath et al. 2019). Berberine, a benzylisoquinoline alkaloid found in many taxonomically diverse plants, especially *Coptis* spp., *Berberis* spp. and *Hydrastis canadensis*, is one of the compounds particularly profound for such characteristics. Various food and herbal supplements containing extracts from roots and rhizomes of these plants are commonly sold in the form of capsules, tablets and tinctures in Asia [e.g. Huang Lian Su Tablets (*Coptis sinensis* extract), Hubei Minkang Pharmaceutical, Yichang, China] and North America (e.g. *Berberis* Formula, Seroyal, Richmond Hill, Canada; Solaray Goldenseal Root Capsules, Nutraceutical Corporation, Park City, USA) to support digestive functions and relive gastrointestinal disorders including diarrhoea (Bruneton 1999). Previously performed *in vitro* experiments of berberine on intestinal diarrheagenic bacteria and cancer cells have indicated both, *in vitro* antibacterial and anticancer effects (Ali et al. 2013; Lyu et al. 2021; Guaman et al. 2014). Another pharmaceutically utilized compound is chloroxine, the synthetic derivative of 8-hydroxyquinoline alkaloid present in *Centaurea diffusa* and *Microstachys corniculata* (Vivanco et al. 2004; Yang et al. 2013). Although international market recognizes this compound as an ingredient of products rather used for the treatment of certain skin conditions, such as seborrheic dermatitis and dandruff in the form of shampoos and

creams (Trousil et al. 2022), there is a chloroxine-containing antimicrobial drug branded under the name Endiaron (Sanofi-aventis, Prague, Czechia) sold in the local market as a popular remedy for infectious diarrhoea. Finally, a simple pyrrolidine alkaloid achyranthine is one of the anticancer substances present in the leaves and roots of Ayurvedic plant *Achyranthes aspera* that is traditionally used as a digestive medicine. Dietary supplements containing these extracts are available at the international market, especially in Asia [e.g. Huai Niu Xi root extract granules, Sun Ten, and Achyranthes Aspera Dilution, Dr. Willmar Schwabe India] (Esmeeta et al. 2022).

2.2.1.2 Phenolic compounds

A chemical structure comprising an aromatic ring with one or more hydroxyl substituents is a general characteristic for phenolic compounds. They can be further divided into several classes among which the main groups are phenolic acids, flavonoids, tannins, coumarins, lignans, stilbenes, quinones, and curcuminoids (Bruneton 1999). These secondary metabolites widely distributed in taxonomically divers higher plants are particularly profound for their antioxidant, antimicrobial, anticarcinogenic, and anti-inflammatory activities. Since phenols represent one of the major groups of nonessential dietary components appearing in large number of vegetable and fruit products, the human gastrointestinal system has naturally adopted to some of the health benefits they can provide. Due to that, they are also broadly available in various digestion-supporting and antidiarrheal dietary supplements (Zhang et al. 2022). For example, bismuth subsalicylate, the analogue of salicylic acid derived from salicin (*Salix alba*), is an active substance of medication sold under the brand name Pepto-Bismol (The Procter & Gamble Company, Cincinnati, USA) in the form of liquid, chewable, and swallowable tablets, that is used to treat temporary discomforts of the stomach and gastrointestinal tract, such as diarrhoea, indigestion, heartburn and nausea (Kokoska et al. 2019). The antimicrobial activity of bismuth subsalicylate to some diarrheagenic bacteria has been previously reported (Pitz et al. 2015). Curcumin is another plant phenolic compound well-known for its positive impact on the digestive health. This linear diarylheptanoid compound present in rhizomes of Zingiberaceae plants, typically *Curcuma longa*, is the primary source of the Indian household spice curry. Curcumin has been reported to possess antioxidant, anti-inflammatory, anti-proliferative, and antimicrobial properties. For example, previous studies have showed its chemopreventive activity against multiple colon cancer cell lines

like HT-29, HCT116, HCT15, and DLD1 using *in vitro* and *in vivo* experiments. Currently, there are countless curcumin-containing dietary supplement products available at the international market (Esmeeta et al. 2022). Another biologically active phenol that is worth naming as an example is delicaflavone, a biflavonoid compound present in *Selaginella doederleinii*. This Chinese medicinal plant has been traditionally used for its anti-tumour properties and its extract is nowadays available as an ingredient of some dietary supplements used for the clearance of gastrointestinal tract and as an overall booster of the immune system in the form of capsules or liquid drops (e.g. Shi Shang Bai, Tianjiang; Gerocel Bioenzym, Diochi) (Yao et al. 2017). The *in vitro* and *in vivo* anticancer effects of delicaflavone have been previously reported against numerous cancer cell lines (Sui et al. 2016).

2.2.2 Traditional herbal medicines

2.2.2.1 Global overview

Herbal preparations have been extensively used in traditional medical systems for over hundreds or even thousands of years, whereas it is estimated that about 75–80% of the world population still rely on herbal medicines for primary health care (Kamboj 2000). There are several important traditional medicine systems that are still extensively practiced in the places of their origin while contributing to a new drug discoveries made by a modern scientific techniques, namely Traditional Chinese medicine, Ayurveda (Indian medicine), Unani (Greco-Arabic medicine), Kampo (traditional Japanese medicine), Traditional Korean medicine, Traditional Aboriginal medicine (Australia), Traditional medicine in Africa (mainly Ethiopia and Ghana), Russian herbal medicine, and Native American medicine (Yuan et al. 2016; Koithan and Farrell 2010). Majority of useful drugs derived from plants have been discovered by follow-up of ethnomedical use, whereas examination of plants traditionally used for the treatment of gastrointestinal complaints has led to the discovery of several bioactive compounds. For example, aesculetin (*Fraxinus rhynchophylla*), andrographolide (*Andrographis paniculata*), cynarin (*Cynara scolymus*), hemsleyadin (*Helmsleya amabilis*), and neoandrographolide (*Andrographis paniculata*) are phytochemicals derived from plants used as remedies for the treatment of bacterial dysentery and cholera (Fabricant and Farnsworth 2001). Herbal medicines intended for internal use to combat disorders of the digestive character

represent a cornerstone common in nearly every indigenous medicine system (Palombo 2006). Referring to plants mentioned in ayurvedic texts for controlling diarrhoea, Mishra et al. (2016) presented ethnopharmacological data on 109 species belonging to 58 plant families. Among them, *Aegle marmelos*, *Cyperus rotundus*, *Feronia limonia*, *Hemidesmus indicus*, *Holarrhena antidysenterica*, *Nelumbo nucifera*, *Pongamia pinnata* were examples of species for which antibacterial, bactericidal, or anti-adherence activity has been proven against some diarrhoeagenic bacteria. Then, *Nigella sativa, Picrorrhiza kurroa,* and ***Rubia cordifolia*** are some of the ayurvedic medicinal plants involved in digestive cancer therapies with reported anticancer property against malignancies such as colon and hepatic cancers (Balachandran and Govindarajan 2005). In Traditional Chinese Medicine there are also several antidiarrheal plant species which use has been supported by biological activity experiments. For example, *in vitro* antibacterial and anticancer properties have been reported in case of *Coptis chinensis* and attributed to the presence of various isoquinoline alkaloids. Similarly, the antimicrobial and antitumor effects were confirmed when examining traditionally used antidiarrheal and anti-dysenteric medicinal plant *Scutellaria baicalensis*. In this case, flavonoids were identified as the main active components (Chen et al. 2021). The same evidence can be found in some of the African herbal systems. For instance, the respective South African and Nigerian medicinal plants *Lauridia tetragona* and *Hypericum roeperianum*, both locally used for the treatment of dysentery and diarrhoea, showed antibacterial activity against several diarrheagenic pathogens (Wintola and Afolayan 2019; Elisha et al. 2017). The extract from stem bark of *Mangifera indica* used by Cameroonian herbalists for the preparation of antidiarrheal medicine has been verified to possess similar properties (Shirinda et al. 2019). Secondary metabolites isolated from traditional Ethiopian anti-dysenteric and anticancer plant *Brucea antidysenterica* then showed cytotoxic activity against some colon cancer lines (Tuasha et al. 2018; Makong et al. 2019).

2.2.2.2 Southeast Asia – Cambodia and Philippines

The Southeast Asian region is one of the world's major sources of useful plant resources and has long been recognized as a centre of plant biodiversity (Duriyaprapan et al., 2005). Situated in the humid tropics with areas of high rainfall, Southeast Asia has one of the largest numbers of vascular plants species globally. For centuries, people living in this region have relied on traditional medicine using available plants for daily

healthcare. Cambodia and the Philippines are two geographically distinct Southeast Asian countries, each having numerous plant biodiversity hotspots and a long tradition of herbalism (de Padua et al., 1999). While the former is situated in the mainland, having rich ecosystems, especially around the Mekong River (Chassagne et al., 2016), the latter is a huge archipelago consisting of approximately 7,107 islands, many of which are the centre of endemicity and biodiversity (Guzman et al., 2016).

Diarrhoea has been a significant issue in both Cambodia and the Philippines (Our World in Data, 2011). Therefore, plant resources in these countries have extensively been utilized medicinally to treat this ailment. The Philippines also has the highest estimated number of cases of colorectal cancer in Southeast Asia and the tenth highest number of deaths in the world (Rawla et al., 2019). In certain provinces of Cambodia, treatment of digestive disorders, such as abdominal pain (chhu poh), diarrhoea (reak ach), and dysentery (reak muol), has particularly been based on herbal medicine. Alcohol maceration is a common method of preparation of antidiarrheal medicines, whereas a majority of the preparations are administered orally: drunk, eaten, or chewed (Kham, 2004). Grilling the plant part over a fire and then boiling it into a form of decoction is also common. As an example, Bunong people in Mondulkiri province treat diarrhoea using a "step-by-step" process using a sole ingredient from one plant that is substituted by a different species if the condition becomes persistent. In the Philippines, conditions such as diarrhoea (pagtatae) and dysentery (pagdidisenyo) have similarly been treated by orally administered herbal preparations that are processed by alcohol maceration, decoction, or infusion or eaten and chewed raw. According to the Philippine traditional medicinal system, the disease is usually conceptualized as a disruption (dys-krasia) of the balance of forces (whether germs or evil spirits), both external and internal to humans. Therefore, it can be assumed that the use of herbal preparations is intended to also defend the immunological mechanisms, helping the body to overcome the disease itself (Tan, 1980). Despite the existence of several reports on the antibacterial and antiproliferative effects of Cambodian and Philippine medicinal plants used for the treatment of diarrhoea (Beloy et al., 1976; Chea et al., 2007), there are several species in both regions that have not yet been appropriately studied using modern scientific techniques.

2.2.3 Effect on human intestinal ecosystem

It has been previously reported that food and orally taken medicines can significantly influence human gut microbiota, especially in terms of its composition and metabolism. A notable number of studies have showed that phytochemicals and herbal formulas are capable of reversing the abnormal gut microbiota composition in diseased human cohorts and model animals. Since most herbal medicines exhibit poor oral bioavailability (e.g., only 5–10% of polyphenols can be absorbed in small intestine), these molecules can easily pass through the upper sections of gastrointestinal tract and reach bio-relevant concentrations in the colon to interact with the microbial communities and their habitat (Feng et al. 2018). Generally, there are two types of mechanisms that herbal medicines employ to modulate the composition of gut microbiota: direct or indirect promotion or inhibition of the growth of specific species. As these microbial communities can convert many of the plant-derived products into a series of metabolites such as short-chain fatty acids, indole derivatives, polyamines, organic acids, and vitamins, they can indirectly prevent the colonization of extraneous or indigenous pathogen via competitive exclusion, competitive consumption of nutrients, and induction of host immune response (Xu et al. 2017). However, majority of herbal medicines consisting of secondary metabolites have been shown to be able to modulate gut microbiota by the direct inhibition of pathogens and pathobionts and promotion of probiotic bacterial species (Chen et al. 2016).

The *in vitro* selective antibacterial effects of plant-derived products have been previously reported. For example, in the study of Chan et al. (2018), phenolic-rich extracts from various dietary spices and medicinal herbs (*Cinnamomum burmannii*, *Cinnamomum cassia*, *Origanum vulgare*, *Punica granatum*, *Reynoutria japonica*, and *Syzygium aromaticum*) exerted growth-inhibitory effects on selected foodborne pathogenic bacteria but not on lactic-acid bacteria. Selective antibacterial activity was also described in the study of Novakova et al. (2013), where *in vitro* anticlostridial properties of 8-hydroxyquinoline (*C. diffusa* and *M. corniculata*) notably exceeded the concentration-dependent toxicities to different strains of bifidobacteria. Correspondingly, earlier mentioned Endiaron (Sanofi-aventis, Prague, Czechia), a 8-hydroxyquinoline derivative chloroxine, is marketed as antidiarrheal antimicrobial drug with no harmful impact on patient's indigenous microbiota. As another examples, quinaldic acid isolated from

Ephedra pachyclada and quinoline-4-carboxaldehyde isolated from *Ruta chalepensis* both exerted *in vitro* anticlostridial effects without affecting strains of bifidobacteria and lactobacilli in the respective studies of Lee and Lee (2009) and Cho et al. (2005). Finally, the *in vitro* study of Guo et al., (2015) showed that red ginseng (the streamed root from *Panax ginseng*) and *Semen Coicis* (dried seed of *Coix lacryma-jobi*) were capable of inhibiting the growth of some intestinal pathogenic strains while promoting the growth of the probiotic ones (*Bifidobacterium* and *Lactobacillus*). The selectivity of *in vitro* antiproliferative actions of some plant-derived products against intestinal cells have also been reported. For example, Doskocil et al. (2015) and Vaneckova et al. (2016) published studies in which Amaryllidaceae alkaloids (acetylcaranine, haemanthamine, caranine, crinine, and lycorine) from the plants *Nerine bowdenii* and *Zephyranthes robusta* produced inhibitory actions against intestinal cancer cells HT-29 and Caco-2 with comparably lowered toxicities to the non-cancer cell FHs 74 Int. In another study, berberine exhibited *in vitro* antiproliferative actions against human colon cancer cell line HCT116 while possessing no toxicity to the non-cancer intestinal line NCM460 (Hijazi et al. 2017). In addition to the selective actions based on producing inhibition of exclusively the targeted agent(s), it has been previously reported that plant-derived products can also directly promote the growth of some gut microbiota species by acting as prebiotics (Feng et al. 2018). While examining the selectivity of bioactive properties of the tested natural products *in vitro*, it is important to consider that gut microbiota in *in vivo* conditions can potentially transform the substances into metabolites that might exhibit different bioactivity and bioavailability compared with their precursors (Xu et al. 2017).

Considering that a large number of plant-derived products have not been systematically studied for their biological activities against appropriate amounts of agents representing both pathological and healthy subjects of human intestinal ecology, this dissertation examines *in vitro* selective inhibitory effects of phytochemicals, phytochemical analogues, and medicinal plant extracts on human intestinal bacteria and cells, and analyses pharmacological, phytochemical, and ethnobotanical literature data related to their antibacterial and anticarcinogenic properties.

3. Hypotheses

One of the partial reasons why intestinal infections and cancers continue to pose a substantial global health challenge is the fact that most of the currently used antimicrobial drugs disrupt gut microbiome thereby indirectly promote proinflammatory processes that can turn into oligosymptomatic carcinogenesis.

1. Screening different classes of commercially available antidiarrheal phytochemicals, synthetic phytochemical analogues, and antibiotics for *in vitro* inhibitory effects on intestinal diarrheagenic/probiotic bacteria and cancer/non-cancer cells will provide indications on structures that tend to produce combination of these biological actions whilst keeping safety to representatives of indigenous gastrointestinal ecosystem.

2. Products derived from some plant species reported as traditional antidiarrheal and/or intestinal anticancer medicines in Southeast Asia can produce *in vitro* selective inhibitory effects on intestinal bacteria and cells due to their time-proven efficacy and safety.

3. Certain structural configurations of compounds from pharmacologically perspective phytochemical class (as referred in hypothesis no. 1) positively or negatively correlate with the degree of *in vitro* inhibitory effects produced on intestinal bacteria and cells as well as with their selectivity.

4. Plant taxa significant in terms of the presence of compounds of biologically active phytochemical class statistically involve a high number of medicinally important species utilized in the treatment of various digestive complaints in traditional herbal systems around the world. Therefore, a new pharmacologically important plants can be discovered while combining chemotaxonomic and ethnobotanical procedures.

4. Research questions

1. Which chemical class of commercially available antidiarrheal phytochemicals, synthetic phytochemical analogues, and antibiotics does tend to produce selective *in vitro* inhibitory effects on intestinal diarrheagenic/probiotic bacteria and cancer/non-cancer cells?

2. Which Southeast Asian plants reported as traditional medicines for the treatment of diarrhoea and/or intestinal cancers can produce *in vitro* selective inhibitory effects on intestinal bacteria and cells?

3. What structural configurations of compounds from previously selected phytochemical class (question no. 1) positively or negatively correlate with the degree of *in vitro* inhibitory effects produced on intestinal bacteria and cells as well as with their selectivity.

4. Which plant taxa are significant in terms of the presence of compounds of biologically active phytochemical class whilst involving a high number of medicinally important species utilized in the treatment of various digestive complaints in traditional herbal systems around the world?

5. Objectives

The main aim of the study was to examine *in vitro* selective inhibitory effects of plant-derived extracts and compounds on human intestinal bacteria and cells, and to analyse pharmacological, phytochemical, and ethnobotanical literature data related to their antibacterial and anticarcinogenic properties.

The specific objectives of this study were:

1. To identify the main class of compounds producing *in vitro* selective inhibitory effects on intestinal diarrheagenic/probiotic bacteria and cancer/non-cancer cells by screening a spectrum of phytochemicals and their synthetic analogues.

2. To identify the main plant taxa producing *in vitro* selective inhibitory effects on intestinal bacteria and cells by assessment of extract from Southeast Asian species used in traditional medicine for the treatment of diarrhoea.
3. To determine relationships between chemical structure of previously identified classes of phytochemicals and their effects against intestinal bacteria and/or cells by analysis of literature data reporting their antibacterial and cytotoxic properties.
4. To identify plant taxa representing important sources of the most active compounds and to determine their ethnopharmacological role in the treatment of digestive complaints related to gastrointestinal infections and cancer by analysing literature on their phytochemical and ethnobotanical data.

6. Materials and methods

6.1 Chemicals

Phytochemicals (berberine chloride, 8-hydroxyquinoline, salicylic acid, tannic acid, and sanguinarine chloride) and their synthetic analogues [chloroxine (5,7-dichloroquinolin-8-ol), nitroxoline (5-nitroquinolin-8-ol), ferron (7-iodo-8-hydroxyquinoline-5-sulfonic acid), bismuth subsalicylate, and zinc pyrithione], as well as antibiotics (ceftriaxone sodium, ciprofloxacin, chloramphenicol, metronidazole, tetracycline, and vancomycin hydrochloride), used in this study were purchased from Sigma-Aldrich (Prague, Czechia). Dimethyl sulfoxide (DMSO) (Sigma-Aldrich, Prague, Czechia) was used to prepare the stock solutions of the test compounds, except those of ciprofloxacin, metronidazole, salicylic acid, vancomycin, and zinc pyrithione, which were prepared using distilled water. In case of ciprofloxacin, distilled water was supplemented by 0.1 M hydrochloric acid. Stock solutions of chloramphenicol, tannic acid, and tetracycline were prepared using 96% ethanol (Sigma-Aldrich, Prague, Czechia). The chemical structures of individual compounds tested are shown in Figure 1.

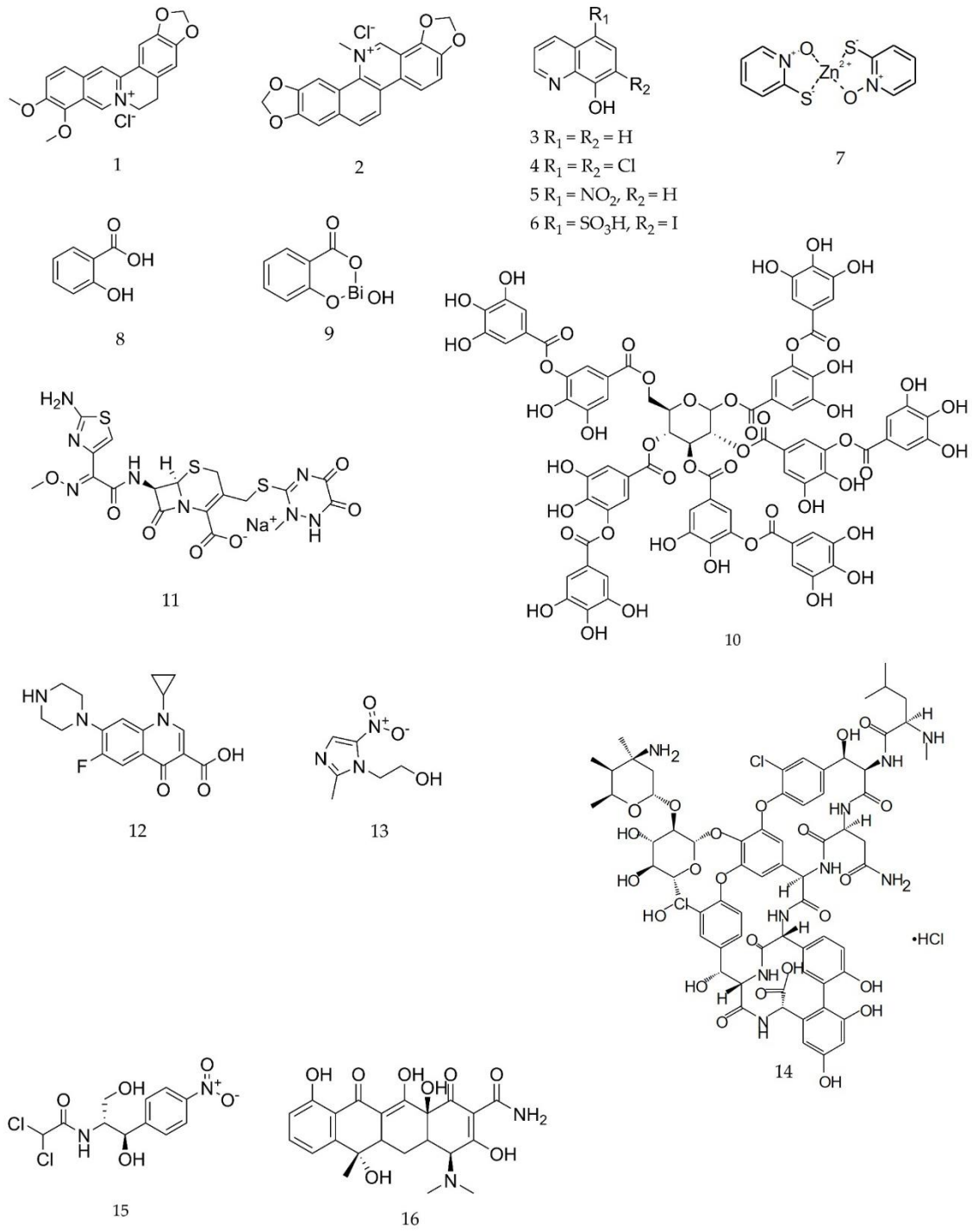


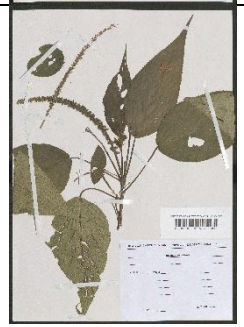
Figure 1 The chemical structures of the tested phytochemicals, their synthetic analogues, and antidiarrheal antibiotics. 1. berberine chloride, 2. sanguinarine chloride, 3. 8-hydroxyquinoline, 4. chloroxine, 5. nitroxoline, 6. ferron, 7. zinc pyrithione, 8. salicylic acid, 9. bismuth subsalicylate, 10. tannic acid, 11. ceftriaxone sodium, 12. ciprofloxacin, 13. metronidazole, 14. vancomycin hydrochloride, 15. chloramphenicol, 16. tetracycline.

6.2 Plant materials

The criteria for selection of promising plant species included their uses for the treatment of diarrhoea, dysentery, abdominal pain, and other gastrointestinal complaints in traditional herbal systems of Southeast Asia, particularly Cambodia and the Philippines. At the same time, these plants had to own no or limited records on their bioactivities *in vitro*. First, the appropriate literature on ethnobotany and ethnomedicine of the studied area was used (Chassagne et al., 2016; de Padua et al., 1999; van Duong, 1993; Kham, 2004; Langenberger et al., 2008; Lemmens and Bunyapraphatsara, 2003; Lim, 2012; Stuart, 2017; Tan, 1980; van Valkenburg and Bunyapraphatsara, 2001). Additionally, names of several other species were obtained through meetings with local herbalists in Cambodia (2) and the Philippines (1), assembled by local experts Dr. Nguon and Dr. Bande, respectively. Finally, more than 100 plant species were identified as eligible for the collection. Out of them, 32 species (13 Cambodian and 19 Philippine) were eventually located and identified on-site. A total of 35 samples from different parts of these species (bark, fruit, leaves, or roots, one per plant except three of the species) were collected from various locations in the Republic of the Philippines in April–May 2017 and 2018 and in the Kingdom of Cambodia in March–April 2019. Majority of the species were collected from the wild, except three which were purchased at Orussey Market in Phnom Penh. The collected fresh samples were subsequently air-dried for several days and sent to the Czechia. After the transportation, each sample was homogenized using Grindomix mill (Retsch, Haan, Germany) and 15 g of dry matter was extracted for 24 h in 450 ml 80% ethanol (Sigma-Aldrich, Prague, Czechia) at room temperature using laboratory shaker (GFL, Burgwedel, Germany). The extract was then filtered and concentrated using rotary evaporator (Büchi Labortechnik, Flawil, CH) *in vacuo* at 40 °C. Dried residues were subsequently diluted in 100 % DMSO (Sigma-Aldrich, Prague, Czechia) to obtain stock solution of the final concentration 51.2 mg/ml and stored at -20 °C until their use. Ethnobotany expert Prof. Kokoska and local experts Dr. Bande and Dr. Nguon authenticated the species. Their voucher specimens have been deposited in the herbarium of the Department of Botany and Plant Physiology of the Faculty of Agrobiology, Food and Natural Resources of the Czech University of Life Sciences Prague (Prague, Czechia). The scientific names of the collected species were reviewed using (The Plant List, 2013), and their local names were verified with data from

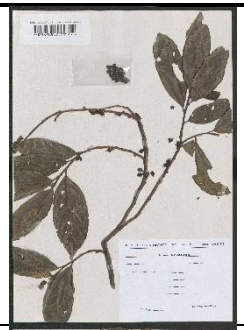
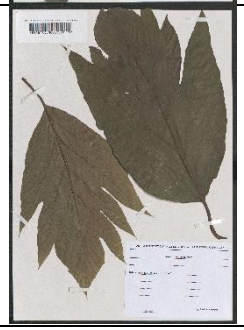
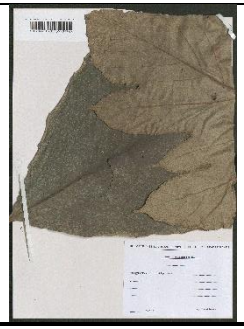
literature and local herbalis (Tan, 1980; van Duong, 1993; de Padua et al., 1999; van Valkenburg and Bunyapraphatsara, 2001; Lemmens and Bunyapraphatsara, 2003; Kham, 2004; Langenberger et al., 2008; Lim, 2012; Chassagne et al., 2016; Stuart, 2017). For all assayed species, the scientific names, families, photographs, local names, voucher specimen codes, GPS coordinates, collected parts (plant samples), life-forms, and their uses in folk medicine are presented in Table 1. Additionally, the locations of the plant samples' and voucher specimens' collection are displayed in Figure 2.

Table 1 Ethnobotanical data on Cambodian and Philippine medicinal plants

Latin name (Family)	Photographs		GPS coordinates (country)	Local name	Voucher specimen	Tested part(s)	Extract yield (%)	Life-form	Ethnomedicinal use
Aganonerion polymorphum Spire (Apocynaceae)			12.3966000N, 107.1934975E (C)	Vor Thneung	02559KBFRC	Whole plant	19.7	H	Diarrhea (Chassagne et al., 2016)
Acalypha grandis Benth. (Euphorbiaceae)			10.7623297N, 124.8062889E (P)	Unknown	02537KBFR8	Leaves	23.6	S/ST	Diarrhoea and dysentery; sapped/crushed into water/food (van Valkenburg and Bunyapraphatsara, 2001)
Acanthus ebracteatus Vahl (Acanthaceae)			10.6888289N, 124.7956483E (P)	Diluario	02505KBFR3	Whole plant	17.9	S	Abdominal pain; decoction of 30-60 gDW (Stuart, 2017)
Ancistrocladus tectorius (Lour.) Merr. (Ancistrocladaceae)			13.7333775N, 107.0151108E (C)	Khan Maa	02560KBFR4	Leaves	16	CB	Dysentery; decoction (Lemmens and Bunyapraphatsara, 2003; interviewed herbalist)

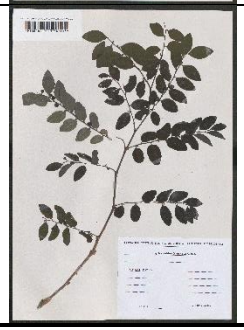
C: Cambodia, P: Philippines, H: herb, S: shrub, S/ST: shrub or small tree, T: tree.

Table 1 (*continued*)

Latin name (Family)	Photographs		GPS coordinates (country)	Local name	Voucher specimen	Tested part(s)	Extract yield (%)	Life-form	Ethnomedicinal use
Aporosa villosa (Lindl.) Baill. (Phyllanthaceae)			12.3965292N, 107.1938597E (C)	Krong	02561KBFR5	Leaves	6.1	S	Diarrhea and abdominal pain; decoction (Chassagne et al., 2016)
Artocarpus blancoi (Elmer) Merr. (Moraceae)			10.7435833N, 124.8020564E (P)	Antipolo	02538KBFR9	Fruit	25.7	T	Diarrhea; cooked (Tan, 1980; Stuart, 2017)
Artocarpus camansi Blanco (Moraceae)			10.6819242N, 124.8001064E (P)	Kamansi	02512KBFR1	Bark	13.3	T	Diarrhea; cooked (Tan, 1980; Stuart, 2017)
Artocarpus elasticus Reinw. ex Blume (Moraceae)			10.7435939N, 124.8019275E (P)	Terap	02539KBFRA	Bark	11.8	T	Dysentery (Lim, 2012; interviewed herbalist)

C: Cambodia, P: Philippines, H: herb, S: shrub, S/ST: shrub or small tree, T: tree.

Table 1 (*continued*)

Latin name (Family)	Photographs		GPS coordinates (country)	Local name	Voucher specimen	Tested part(s)	Extract yield (%)	Life-form	Ethnomedicinal use
Artocarpus odoratissimus Blanco (Moraceae)			10.7436072N, 124.8017989E (P)	Marang	02540KBFR2	Fruit	22.9	T	Diarrhea (Lim, 2012; interviewed herbalist)
Bauhinia malabarica Roxb. (Leguminosae)			12.4428908N, 107.1592217E (C)	Choeung Koo	02562KBFR6	Bark & Leaves	14.7 and 11.2	T	Diarrhea and abdominal pain; alcohol maceration or decoction (Chassagne et al., 2016)
Breynia cernua (Poir.) Müll.Arg. (Phyllantaceae)			9.8153556N, 124.3597258E (P)	Mutang-Ulang	02541KBFR3	Bark	10.6	S/ST	Dysentery; infusion (van Valkenburg and Bunyapraphatsara, 2001)
Breynia vitis-idaea (Burm.f.) C.E.C.Fisch. (Phyllanthaceae)			11.5627122N, 104.9167906E (C)	Phnek Preab	02563KBFR7	Wood with bark	9.9	T	Dysentery; infusion (Kham, 2004)

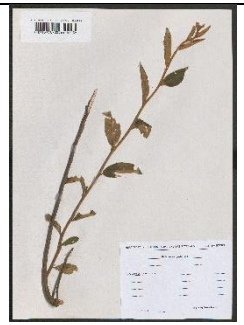
C: Cambodia, P: Philippines, H: herb, S: shrub, S/ST: shrub or small tree, T: tree.

Table 1 (*continued*)

Latin name (Family)	Photographs		GPS coordinates (country)	Local name	Voucher specimen	Tested part(s)	Extract yield (%)	Life-form	Ethnomedicinal use
Commelina communis L. (Commelinaceae)			10.6159294N, 124.9272431E (P)	Alibangon	02542KBFR4	Whole plant	13.3	H	Diarrhea (van Valkenburg and Bunyapraphatsara, 2001)
Cyathula prostrata (L.) Blume (Amaranthaceae)			10.7433806N, 124.8001225E (P)	Dayang	02543KBFR5	Whole plant	12.8	H	Dysentery and cholera; decoction or infusion (van Valkenburg and Bunyapraphatsara, 2001; Stuart, 2017).
Diplazium esculentum (Retz.) Sw. (Athyriaceae)			10.7577433N, 124.7975153E (P)	Paco	02545KBFR7	Rhizome	5.4	F	Diarrhea and dysentery; pulverization and cold water maceration (Stuart, 2017; interviewed herbalist)
Ehretia microphylla Lam. (Boraginaceae)			10.7442369N, 124.7897825E (P)	Tsaang-Gubat	02489KBFRE	Leaves	15.3	S	Diarrhea, dysentery, and abdominal pain; decoction or infusion (8 tbsp of chopped leaves in 2 glasses) (de Padua et al., 1999; Stuart, 2017).

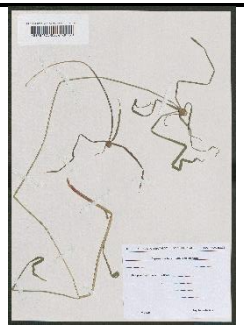
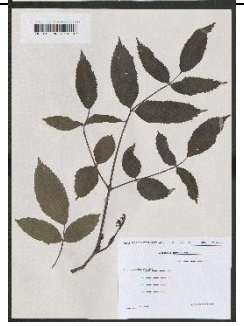
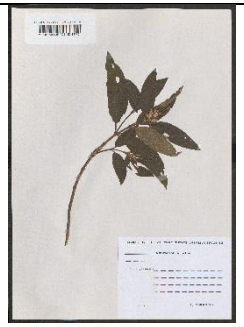
C: Cambodia, P: Philippines, H: herb, S: shrub, S/ST: shrub or small tree, T: tree.

Table 1 (*continued*)

Latin name (Family)	Photographs		GPS coordinates (country)	Local name	Voucher specimen	Tested part(s)	Extract yield (%)	Life-form	Ethnomedicinal use
Emilia sonchifolia (L.) DC. ex DC. (Compositae)			10.7407072N, 124.8002914E (P)	Tagulinaw	02520KBFR0	Whole plant	20.9	H	Diarrhea, dysentery, and enteritis; decoction (6–15 gDW) (Tan, 1980; Stuart, 2017)
Helicteres angustifolia L. (Malvaceae)			12.3963028N, 107.1938622E (C)	Sambok Cheas	02564KBFR8	Root	9.2	H	Diarrhea, dysentery, and abdominal pain; decoction (Chassagne et al., 2016)
Hyptis capitata Jacq. (Lamiaceae)			10.7590292N, 124.8020589E (P)	Botonesan	02546KBFR8	Whole plant	10.1	S	Gastro-intestinal problems; decoction (Lemmens and Bunyapraphatsara, 2003)
Ixora nigricans R.Br. ex Wight & Arn. (Rubiaceae)			13.7291931N, 107.0113667E (C)	Phka Mochul Pich	02565KBFR9	Leaves	10.8	S/ST	Dysentery and abdominal pain (Kham, 2004)

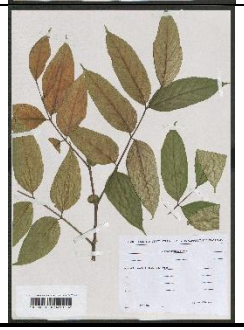
C: Cambodia, P: Philippines, H: herb, S: shrub, S/ST: shrub or small tree, T: tree.

Table 1 (*continued*)

Latin name (Family)	Photographs		GPS coordinates (country)	Local name	Voucher specimen	Tested part(s)	Extract yield (%)	Life-form	Ethnomedicinal use
Kyllinga brevifolia Rottb. (Cyperaceae)			11.0610592N, 124.7009597E (P)	Pugo-Pugo	02544KBFR6	Whole plant	11.4	H	Diarrhoea (de Padua et al., 1999; Stuart, 2017)
Lagerstroemia cochinchinensis Pierre ex Gagnep. (Lythraceae)			13.4692872N, 105.8909203E (C)	Sralao	02566KBFRA	Bark	2.8	T	Diarrhea; decoction (Chassagne et al., 2016)
Leea indica (Burm. f.) Merr. (Vitaceae)			11.5627122N, 104.9167906E (C)	Kdaing Baay	02567KBFRB	Root	8.3	S	Diarrhea, dysentery, digestive and intestinal complaints; decoction or infusion (Kham, 2004)
Melastoma dodecandrum Lour. (Melastomataceae)			12.4089644N, 107.3133011E (C)	Unknown	02568KBFRC	Bark & Leaves with flower buds	12.7 and 9.9	S	Diarrhea (van Duong, 1993)

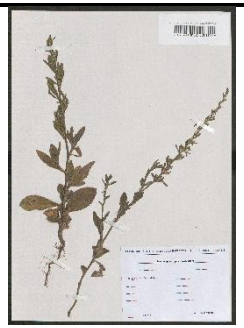
C: Cambodia, P: Philippines, H: herb, S: shrub, S/ST: shrub or small tree, T: tree.

Table 1 (*continued*)

Latin name (Family)	Photographs		GPS coordinates (country)	Local name	Voucher specimen	Tested part(s)	Extract yield (%)	Life-form	Ethnomedicinal use
Melastoma saigonense (Kuntze) Merr. (Melastomataceae)			11.5627122N, 104.9167906E (C)	Baay Nhenh	02569KBFRD	Wooden stem & Leaves with flower buds	7.3 and 17.3	S	Diarrhea (Chassagne et al., 2016)
Parkia javanica (Lam.) Merr. (Leguminosae)			10.7448892N, 124.8059375E (P)	Kupang	02547KBFR9	Bark	25.7	T	Diarrhea and dysentery; decoction (Tan, 1980; Stuart, 2017)
Pentacme siamensis (Miq.) Kurz (Dipterocarpaceae)			13.4474300N, 105.8756317E (C)	Raing Phnom	02571KBFR6	Bark	5.8	T	Diarrhea (Chassagne et al., 2016)
Picrasma javanica Blume (Simaroubaceae)			10.7438825N, 124.8039956E (P)	Manunggal	02548KBFRA	Bark	6.3	T	Digestive and abdominal pain; decoction (Langenberger et al., 2009)

C: Cambodia, P: Philippines, H: herb, S: shrub, S/ST: shrub or small tree, T: tree.

Table 1 (*continued*)

Latin name (Family)	Photographs		GPS coordinates (country)	Local name	Voucher specimen	Tested part(s)	Extract yield (%)	Life-form	Ethnomedicinal use
Pseudelephantopus spicatus (Juss. ex Aubl.) Rohr (Compositae)			9.8110686N, 124.3551231E (P)	Kokunbanog	02553KBFR6	Whole plant	12.5	H	Diarrhea; decoction (Langenberger et al., 2009)
Rourea minor (Gaertn.) Alston (Connaraceae)			12.3965372N, 107.1933392E (C)	Unknown	02570KBFR5	Leaves	11.4	S	Diarrhea (Chassagne et al., 2016)
Tabernaemontana pandacaqui Lam. (Apocynaceae)			14.1667808N, 121.2143336E (P)	Pandakaking-Puti	02503KBFR1	Bark	10.1	S/ST	Gastroenteritis (Tan, 1980)
Triumfetta bartramia L. (Malvaceae)			10.7467864N, 124.8152500E (P)	Kulutkulutan	02554KBFR7	Root	14.9	H	Diarrhea and intestinal ulcers (van Valkenburg et al., 2001; Stuart, 2017)

C: Cambodia, P: Philippines, H: herb, S: shrub, S/ST: shrub or small tree, T: tree, CB: climber, F: fern

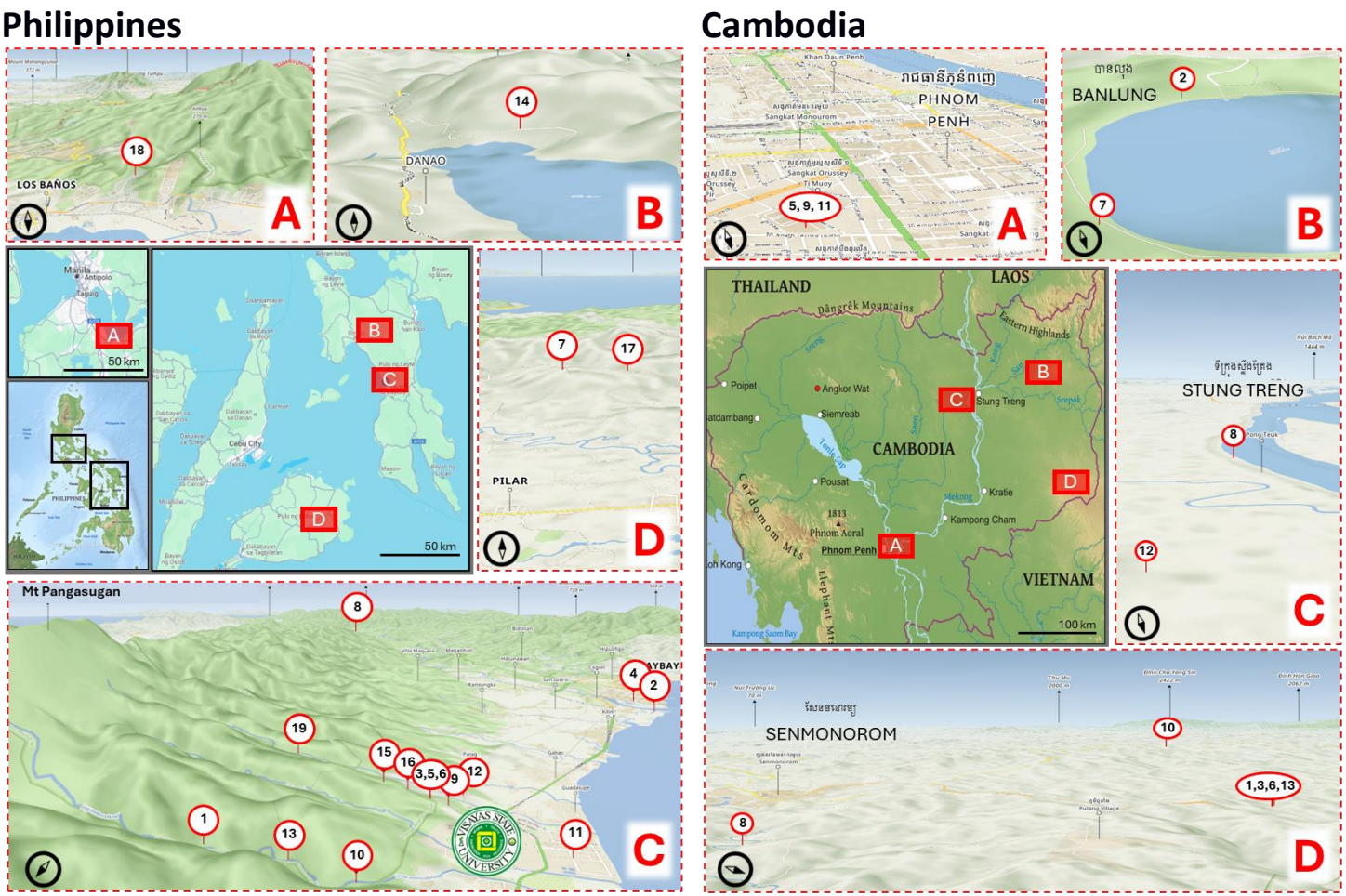


Figure 2 Locations of the plant samples' and voucher specimens' collected in Cambodia and the Philippines (2017-2019).

Philipines: 1. *Acalypha grandis*, 2. *Acanthus ebracteatus*, 3. *Artocarpus blancoi*, 4. *Artocarpus camansi*, 5. *Artocarpus elasticus*, 6. *Artocarpus odoratissimus*, 7. *Breynia cernua*, 8. *Commelina communis*, 9. *Cyathula prostrata*, 10. *Diplazium esculentum*, 11. *Ehretia microphylla*, 12. *Emilia sonchifolia*, 13. *Hyptis capitata*, 14. *Kyllinga brevifolia*, 15. *Parkia javanica*, 16. *Picrasma javanica*, 17. *Pseudelephantopus spicatus*, 18. *Tabernaemontana pandacaqui*, 19. *Triumfetta bartramia*

Cambodia: 1. *Aganonerion polymorphum*, 2. *Ancistrocladus tectorius*, 3. *Aporosa villosa*, 4. *Bauhinia malabarica*, 5. *Breynia vitis-idaea*, 6. *Helicteres angustifolia*, 7. *Ixora nigricans*, 8. *Lagerstroemia cochinchinensis*, 9. *Leea indica*, 10. *Melastoma dodecandrum*, 11. *Melastoma saigonense*, 12. *Pentacme siamensis*, 13. *Rourea minor*

6.3 Bacterial strains and growth media

The intestinal bacterial type strains were obtained from the American Type Culture Collection (ATCC, Rockville, MD, USA), Czech Collection of Microorganisms (CCM, Brno, Czechia), German Collection of Microorganisms and Cell Cultures (DSMZ, Braunschweig, Germany), and National Collection of Type Cultures (NCTC, London, UK). In accordance with the diversity of diarrheagenic Gram-positive and Gram-negative bacteria responsible for globally distributed foodborne, waterborne, and nosocomial infections (Diniz-Santos 2006; Rajkovic et al. 2020), the following 12 strains were used in this study: *B. cereus* (ATCC 14579), *C. difficile* (DSMZ 12056), *C. perfringens* (DSMZ 11778), *E. faecalis* (ATCC 29212), *E. coli* (ATCC 25922), *E. coli* 0175:H7 (NCTC 12900), *L. monocytogenes* (ATCC 7644), *S. flexneri* (ATCC 12022), *Salmonella enterica* ssp. *enterica* serovar Enteritidis (ATCC 13076), *S. enterica* ssp. *enterica* serovar Typhimurium (ATCC 14028), *V. parahaemolyticus* (ATCC 17802), and *Yersinia enterocolitica* (ATCC 9610). The above-mentioned strains were considered as obligate/facultative pathogens or also diarrheagenic bacteria. The following nine bacterial strains, which belong to three predominant bacterial phyla in the human gut and exhibit probiotic functions (Sun et al. 2019; Behnsen et al. 2013), were used in this study: *Bacteroides fragilis* (ATCC 25285), *Bifidobacterium adolescentis* (DSMZ 20087), *Bifidobacterium animalis* spp. *lactis* (DSMZ 10140), *Bifidobacterium bifidum* (ATCC 29521), *Bifidobacterium breve* (ATCC 15700), *Bifidobacterium longum* ssp. *longum* (DSMZ 20219), *Lacticaseibacillus casei* (DSMZ 20011), *Lactobacillus reuteri* (CCM 3625), and *Lacticaseibacillus rhamnosus* (CCM 7091). All these strains were considered as probiotic or also beneficial bacterial strains. As the maintenance and growth medium, Mueller–Hinton broth (Oxoid, Basingstoke, UK) was used for bacteria that grow aerobically (*E. faecalis* supp. 1% glucose, *V. parahaemolyticus* supp. 3% NaCl). *Y. enterocolitica* was stored and cultured in Brain Heart Infusion Broth (Oxoid, Basingstoke, United Kingdom). Bifidobacteria and lactobacilli were maintained and cultured in Wilkins-Chalgren Broth (Oxoid, Basingstoke, United Kingdom) supplemented with 5 g/L soya peptone and 0.5 g/L cysteine. Although the same growth medium was used for clostridia, they were stored in cooked meat medium (both from Oxoid, Basingstoke, United Kingdom) at room temperature. The standard safety guidelines for handling

microorganisms were followed. Therefore, all items, such as culture tubes, syringes, and gloves, were discarded in the biohazard autoclave bag after every use.

6.4 Cell cultures

One representative of non-cancer intestinal cell line (FHs 74 Int [ATCC CCL 241]) and two of cancer intestinal cell lines (Caco-2 [ATCC HTB 37]) and HT-29 [ATCC HTB 38]) were purchased from ATCC (Rockville, MD, United States). Non-cancer cells were cultured in Hybri-Care medium supplemented with 10% foetal bovine serum, 1% sodium bicarbonate, 1% nonessential amino acids, 30 ng/ml of epidermal growth factor, and 1% penicillin-streptomycin solution (10,000 units/ml and 100 mg/ml, respectively). The cancer cells were cultured in Eagle's Minimum Essential Medium (EMEM) supplemented with 1% sodium pyruvate, 10% foetal bovine serum, 1% sodium bicarbonate, 1% nonessential amino acids, and 1% penicillin-streptomycin solution (10,000 units/ml and 100 mg/ml, respectively) (all purchased from Biowest, Nuaille, France). The cultures were incubated at 37°C and 5% CO_2. The culture medium was replaced every 2–3 days, and cells were passaged every 7 days.

6.5 Antibacterial assay

Initially, the compounds and extracts were evaluated for their antibacterial activities against the pathogenic strains. The toxicity against several probiotic strains was subsequently evaluated in case of those showing any inhibitory action against the pathogens. The growth-inhibitory activities were evaluated by the broth microdilution method using 96-well microtiter plates, following the protocols of CLSI (2021) guidelines and Hecht (1999), respectively. For the effective assessment of the anti-infective potential of natural products, slight modifications were implemented as described by Cos et al. (2006).

Prior to testing, the strains that grow aerobically were subcultured in the appropriate media at 37°C (*Y. enterocolitica* at 30°C) for 24 h. Bifidobacteria, clostridia, and lactobacilli were cultured at 37°C for 48 h using Whitley A35 Anaerobic Workstation (Don Whitley Scientific, Bingley, United Kingdom). The anaerobic conditions were created by supplying a standard anaerobic gas mixture of 10% H_2, 10% CO_2, and 80%

N_2 (Linde Gas, Prague, Czechia). Test agents were diluted 2-fold in appropriate growth media using the Freedom EVO 100 automated pipetting platform (Tecan, Männedorf, Switzerland) and multichannel pipette (Eppendorf, Hamburg, Germany) (initial concentration of 512 μg/mL) in case of aerobic and anaerobic bacteria, respectively. After the optimalization of bacterial cultures to inoculum density of 1.5×10^8 CFU/ml by 0.5 McFarland standard using Densi-La-Meter II (Lachema, Brno, Czechia), the cultures were inoculated in 96-well plates (5 μl/well). The plates containing the volatile compound, 8-hydroxyquinoline, were covered using EVA capmats (Micronic, Lelystad, Netherlands) after inoculation to prevent evaporation (Houdkova et al. 2017). Bacterial cultures in microplates were incubated by employing the same protocols as used for their cultivation prior to the test. The optical density of the cultures was measured at 405 nm ($OD_{450\ nm}$) using a Cytation 3 Imaging Reader (BioTek, Winooski, VT, USA) before and after the growth. The lowest concentration (μg/ml) of the compounds and extracts that inhibited the bacterial growth by ≥80% was defined as the minimum inhibitory concentration (MIC). All tests were performed as three independent experiments each carried out in triplicate. The mode and median were used for the final MIC value calculation when the triplicate endpoints were within the two- and three-dilution ranges, respectively. Depending on whether it was a compound or an extract, the antibacterial activities were classified as strong (respective MICs ≤ 8 and ≤ 64 μg/ml), moderate (respective MICs = 16–128 and 128–256 μg/ml), and weak (respective MIC = 256–512 and 512 μg/ml) (Cos et al. 2006; Kokoska et al. 2019). As a result of experiments performed without dissolved test compounds nor the extracts, DMSO, 96% ethanol (both from Sigma-Aldrich, Prague, Czechia), and 0.1M hydrochloric acid did not inhibit bacterial growth of any strain at the tested concentrations (≤1%).

6.6 Cytotoxicity assay

The antiproliferative activities of the compounds and extracts that showed some inhibitory action against the tested bacteria were further assessed using the modified thiazolyl blue tetrazolium bromide (MTT) cytotoxicity assay developed by Mosmann (1983). The cancer (2.5×10^3) and non-cancer intestinal (2.5×10^5) cells were seeded in a 96-well microtiter plate for 24 h. Cells were incubated with two-fold serially diluted test agents (0.25–512 μg/mL) for 72 h. Plates containing 8-hydroxyquinoline were

covered using EVA capmats. Next, the cells were incubated with MTT reagent (1 mg/mL) (Sigma-Aldrich, Prague, Czechia) in DMEM or Hybri-Care medium for an additional 2 h at 37 °C and 5% CO_2. The medium with MTT was removed and the intracellular formazan product was dissolved in 100 μL of DMSO. The absorbance was measured at 555 nm using a Tecan Infinite M200 spectrometer (Tecan, Männedorf, Switzerland), and the percentage of viability was calculated when compared to an untreated control. The antiproliferative activity was represented as half-maximal inhibitory concentration (IC_{50}; μg/ml). The colon cancer chemotherapeutic drug 5-fluorouracil (Sigma-Aldrich, Prague, Czechia) was used as a positive control (Fuente et al., 2020). Three independent experiments (two replicates each) were performed for every test. Data are presented as mean ± standard deviation. Depending on whether it was a compound or an extract, the antiproliferative activities were evaluated as follows: cytotoxic (respective IC_{50} values ≤2 and ≤100 μg/ml), moderately cytotoxic (IC_{50} values = 4–128 and 100–400 μg/ml), and weakly cytotoxic/non-toxic (respective IC_{50} values = 256–512 μg/ml) (Srisawat et al. 2013; Houdkova et al. 2018). The solvents did not affect the viability of non-cancer and cancer intestinal cell lines at the tested concentration (≤1%).

6.7 Calculations and statistics

For comparison of microbiological and toxicological data, 80% bacterial growth inhibition (IC_{80}) was calculated as equivalent to the MIC endpoint (Houdkova et al., 2018). Subsequently, $\bar{x}$-MIC, $\bar{x}$-IC_{50}, and $\bar{x}$-IC_{80} values (±standard deviations) were calculated to quantify the inhibitory activity of the tested compounds and extracts against pathogenic/probiotic bacteria and intestinal cancer/non-cancer cells. Then, the selectivity index (SI) was calculated between non-cancer intestinal cells and pathogenic strains (SIa), probiotic and pathogenic strains (SIb), non-cancer and cancer intestinal cells (SIc), and probiotic strains and cancer intestinal cells (SId) using the following formulas where X1 = IC_{80} against non-cancer intestinal cells; X2 = $\bar{x}$-MIC against probiotic strains; X3 = IC_{50} against non-cancer intestinal cells; Y1 = $\bar{x}$-MIC against pathogenic strains; Y2 = $\bar{x}$-IC_{50} against cancer intestinal cells; and Y3 = IC_{80} against cancer intestinal cells:

$$SIa = \log (X_1/Y_1),$$

$$SIb = \log (X_2/Y_1)$$

$$SIc = \log (X_3/Y_2)$$

$$SId = \log (X_2/Y_3)$$

The SI values >0 and <0 indicate selective toxicity against pathogenic strains/cancer cell lines and probiotic strains/non-cancer cell lines, respectively.

The correlation between the combination of activities revealed by test compounds and their chemical classes was analysed using Principal component analysis (PCA) & Heatmap cluster analysis with Statistica 13 software (2017). In case of PCA, all data for particular activities were grouped into four types of targets (cancer cells, diarrheagenic strains, non-cancer cells, and probiotic strains). MIC and IC_{80} values were used for both kinds of analyses. There was no adjustment of the PCA parameters. For the calculation of each $\bar{x}$-MIC, $\bar{x}$-IC_{50}, $\bar{x}$-IC_{80} and for PCA & Heatmap cluster analysis, values greater than the maximum tested concentration (512 μg/mL) were replaced with 1024 μg/mL.

6.8 Chemotaxonomic distribution and quantitative structure-property relationship data analyses

Based on results of laboratory experiments, the literature analysis focused on chemotaxonomic distribution and structure activity relationship of the most effective compounds was performed. Only the chemicals that naturally occur in plants and have been tested for *in vitro* activities against intestinal diarrheagenic/probiotic bacteria and/or cancer/non-cancer cells were included. These data were particularly expressed as MICs and IC_{50} values in μg/ml, whereas those available in molar concentrations were recalculated. Studies examining the compounds using some non-quantitative methods were also considered evaluating their biological effects as active (A) or non-active (NA). If applicable, the selectivity between inhibitory actions of the compounds was determined by the calculation of selectivity indices (SI values) using the following formula: SI = log (X1/Y1); where X1 and Y1 are mean values of MIC/IC_{50} values against non-cancer cells/probiotic bacteria and cancer cells/diarrheagenic bacteria, respectively. The functional groups of the most effective compounds were identified using quantitative structure-property relationship analysis. Finally, the analysis of their chemotaxonomic distribution in relation to ethnobotanical profile (plants used for the treatment of various digestive complaints) was analysed in order to identify plant taxa that are prospective for further phytochemical and pharmacological research.

7. Results and discussion

7.1 Effect of phytochemicals and their synthetic analogues on human intestinal bacteria and cells

As far as the antibacterial activity of the tested antidiarrheal antibiotics against pathogenic strains is considered, ciprofloxacin and tetracycline exhibited strong growth-inhibitory effect ($\bar{x}$-MICs = 2 ± 4 and 4.8 ± 8 μg/mL, respectively), while chloramphenicol and ceftriaxone exhibited moderate growth-inhibitory activities ($\bar{x}$-MIC = 16.5 ± 34 and 61.8 ± 141 μg/mL, respectively). However, there was significant degree of variation between MICs of these compounds as particular types of pathogenic strains were highly susceptible while some other species were distinctly more resistant. For example, all gram-negative diarrheagenic bacteria were highly susceptible to ciprofloxacin (MICs = 0.016–0.125 μg/mL) and ceftriaxone (MICs = 0.062–0.5 μg/mL). In contrast, their MICs produced against gram-positive pathogens were comparably higher; for the former ranging from 1 to 16 μg/ml and for the latter in the range of 4–512 μg/mL. At least half of the diarrheagenic bacteria were inhibited at the low MICs (1–4 μg/mL) by chloramphenicol and tetracycline, whereas the variations were particularly caused by the weak activities revealed against *Enterococcus faecalis* (MIC = 128 μg/mL) and *Clostridium perfringens* (32 μg/mL), respectively. At the low concentration (MICs = 0.5 μg/ml), tetracycline also inhibited *Clostridium difficile* and *Bacillus cereus.* Although metronidazole and vancomycin were generally inactive against diarrheagenic bacteria ($\bar{x}$-MIC = 651.4 ± 459 and 512.9 ± 404, respectively), they produced a strong inhibitory effect against both clostridial species tested (MICs = 0.5–8 μg/ml), whereas the former also exhibited strong activity against *Escherichia coli* (MIC = 0.062 μg/ml).

The synthetic analogues of phytochemicals, namely, zinc pyrithione, nitroxoline, and chloroxine, exhibited strong to moderate growth-inhibitory activity against all diarrheagenic bacteria ($\bar{x}$-MICs = 7.1 ± 4, 12 ± 10, and 24 ± 19 μg/ml, respectively). The activities of these compounds against particular pathogenic bacteria did not vary greatly, however, some of the strains were comparably more susceptible. For example, *B. cereus*, *E. coli*, *Shigella flexneri*, and *Vibrio parahaemolyticus* were highly susceptible to zinc pyrithione (MICs = 1–4 μg/ml). The MIC of chloroxine against both *B. cereus* and *C. difficile* was 8 μg/ml. Nitroxoline exhibited strong growth-inhibitory activities (MICs =

2–4 μg/ml) against *B. cereus*, clostridial species, *E. coli*, and *S. flexneri*. Although the overall antibacterial activity of 8-hydroxyquinoline against the pathogens was not significant ($\bar{x}$-MIC = 224.4 ± 181), it produced strong action against *E. faecalis* (MIC = 4 μg/ml) and *Listeria monocytogenes* (MIC = 1 μg/ml). The complete data on growth-inhibitory activities of test compounds against diarrheagenic including calculated mean values ($\bar{x}$-MIC) are presented in Table 2.

Table 2 *In vitro* selective inhibitory activities of phytochemicals, their synthetic analogues, and antibiotics against intestinal bacteria and cells.

Cultures tested		Alkaloids							Phenolic compounds			Antibiotics and Anticancer drug						
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Bacterial strain/MIC (μg/ml)	BC	-[a]	128	512	8	4	512	4	-	512	512	128	1	128	256	8	0.5	nd
	CD	-	64	128	8	2	64	8	256	128	-	64	16	0.5	2	4	0.5	nd
	CP	256	128	128	16	4	64	8	-	512	512	4	1	8	1	4	32	nd
	EF	-	32	4	16	32	-	8	-	-	-	512	2	-	-	128	4	nd
	EC	-	256	128	16	4	-	4	-	-	-	0.062	0.062	0.062	-	4	1	nd
	ECS	-	128	256	64	32	-	8	-	-	512	0.5	0.016	-	512	8	4	nd
	LM	-	16	1	32	16	512	8	-	256	-	32	4	512	8	8	2	nd
	SF	-	64	128	16	2	-	1	-	-	-	0.5	0.016	-	-	4	2	nd
	SE	-	256	256	64	16	-	8	-	-	-	0.25	0.031	-	512	4	4	nd
	ST	512	512	512	16	16	-	8	-	512	-	0.25	0.031	-	512	8	4	nd
	VP	512	32	128	16	8	256	4	-	-	128	0.125	0.062	-	256	2	1	nd
	YE	-	256	512	16	8	-	16	-	-	512	0.25	0.125	-	-	16	2	nd
	x̄-DB ± SD	*874.7 ± 256*	*156 ± 137*	*224.4 ± 181*	*24 ± 19*	*12 ± 10*	*714.7 ± 388*	*7.1 ± 4*	*960 ± 212*	*757.3 ± 332*	*778.7 ± 307*	*61.8 ± 141*	*2 ± 4*	*651.4 ± 459*	*512.9 ± 404*	*16.5 ± 34*	*4.8 ± 8*	nd
	BF	-	32	32	32	4	128	8	128	32	-	128	8	0.5	32	4	0.5	nd
	BA	128	16	512	128	16	256	16	-	32	-	1	8	64	2	4	64	nd
	BLC	32	32	-	512	32	512	16	128	64	-	2	32	32	2	4	32	nd
	BBF	64	32	512	-	16	512	8	-	64	-	4	16	-	4	4	16	nd
	BB	64	32	-	64	32	512	16	-	64	256	32	64	32	4	4	16	nd
	BL	32	64	512	64	16	256	16	512	64	128	8	16	8	2	4	2	nd
	LC	64	32	-	128	32	256	16	512	128	512	32	32	-	256	16	8	nd
	LR	-	32	-	128	16	512	64	512	64	512	0.5	32	256	64	8	32	nd
	LRM	64	64	-	128	16	512	32	512	128	-	32	4	-	64	8	8	nd
	x̄-PB ± SD	*277.3 ± 400*	*37.3 ± 15*	*743.1 ± 343*	*245.3 ± 306*	*20 ± 9*	*384 ± 148*	*21.3 ± 16*	*597.3 ± 336*	*71.1 ± 33*	*725.3 ± 352*	*26.6 ± 38*	*23.6 ± 18*	*384.9 ± 458*	*47.8 ± 78*	*6.2 ± 4*	*19.8 ± 19*	*nd*
Cell line (μg/ml) IC_{50} ± SD	HT29	5 ± 1	0.9 ± 0.2	1.3 ± 0.3	3.7 ± 0.3	2.6 ± 0.3	86.3 ± 12	0.6 ± 0.01	-	461.9 ± 17	35.9 ± 4.9	-	130.3 ± 13	-	-	271.1 ± 1	392.9± 20	6.35 ± 2
	Caco-2	19.4 ± 2.9	0.8 ± 0.1	0.3 ± 0.1	1.3 ± 0.04	1.1 ± 0.03	55.2 ± 4.8	0.7 ± 0.2	-	45.3 ± 5	27.6 ± 1.5	-	69.9 ± 4.9	-	-	439.3 ± 4	70.4 ± 15	181. 8 ± 151.5
	x̄-CC ± SD	12.2 ± 7	0.8 ± 0.05	0.8 ± 0.5	2.5 ± 1.2	1.8 ± 0.8	70.8 ± 16	0.6 ± 0.05	-	253.6 ± 208	31.7 ± 4	-	100.1 ± 30	-	-	355.2 ± 84	231.6± 161	94 ± 88
	FHs 74 Int	1 ± 0.1	1 ± 0.1	10.7 ± 0.2	0.5 ± 0.02	0.4 ± 0.05	22.6 ± 3.3	0.3 ± 0.1	73.2 ± 4.6	8.7 ± 1.3	5.9 ± 1.2	-	51.8 ± 27	-	-	30.7 ± 5.6	14.7 ± 2.3	492.4 ± 22.9
Cell line (μg/ml) IC_{80} ± SD	HT29	42.1 ± 7.3	1.8 ± 0.4	4.8 ± 2.8	5 ± 0.7	3.7 ± 0.4	149.4 ± 6	0.7 ± 0.01	-	-	43 ± 2.2	-	-	-	-	-	-	367.3 ± 0.6
	Caco-2	78.9 ± 0.3	1.5 ± 0.1	0.9 ± 0.1	5.9 ± 0.7	5 ± 1.5	139.9 ± 26	0.7 ± 0.01	-	454.9 ± 43	-	-	-	-	-	-	-	-
	x̄-CC ± SD	60.5 ± 18.4	1.6 ± 0.2	2.9 ± 2	5.4 ± 0.5	4.4 ± 0.7	144.7 ± 4.8	0.7 ± 0.01	-	740 ± 285	534 ± 491	-	-	-	-	-	-	695.6 ± 328.4
	FHs 74 Int	26.4 ± 0.8	1.9 ± 0.2	20.3 ± 2.4	2 ± 0.1	0.8 ± 0.05	46 ± 2.2	0.5 ± 0.03	206.9 ± 69	31.4 ± 6.6	10.2 ± 2.4	-	129.5 ± 24	-	-	-	108.2 ± 5	-
SI	(a)	-1.5	-1.9	-1	-1.1	-1.2	-1.2	-1.1	-0.7	-1.4	-1.9	1.2	1.8	0.2	0.3	1.8	1.4	nd
	(b)	-0.5	-0.6	0.5	1	0.2	-0.3	0.5	-0.2	-1	-0.03	-0.4	1.1	-0.2	-1	-0.4	0.6	nd
	(c)	-1.1	0.1	1.1	-0.7	-0.6	-0.5	-0.4	-1.1	-1.5	-0.7	0	-0.3	0	0	-1.1	-1.2	0.4
	(d)	0.66	1.36	2.6	1.65	0.65	0.42	1.4	-0.23	-1	0.13	-1.6	-1.6	-0.42	-1.33	-2.21	-1.71	nd

MIC: minimum inhibitory concentration; IC_{50}: half maximal inhibitory concentration; IC_{80}: 80% inhibitory concentration of proliferation; SD. standard deviation; [a]Not active (MIC/$IC_{50/80}$ >512 μg/ml, the value 1,024 μg/ml was used for average calculation); nd: no data; 1: berberine, 2: sanguinarine, 3: 8-hydroxyquinoline, 4: chloroxine, 5: nitroxoline, 6: ferron, 7: zinc pyrithione, 8: salicylic acid, 9: bismuth subsalicylate, 10: tannic acid, 11: ceftriaxone, 12: ciprofloxacin, 13: metronidazole, 14: vancomycin, 15: chloramphenicol, 16: tetracycline; 17: 5-fluorouracil; BC: *Bacillus cereus*, CD: *Clostridium difficile*, CP: *Clostridium perfringens*, EF: *Enterococcus faecalis*, EC: *Escherichia coli*, ECS: *E. coli* 0175:H7, LM: *Listeria monocytogenes*, SF: *Shigella flexneri*, SE: *Salmonella* Enteritidis, ST: *Salmonella* Typhimurium, VP: *Vibrio parahaemolyticus*, YE: *Yersinia enterocolitica*, BF: *Bacteroides fragilis*, BA: *Bifidobacterium adolescentis*, BLC: *Bifidobacterium animalis* spp. *lactis*, BBF: *Bifidobacterium bifidum*, BB: *Bifidobacterium breve*, BL: *Bifidobacterium longum* ssp. *longum*, LC: *Lacticaseibacillus casei*, LR: *Lactobacillus reuteri*, LRM: *Lacticaseibacillus rhamnosus*; *x̄-DB*: mean MIC for diarrheagenic bacteria, *x̄-PB*: mean MIC for probiotic bacteria, *x̄-CC*: mean $IC_{50/80}$ for intestinal cancer cells, FHs 74 Int (intestinal non-cancer cells), SD: standard deviation. SI (Selective Index): (a) non-cancer cells/diarrheagenic bacteria, (b) probiotic bacteria/diarrheagenic bacteria, (c) non-cancer cells/cancer cells, (d) probiotic bacteria/cancer cells.

Subsequently, the growth-inhibitory activities against probiotic intestinal strains were evaluated. Regarding the tested compounds, these bacteria exhibited high susceptibility to antibiotic compound chloramphenicol ($\bar{x}$-MIC = 6.2 ± 4 μg/ml) and medium susceptibility to tetracycline, nitroxoline, zinc pyrithione, ciprofloxacin, ceftriaxone, sanguinarine, and vancomycin ($\bar{x}$-MICs = 19.8 ± 19–47.8 ± 78 μg/ml). The MICs (2–4 μg/ml) of both chloramphenicol and vancomycin against bifidobacteria were similarly low, but the latter was significantly less harmful to lactobacilli (MICs = 64–256 μg/ml) and *B. fragilis* (MIC = 32 μg/ml). With the exception of *Bifidobacterium breve* and *Bifidobacterium longum* ssp. *longum* (MICs = 8–32 μg/ml), the remaining bifidobacteria were also susceptible to ceftriaxone (MICs = 1–4 μg/ml). However, considering the MIC range (MICs = 0.5–32 μg/ml) shown against lactobacilli and *B. fragilis* (MIC = 128 μg/ml), the variations of susceptibilities are quite high. Exceptionally susceptible was *B. fragilis* to metronidazole and tetracycline (MICs = 0.5 μg/ml), whereas the MIC (4 μg/ml) of nitroxoline in case of this bacterium was the same as in the case of chloramphenicol. In general, berberine (MICs ≥ 32 μg/ml), ferron (MICs ≥ 64 μg/ml), and phenolic compounds (MICs ≥ 64 μg/ml) did not exhibit any significant toxicity to any of the 21 strains. The complete data on growth-inhibitory effects of test compounds against probiotic strains, including calculated mean values ($\bar{x}$-MIC) are presented in Table 2.

Regarding the cytotoxic activity of the test compounds, only alkaloids and related structures exhibited strong *in vitro* effects, while other agents, especially antibiotics, exhibited moderate or no cytotoxic activity. Considering the activities on intestinal cancer cells, zinc pyrithione, 8-hydroxyquinoline, and sanguinarine were cytotoxic to HT29 (IC_{50} values = 0.6, 1.3, and 0.9 μg/ml, respectively) and Caco-2 (IC_{50} values = 0.7, 0.3 and 0.8 μg/ml, respectively). Nitroxoline (IC_{50} = 1.1 μg/ml) and chloroxine (IC_{50} = 1.3 μg/ml) exhibited comparable cytotoxic activity against Caco-2 cells. Zinc pyrithione had the lowest $\bar{x}$-IC_{50} value (0.6 ± 0.05 μg/ml) against cancer cells, followed by 8-hydroxyquinoline (0.8 ± 0.5 μg/ml), sanguinarine (0.8 ± 0.05 μg/ml), nitroxoline (1.8 ± 0.8 μg/ml), and chloroxine (2.5 ± 1.2 μg/ml). Berberine ($\bar{x}$-IC_{50} = 12.2 ± 7 μg/ml), tannic acid ($\bar{x}$-IC_{50} = 31.7 ± 4 μg/ml), and ferron ($\bar{x}$-IC_{50} = 70.8 ± 16 μg/ml), produced moderate cytotoxic activity, while salicylic acid and bismuth subsalicylate ($\bar{x}$-IC_{50} ≥ 253.6 ± 208 μg/ml) did not exhibit significant cytotoxic activity against cancer cells. At relatively high concentrations, some antibiotics exhibited antiproliferative activity against cancer cells,

namely: ciprofloxacin, tetracycline, and chloramphenicol ($\bar{x}$-IC_{50} = 100.1 ± 30–355.2 ± 84 μg/ml). Considering the antiproliferative effect on non-cancer intestinal cells (FHs 74 Int), the antibiotics ceftriaxone, metronidazole, and vancomycin were not cytotoxic at all tested concentrations (IC_{50} and IC_{80} > 512 μg/ml), whereas tetracycline (IC_{50} = 14.7 ± 2.3 μg/ml; IC_{80} = 108.2 ± 5 μg/ml), chloramphenicol (IC_{50} = 30.7 ± 5.6 μg/ml; IC_{80} > 512 μg/ml), and ciprofloxacin (IC_{50} = 51.8 ± 27 μg/ml; IC_{80} = 129.5 ± 24 μg/ml) were moderately cytotoxic. In case of phytochemicals and their synthetic analogues, salicylic acid (IC_{50} = 73.2 ± 4.6 μg/ml; IC_{80} = 206.9 ± 69 μg/ml), ferron (IC_{50} = 22.6 ± 3.3 μg/ml; IC_{80} = 46 ± 2.2 μg/ml), and 8-hydroxyquinoline (IC_{50} = 10.7 ± 0.2 μg/ml; IC_{80} = 20.3 ± 2.4 μg/ml), revealed moderately cytotoxic effects against FHs 74 Int, whereas the other compounds were cytotoxic (IC_{50} values = 0.3 ± 0.1–1 ± 0.1 μg/ml; IC_{80} values = 0.5 ± 0.03–26.4 ± 0.8 μg/ml). The complete data on all antiproliferative actions of test compounds against non-cancer and cancer intestinal cells, including calculated mean values for the latter ($\bar{x}$-IC_{50} and $\bar{x}$-IC_{80}), are presented in Table 2.

Evaluating the selectivity of inhibitory actions of the pure chemicals tested, those exhibiting strong to moderate inhibitory effects on diarrheagenic bacteria produced relatively lower activity against probiotic strains (SIb values range from 0.2–1.1), namely: nitroxoline, zinc pyrithione, tetracycline, chloroxine, and ciprofloxacin. In contrast, antibiotics chloramphenicol and ceftriaxone were more toxic to probiotic strains (SIbs = −0.4 for both). Although the antibacterial activity of berberine, ferron, phenolic compounds, and sanguinarine was in cases of both diarrheagenic and probiotic strains generally insignificant, the results show that these agents were rather toxic to the latter (SIb values range from −1 to −0.03). Due to the minor cytotoxicity revealed against FHs 74 Int, none of the antibiotics exhibited an increased toxicity to non-cancer intestinal cells at the inhibitory concentrations active against diarrheagenic bacteria (SIa values = 0.2–1.8), especially ciprofloxacin and chloramphenicol. In contrast, all of the phytochemicals and their synthetic analogues revealed cytotoxicity to non-cancer intestinal cells at the concentrations they were generally inactive against diarrheagenic bacteria (SIa values range from −1.9 to −0.7). Only 8-hydroxyquinoline (SIc = 1.1) and sanguinarine (SIc = 0.1) exhibited selective antiproliferative activity against cancer cells with the decreased cytotoxic effect on non-cancer intestinal cells. Except these two, other tested compounds were more toxic to non-cancer than to cancer intestinal cells (SIcs = from −1.5 to −0.3), or in the case of ceftriaxone, metronidazole, and vancomycin, they did not show any

selectivity (SIcs = 0), as they did not inhibit cell lines at any concentration tested. All alkaloids and related structures produced significant selectivity if comparing their anticancer actions with toxicities produced against probiotic bacteria, especially chloroxine, 8-hydroxyquinoline, and sanguinarine (SIds = 1.36–2.6). The data on selective toxicities of the compounds, including all calculated SI values are presented in Table 2. The curves of *in vitro* selective concentration-dependent effect of ciprofloxacin, chloroxine, nitroxoline, tetracycline, and zinc pyrithione on the growth of diarrheagenic and probiotic bacteria and of 8-hydroxyquinoline on intestinal non-cancer and cancer cells proliferation are shown in Figure 3.

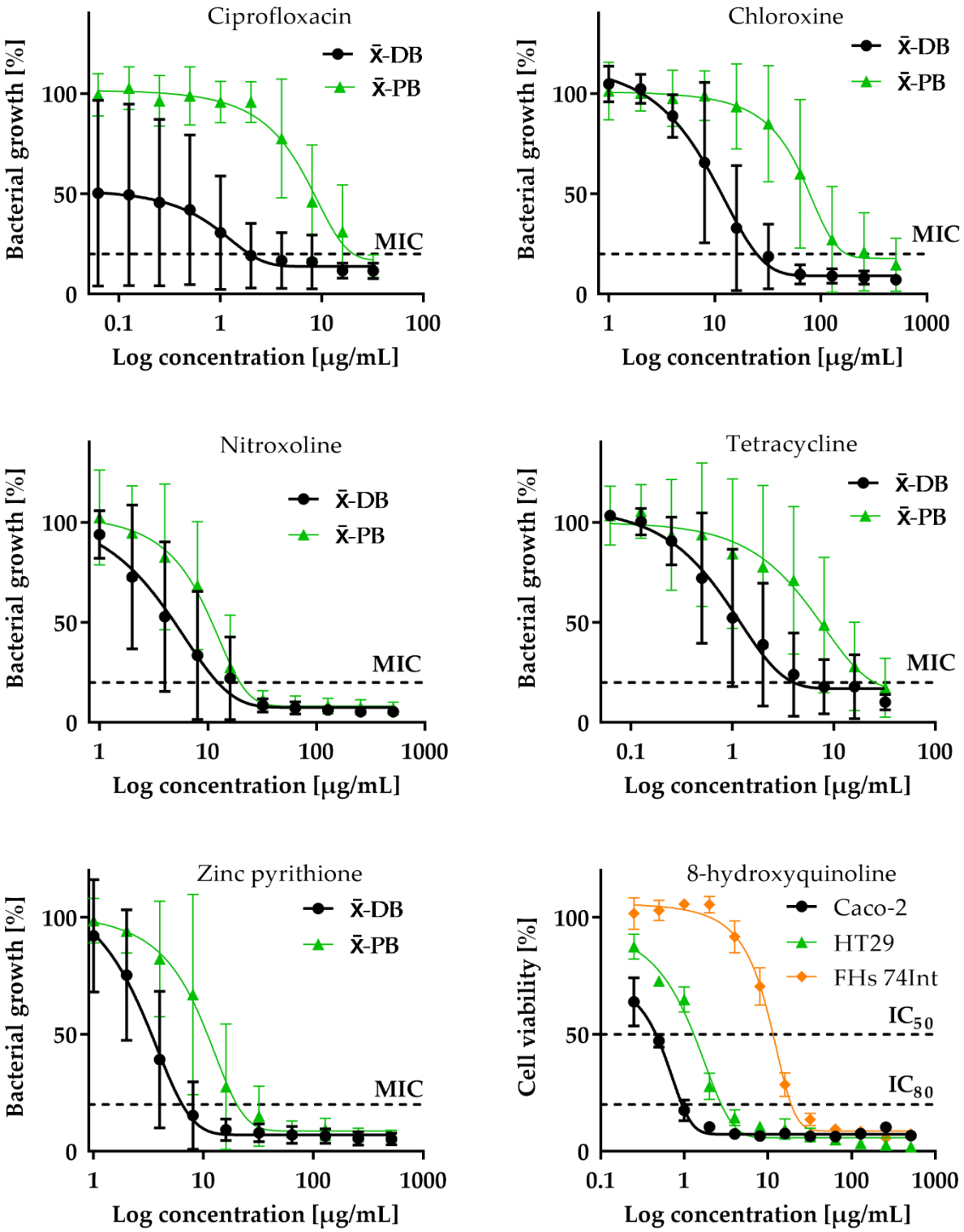


Figure 3 Selective concentration-dependent effect of chloroxine, ciprofloxacin, nitroxoline, tetracycline, and zinc pyrithione on the growth of diarrheagenic and probiotic bacteria and of 8-hydroxyquinoline on intestinal non-cancer and cancer cells proliferation *in vitro*. MIC: minimum inhibitory concentration; IC_{50}: half maximal inhibitory concentration; IC_{80}: 80% inhibitory concentration of proliferation. $\bar{x}$-DB: mean MIC for 12 diarrheagenic bacteria, $\bar{x}$-PB: mean MIC for 9 probiotic bacteria; Caco-2 and HT29: intestinal cancer cells; Fhs74 Int: intestinal non-cancer cells.

The correlation between biological activities and chemical structures of the tested compounds and their groups (antibiotics, phenolic compounds, alkaloids, and related structures) was also analysed using PCA & Heatmap cluster analysis (Figure 4). The distribution of compounds among PCA quadrants correspond to some degree with their clustering in the heatmap, which helped to identify the similarities in bioactivities produced. The closest correlation was observed in the lower-left quadrant between four antibiotics (ceftriaxone, ciprofloxacin, chloramphenicol, and tetracycline), which is associated to the strong inhibitory activities produced against diarrheagenic and probiotic strains but not against non-cancer and cancer intestinal cell lines. This strong correlation was also easy to identify in the heatmap. The second highest correlation observed in the lower right quadrant between zinc pyrithione and 8-hydroxyquinolines (excluding ferron) was probably derived from their ability to exhibit slightly selective antibacterial activity against diarrheagenic strains along with strong to moderate cytotoxic activity against both types of the tested cell lines. This corresponds with the clustering observed in the heatmap except for 8-hydroxyquinoline. Unlike others, this compound produced weaker antibacterial actions but with significantly higher degree of selectivity. The correlation observed in the upper right quadrant indicated that tannic acid, benzylisoquinoline alkaloids, and ferron exhibited moderate to no antipathogenic effect (with negative SIbs) and overall moderate to strong cytotoxic activity. The clustering in the heatmap particularly indicated the similarities between berberine and ferron in their increased toxicities to probiotic bacteria in comparison to the pathogens. Similar features are also visible in case of tannic acid. Sanguinarine, on the other hand, was rather associated with nitroxoline and zinc pyrithione, probably due to its ability to produce certain degree of inhibitory effect on most of the microbial agents and cell lines. The upper left quadrant of PCA contains the remaining antibiotics (metronidazole and vancomycin) and both simple phenols with minimal correlation. These agents exhibited moderate to no growth-inhibiting activity against diarrheagenic strains and practically no cytotoxic activity. Correspondingly, the heatmap displayed the similarities between the mentioned antibiotics and bismuth subsalicylate. However, salicylic acid was rather associated with tannic acid due to the increased toxicities towards intestinal non-cancer line. Whereas all alkaloids are distributed in lower and upper right PCA quadrants indicating their capability to reveal any type of the tested bioactivities, phenols are spread in the right and left upper quadrants which shows their lack of significant antibacterial activity but a

certain degree of cytotoxicity. In contrast, antibiotics are concentrated in the lower-left quadrant slightly overlapping the upper left one, therefore they usually display a significant antibacterial effect which is rarely accompanied by cytotoxicity. In summary to the results of the Heatmap cluster analysis, there is a clear division between the significant bioactivities produced by most of the alkaloid-related structures, and antibiotics, and those produced by phenolic compounds. Due to the similarities in susceptibility of probiotic bacteria, these strains and the pathogens were also clearly divided in the heatmap.

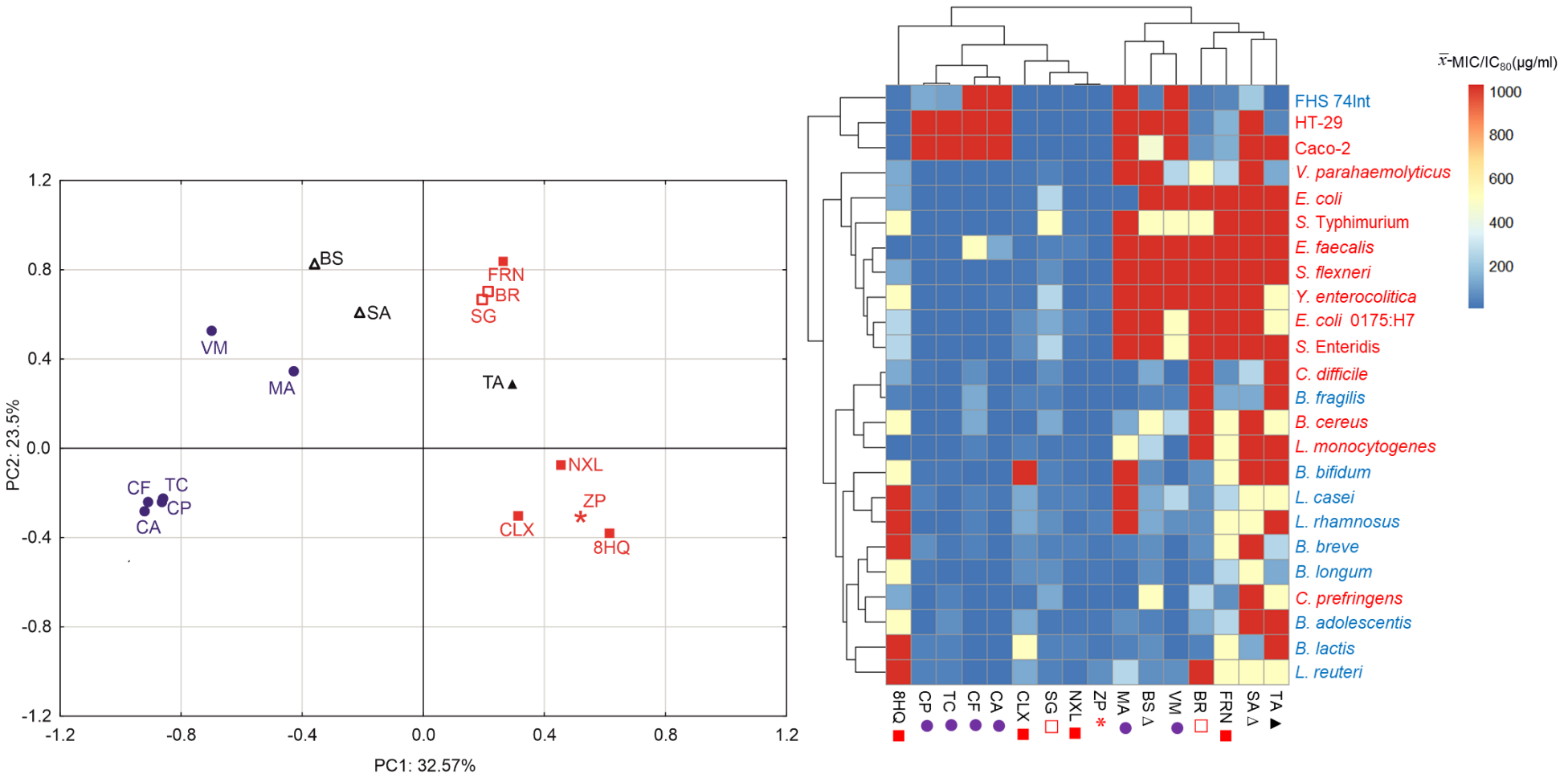


Figure 4 Principal component analysis (left) & Heatmap cluster analysis (right) of antibacterial and cytotoxic activities of phytochemicals, their synthetic analogues, and antibiotics against intestinal bacteria and cells *in vitro*. BR: berberine, SG: sanguinarine, 8HQ: 8-hydroxyquinoline, CLX: chloroxine, NXL: nitroxoline, FRN: ferron, ZP: zinc pyrithione, SA: salicylic acid, BS: bismuth subsalicylate, TA: tannic acid, CF: ceftriaxone, CP: ciprofloxacin, MA: metronidazole, VM: vancomycin, CA: chloramphenicol, TC: tetracycline. Antibiotics [●]; Phenolic compounds [poly- (▲), simple (Δ)]; Alkaloids and related structures [benzylisoquinolines (□), 8-hydroxyquinolines (■), metal-pyridine derivative complex (*).

Unsurprisingly, the chosen antidiarrheal antibiotics have previously been involved in experiments testing *in vitro* growth-inhibitory against number of diarrheagenic and even probiotic bacteria. However, the bacterial strains tested as well as the methods with criteria used for antimicrobial activity assessment vary frequently among the previous studies. Moreover, the studies reporting the *in vitro* susceptibilities of probiotic bacteria deal more with clinical isolates (Merriam et al. 2006), and less with standard strains (Kheadr et al. 2004). The present study, therefore, provides the data on *in vitro* selective antibacterial activities of these antibiotics that can be fairly compared with the same data obtained for phytochemicals and their synthetic analogues. We suggest that the reason behind the increased resistance of probiotic strains differ for particular compounds that showed a selective antipathogenic effect. The growth-inhibitory activities of fluoroquinolones against Gram-positive bacteria are reported to be lower than those against Gram-negative bacteria (Oliphant & Green 2002). Consistent with this finding, bifidobacteria and lactobacilli (Gram-positive) were generally less susceptible to ciprofloxacin than Gram-negative diarrheagenic bacteria that predominate over Gram-positive pathogens in this study. The decreased susceptibility of bifidobacteria to tetracycline might be caused by the presence of specific antibiotic resistance genes (Moubareck et al. 2005). Similar to other third-generation cephalosporins (Sharma et al. 2016), the growth-inhibitory activity of ceftriaxone against Gram-negative bacteria was higher than that against Gram-positive bacteria. However, as a result of significant resistance of the tested Gram-positive pathogens and susceptibility of bifidobacteria, ceftriaxone showed increased toxicity to probiotic strains. The growth-inhibitory activities of some alkaloids and related structures were comparable with those of antibiotics. The antibacterial activity of 8-hydroxyquinoline alkaloids is mediated through the chelation of metals that function as co-factors in various enzymes, which results in the inhibition of RNA synthesis. We suggest that probiotic strains (mainly bifidobacteria) are more resistant to 8-hydroxyquinolines as they are able to sequester iron from the environment (Novakova et al. 2013). The selective antibacterial activity of 8-hydroxyquinoline against diarrheagenic pathogens seems to be enhanced with chlorine halogenation or by the presence of a nitro group and decreased with iodine halogenation and the presence of a sulfo group, as respectively observed for chloroxine, nitroxoline, and ferron in our study. The *in vitro* selective anticlostridial effect of 8-hydroxyquinoline with increased resistance of bifidobacteria was previously described in studies of

Novakova et al. (2013; 2014; 2016), Skrivanova et al. (2016), and Kim et al. (2006). However, data on its *in vitro* growth-inhibitory effects against a broader selection of diarrheagenic bacteria are limited. The present study also provides new data on *in vitro* antibacterial activities of chloroxine against diarrheagenic bacteria in addition to those previously published (Prapasarakul et al. 2010; Tranter 1968). It has been reported that Endiaron, a chloroxine-containing antimicrobial product used for infectious diarrhoea, exhibits antimicrobial activity against the pathogens and does not affect the host indigenous microbiota (WikiZero 2020), which is in agreement with the increased resistance of probiotic bacteria described in the present study. Interestingly, the antipathogenic activity of nitroxoline, used to treat urinary tract infections, was higher than that of chloroxine. However, the antibacterial selectivity of nitroxoline against diarrheagenic strains was lower. Out of the intestinal bacteria tested herein, there are only data on *in vitro* inhibitory effects of nitroxoline against *E. coli* and *E. faecalis* that have been reported before (Sobke et al. 2018). In spite of zinc pyrithione being only used topically for dermatological infections (Kokoska et al. 2019), in relation to the plant compounds and their synthetic analogues in this study, it exhibited the highest growth-inhibitory activity against diarrheagenic bacteria with lowered toxicity to probiotic bacteria. According to our best knowledge, this is the first report on *in vitro* selective antibacterial activities of zinc pyrithione on intestinal diarrheagenic and probiotic bacteria. Although there is limited knowledge on the mechanism underlying the antibacterial activity of zinc pyrithione, the mechanism may be similar to that of 8-hydroxyquinolines (Chandler and Segel 1978). The weak antimicrobial activities of phenols against diarrheagenic strains are consistent with those reported in previous studies. The effectiveness of phenols in infectious diarrhoea may be based on other mechanisms, such as astringent, mucosa-protective, and anti-inflammatory properties, or inhibition of pathogenic enterotoxins (Kokoska et al. 2019). Moreover, polyphenols have always been abundant in human diet, thus their exposure to intestinal bacteria must have resulted in overall increased resistance to these plant compounds (Kemperman 2010). Although clinical studies on extensively used phytochemical berberine have reported comparably higher efficiency than certain antibiotics (e.g., chloramphenicol) (Lahiri 1967), our results did not show its significant *in vitro* antibacterial activity. A possible reason for this discordance is that berberine rather neutralizes diarrheagenic action of bacteria by inhibiting their enterotoxins, as described by Sack and Froelich (1982). The

MICs of both benzylisoquinoline alkaloids against some diarrheagenic bacteria reported in this study were higher than those reported in previous studies. This may be because the inoculum density used in this study was higher than that used in previous studies (Kokoska et al. 2019; Hamoud et al. 2014).

The mechanisms underlying the antiproliferative activity of some antibiotics against intestinal cell lines, namely ciprofloxacin, tetracycline, and chloramphenicol, may be similar or identical to those they employ while producing *in vitro* effect on some bacterial cells (Elsea et al. 1992; Chukwudi 2016; Hu et al. 2016). Previous studies have evaluated the antiproliferative activity of chemicals derived from ciprofloxacin and tetracycline against cancer cells and suggested their applications in cancer therapy (Elsea et al. 1992; Onoda et al. 2005). Consistent with the results of this study, previous studies have revealed that other antibiotics are not cytotoxic to eukaryotic cells (Dewdney 1986; Eisenstein & Schaechter 2007; Hanaki et al. 1998). The antitumor activities of some plant compounds and their synthetic analogues have been investigated previously. In the case of 8-hydroxyquinoline and its derivatives, the interaction with metal ions, namely copper and iron, and their transportation into cells has been reported as crucial for its antiproliferative activity (Oliveri & Vecchio 2016). Freitas et al. (2014) reported that 8-hydroxyquinoline derivatives with potent anticancer potential often contain halogen substituents. However, in the present study, nitroxoline exhibited stronger antiproliferative activity against cancer cells than chloroxine and ferron. Previous studies have reported that the underlying mechanism of antitumor activity of zinc pyrithione and sanguinarine involves the inhibition of proteasomal deubiquitinases and microtubule depolymerization, respectively (Slaninova et al. 2013; Zhao et al. 2017). All of the above-mentioned alkaloids and related structures revealed increased toxicity to non-cancer intestinal cells in comparison with their antipathogenic effect, which limits their applications in treating bacterial diarrhoea. Although there are no studies reporting oral toxicity or toxicity to the digestive system from berberine, chloroxine, and nitroxoline, we suggest that their safety profile should be further examined and the potential protective role of indigenous gut microbiota against these cytotoxic chemicals should be more deeply studied. Zinc pyrithione and 8-hydroxyquinoline are not part of any product intended for internal use. Hence, their dose-dependent toxicological profile and oral safety must be carefully elucidated before any consideration for their application for

treating infectious diarrhoea associated with intestinal cancer (Lazar et al. 2018). Although sanguinarine as an active ingredient of the antimicrobial feed supplement Sangrovit was shown to be safe for farm animals, its toxicity to humans should still be tested (Stiborova 2008).

7.2 Effect of extracts from Southeast Asian medicinal plants on human intestinal bacteria and cells

Considering the antipathogenic activity of plant extracts, 16 of 35 revealed a growth-inhibitory effect on at least one of these bacterial strains. While *B. cereus*, *C. difficile*, *E. coli*, and *V. parahaemolyticus* were the most susceptible bacteria inhibited by the highest number of extracts, none of the extracts exerted activity against *E. coli* O157:H7 and *S. flexneri*. There were four extracts showing promising antibacterial actions against multiple pathogenic bacteria, especially the gram-positive strains. Namely, the fruit extract of *Artocarpus blancoi* inhibited *B. cereus* and both clostridia at MICs 64 and 32 μg/ml, respectively. This plant was also moderately active against *E. faecalis* (MIC = 128 μg/ml) and *L. monocytogenes* (MIC = 256 μg/ml). Similarly, the leaf extract of *Ancistrocladus tectorius* revealed a strong inhibitory effect on *B. cereus* (MIC = 64 μg/ml) and moderate activity against *L. monocytogenes* (MIC = 128 μg/ml). However, it produced only weak inhibitory action against both clostridia (MICs = 512 μg/ml). Next, bark extract of *Artocarpus camansi* inhibited *B. cereus* and both clostridia at MICs ranging from 128 to 256 μg/ml. Although the antibacterial activities of bark extract of *Pentacme siamensis* were rather moderate, it exerted inhibitory action against several gram-positive as well as gram-negative pathogenic strains. Namely, it inhibited *B. cereus*, *E. coli*, and *S.* Enteritidis at MICs of 256 μg/ml and *L. monocytogenes* at MIC of 512 μg/ml. Additionally, there were five more plant extracts exerting moderate activity (MIC = 256 μg/ml) against a single gram-negative strain. Namely, *Bauhinia malabarica* (bark), *Breynia vitis-idaea*, *Melastoma dodecandrum* (bark), and *Picrasma javanica* inhibited *E. coli*; *B. vitis-idaea* inhibited *S.* Typhimurium; and *Acalypha grandis* inhibited *V. parahaemolyticus*. Finally, *Aganonerion polymorphum*, *Diplazium esculentum*, *Ehretia microphylla*, *Ixora nigricans*, *Lagerstroemia cochinchinensis*, *Melastoma dodecandrum* (leaves with flower buds), and *Melastoma saigonense* (leaves with flower

buds) produced only weak inhibitory actions at MICs of 512 μg/ml. All MICs (32–512 μg/ml) of 16 plant extracts are presented in Table 3.

The remaining 19 extracts of *Acanthus ebracteatus, Aporosa villosa, Artocarpus elasticus, Artocarpus odoratissimus, B. malabarica* (leaves), *Breynia cernua, Commelina communis, Cyathula prostrata, Emilia sonchifolia, Helicteres angustifolia, Hyptis capitata, Kyllinga brevifolia, Leea indica, M. saigonense* (wooden stem and leaves), *Parkia javanica, Pseudelephantopus spicatus, Rourea minor, Tabernaemontana pandacaqui,* and *Triumfetta bartramia* did not show any inhibitory action; thus, they have not been further discussed.

Table 3 *In vitro* selective inhibitory activities of ethanolic extracts of Cambodian and Philippine plants against intestinal bacteria and cells

Cultures tested		Plant species with their parts and positive antibiotic and anticancer control																
		AP(w)	***AG(l)***	***AT(l)***	***AB (f)***	***AC(b)***	***BM(b)***	***BV(wb)***	***DE(r)***	***EM(l)***	***IN(l)***	***LC(b)***	***MD(b)***	***MD(lf)***	***MS(lf)***	***PJ(b)***	***PS(b)***	**CIP**	**5-FU**
Bacterial strain/MIC (µg/ml)	BC	-[a]	512	64	64	256	512	-	-	512	-	-	-	-	512	-	256	1	nd
	CD	512	512	512	32	128	-	-	-	512	512	-	-	512	512	-	-	16	nd
	CP	-	512	512	32	256	-	-	-	-	-	-	-	-	-	-	-	1	nd
	EF	-	-	-	128	-	-	-	-	-	-	-	-	-	-	-	-	2	nd
	EC	512	-	-	-	-	256	256	512	-	-	-	256	-	-	256	256	0.062	nd
	ECS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.016	nd
	LM	-	-	128	256	-	-	-	-	-	-	-	-	-	512	-	512	4	nd
	SF	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.016	nd
	SE	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	256	0.031	nd
	ST	-	-	-	-	-	-	256	-	-	-	-	-	512	-	-	-	0.031	nd
	VP	-	256	-	-	-	512	-	-	512	-	512	512	512	512	-	-	0.062	nd
	YE	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.125	nd
	$\bar{x}$-PB ± SD	938.7 ±191	832 ± 279	784 ± 390	640 ± 458	821.3 ± 352	874.7 ± 266	896 ± 286	981.3 ± 142	896 ± 222	981.3 ± 142	981.3 142±	917.3 ± 244	896 ± 222	853.3 ± 241	960 ± 212	789.3 ± 338	2 ± 6	nd
	BA	64	512	256	16	-	-	-	-	512	512	-	-	256	512	-	-	8	nd
	BB	-	64	64	16	512	-	-	-	128	128	-	-	-	256	128	-	64	nd
	BLC	-	-	256	16	-	-	-	-	256	512	-	-	-	512	-	-	32	nd
	LC	512	256	128	16	256	-	-	-	128	128	-	-	-	512	512	512	32	nd
	LR	-	-	256	16	-	-	-	-	-	-	-	-	-	-	-	-	32	nd
	LRM	-	-	128	16	512	-	-	-	512	-	-	-	-	-	-	-	4	nd
	$\bar{x}$-BB ± SD	778.7 ± 370	650.7 ± 395	181.3 ± 78	16 ± 0	725.3 ± 311	1,024 ± 0	1,024 ± 0	1,024 ± 0	426.7 ± 311	554.7 ± 367	1,024 ± 0	1,024 ± 0	896 ± 286	640 ± 286	789.3 ± 350	938.7 ± 191	29 ± 20	nd

MIC: minimum inhibitory concentration; SD: standard deviation; [a]Not active (MIC > 512 µg/ml, the value 1,024 µg/ml was used for average calculation). *AP(w)*: *Aganonerion polymorphum* (whole plant), *AG(l)*: *Acalypha grandis* (leaves); *AT(l)*: *Ancistrocladus tectorius* Merr. (leaves), *AB (f)*: *Artocarpus blancoi* (fruit), *AC(b)*: *Artocarpus camansi* (bark), *BM(b)*: *Bauhinia malabarica* (bark), *BV(wb)*: *Breynia vitis-idaea* (wood with bark), *DE(r)*: *Diplazium esculentum* (roots), *EM(l)*: *Ehretia microphylla* (leaves), *IN(l)*: *Ixora nigricans* (leaves), *LC(b)*: *Lagerstroemia cochinchinensis* (bark), *MD(b)*: *Melastoma dodecandrum* (bark), *MD(lf)*: *Melastoma dodecandrum* (leaves with flower buds), *MS(lf)*: *Melastoma saigonense* (leaves with flower buds), *PJ(b)*: *Picrasma javanica* (bark), *PS(b)*: *Pentacme siamensis* (bark), CIP: ciprofloxacin, 5-FU: 5-fluorouracil. BC: *Bacillus cereus*, CD: *Clostridium difficile*, CP: *Clostridium perfringens*, EF: *Enterococcus faecalis*, EC: *Escherichia coli*, ECS*: E. coli* 0175:H7, LM: *Listeria monocytogenes*, SF: *Shigella flexneri*, SE: *Salmonella* Enteritidis, ST: *Salmonella* Typhimurium, VP: *Vibrio parahaemolyticus*, YE: *Yersinia enterocolitica*, BA: *Bifidobacterium adolescentis*, BB: *Bifidobacterium breve*, BLC: *Bifidobacterium animalis* spp. *lactis*, LC: *Lacticaseibacillus casei*,, LR: *Lactobacillus reuteri*, LRM: *Lacticaseibacillus rhamnosus*, $\bar{x}$-PB: mean MIC for pathogenic bacteria, $\bar{x}$-BB: mean MIC for probiotic bacteria.

Table 3 (*continued*)

Cultures tested			Plant species with their parts and positive antibiotic and anticancer control																	
			AP(w)	*AG(l)*	*AT(l)*	*AB (f)*	*AC(b)*	*BM(b)*	*BV(wb)*	*DE(r)*	*EM(l)*	*IN(l)*	*LC(b)*	*MD(b)*	*MD(lf)*	*MS(lf)*	*PJ(b)*	*PS(b)*	CIP	5-FU
Cell line (µg/ml)	IC_{50} ± SD	HT-29	130.5 ± 2.6	96.5 ± 12.4	82.2 ± 17.2	53.7 ± 16	84.8 ± 4.2	35.2 ± 5.3	81.8 ± 20.8	-[a]	130.9 ± 14	125.6 ± 13.9	37.9 ± 2.7	248.6 ± 23.1	210.9 ± 16.8	49.8 ± 3.5	155.9 ± 41.8	52 ± 19.8	88.8 ± 13.4	6.4 ± 2
		Caco-2	149 ± 17.1	78.4 ± 23.2	33.8 ± 10.6	79.4 ± 6.9	48.4 ± 0.9	-	-	-	52.5 ± 8.8	135.6 ± 3.1	122.9 ± 13.2	193.7 ± 1.6	77.6 ± 10.2	87.4 ± 19.2	121.3 ± 15.3	-	90.9 ± 18	181. 8 ± 151.5
		$\bar{x}$-CC ± SD	139.7 ± 9.2	87.5 ± 9	58 ± 24.2	66.5 ± 12.8	66.5 ± 18	529.6 ± 494	552.9 ± 471	-	91.7 ± 39.2	130.6 ± 5	80.4 ± 42.5	221.1 ± 27.4	144.2 ± 66.6	68.575 ± 18.8	138.6 ± 17.3	538 ± 486	89.8 ± 1	94 ± 88
		FHs 74 Int	297.4 ± 22.5	118.8 ± 36	45.5 ± 7.3	273.3 ± 7.5	68.2 ± 12.4	158.4 ± 23.8	68.8 ± 8.9	-	303.4 ± 18	243.5 ± 21.9	282 ± 0.6	-	368 ± 30	195.2 ± 8.9	342.6 ± 3.5	-	58.9 ± 4.3	492.4 ± 22.9
	IC_{80} ± SD	HT-29	130.5 ± 12	-	498.2 ± 16.8	-	356.2 ± 19	-	-	-	-	-	-	351.3 ± 43.2	378.5 ± 34.9	143.7 ± 16.7	-	-	181.5 ± 15.05	367.3 ± 0.6
		Caco-2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		$\bar{x}$-CC ± SD	577.3 ± 446.8	-	761.1 ± 263	-	690.1 ± 333.9	-	-	-	-	-	-	687.6 ± 336.4	701.3 ± 322.8	583.6 ± 440.2	-	-	602.8 ± 421.2	695.6 ± 328.4
		FHs 74 Int	-	-	-	-	264.6 ± 6.8	-	-	-	-	-	-	-	-	-	-	-	83.4 ± 8.6	-
SI		(a)	0.04	0.09	0.12	0.2	-0.49	0.07	0.06	0.02	0.06	0.02	0.02	0.05	0.06	0.08	0.03	0.11	1.62	nd
		(b)	-0.1	-0.1	-0.6	-1.6	-0.1	0.1	0.1	0.02	-0.3	-0.2	0.02	0.05	0	-0.1	-0.04	0.1	1.2	nd
		(c)	0.3	0.1	-0.1	0.6	0.01	-0.5	-0.9	0	0.5	0.3	0.5	0.7	0.4	0.5	0.4	0.3	-0.2	0.4
		(d)	0.13	-0.2	-0.62	-1.81	0.02	0	0	0	-0.38	-0.27	0	0.17	0.11	0.04	-0.11	-0.04	-1.32	nd

IC_{50}: half maximal inhibitory concentration; IC_{80}: 80% inhibitory concentration of proliferation; SD: standard deviation; [a]Not active ($IC_{50/80}$ > 512 µg/ml, the value 1,024 µg/ml was used for average calculation); nd: no data. *AP(w)*: *Aganonerion polymorphum* (whole plant), *AG(l)*: *Acalypha grandis* (leaves); *AT(l)*: *Ancistrocladus tectorius* Merr. (leaves), *AB (f)*: *Artocarpus blancoi* (fruit), *AC(b)*: *Artocarpus camansi* (bark), *BM(b)*: *Bauhinia malabarica* (bark), *BV(wb)*: *Breynia vitis-idaea* (wood with bark), *DE(r)*: *Diplazium esculentum* (roots), *EM(l)*: *Ehretia microphylla* (leaves), *IN(l)*: *Ixora nigricans* (leaves), *LC(b)*: *Lagerstroemia cochinchinensis* (bark), *MD(b)*: *Melastoma dodecandrum* (bark), *MD(lf)*: *Melastoma dodecandrum* (leaves with flower buds), *MS(lf)*: *Melastoma saigonense* (leaves with flower buds), *PJ(b)*: *Picrasma javanica* (bark), *PS(b)*: *Pentacme siamensis* (bark), CIP: ciprofloxacin, 5-FU: 5-fluorouracil. $\bar{x}$-CC: mean $IC_{50/80}$ for intestinal cancer cells, FHs 74 Int (intestinal non-cancer cells), SI (Selective Index): (a) non-cancer cells/diarrheagenic bacteria, (b) probiotic bacteria/diarrheagenic bacteria, (c) non-cancer cells/cancer cells, (d) probiotic bacteria/cancer cells.

Subsequently, 16 extracts that exerted growth-inhibitory effect against diarrheagenic pathogens were verified for their safety to probiotic bacteria. The final MICs are presented in Table 3. Five extracts, namely, *B. malabarica*, *D. esculentum*, *L. cochinchinensis*, and *M. dodecandrum* (bark), did not have any inhibition of these strains (MICs >512 μg/ml), suggesting their harmless effect on gut commensals. The remaining 11 extracts affected to some degree the growth of probiotic gut bacteria, particularly of bifidobacteria and *L. casei*. The single strain was inhibited by *P. siamensis* (*L. casei*) and leaf with flower bud of *M. dodecandrum* (*B. adolescentis*) at MICs of 256 and 512 μg/ml, respectively. Moreover, *P. javanica* inhibited *B. breve* (MIC = 128 μg/ml) and *L. casei* (MIC = 512 μg/ml). Although *A. polymorphum* significantly affected the growth of *B. adolescentis* (MIC = 64 μg/ml), the remaining probiotic strains were rather resistant toward this extract (MICs ≥512 μg/ml). Three and four probiotic bacteria were inhibited (MICs = 256–512 μg/ml) by *A. camansi* and *M. saigonense*, respectively. At MICs ranging from 128 to 512 μg/ml, *E. microphylla* and *I. nigricans* affected the growth of the majority of probiotic strains. Although half of the bacteria were not inhibited by *A. grandis*, this extract inhibited *B. breve* at low MIC (64 μg/ml). Finally, all six strains were inhibited by *A. blancoi* and *A. tectorius*. Whereas the former uniformly affected the growth at very low MICs (16 μg/ml), the latter inhibited *B. breve* (MIC = 64 μg/ml) only.

The outcomes of the MTT assay for all 16 antibacterially active plant extracts against non-cancer and cancer intestinal cells are presented in Table 3. With the exception of *D. esculentum* (IC_{50} values > 512 μg/ml), all the 16 extracts produced a certain antiproliferative effect on at least one of the tested cell lines (IC_{50} values = 33.8 ± 10.6–368 ± 30 μg/ml). Regarding the antiproliferative activities against cancer intestinal cells, the plants producing strong effects on Caco-2 (IC_{50} values = 33.8 ± 10.6–87.4 ± 19.2 μg/ml) have been ordered as follows: *A. tectorius*, *A. camansi*, *E. microphylla*, *M. dodecandrum* (leaves with flower buds), *A. grandis*, *A. blancoi*, and *M. saigonense*. With the exception of moderately cytotoxic *E. microphylla* and *M. dodecandrum* (leaves with flower buds), the same plant extracts with the addition of *B. malabarica*, *B. vitis-idaea*, *L. cochinchinensis*, and *P. siamensis* also produced strong antiproliferative effect on HT-29 (IC_{50} values = 35.2 ± 5.3–96.5 ± 12.4 μg/ml). A moderate cytotoxic effect on both these cancer cell lines was then shown by *A. polymorphum*, *I. nigricans*, *M. dodecandrum* (bark), and *P. javanica* (IC_{50} values = 121.3 ± 15.3–248.6 ± 23.1 μg/ml). The majority of extracts revealed higher activities against Caco-2 than that of 5-fluorouracil (IC_{50} = 181.8

± 151.5 μg/ml). Considering the toxicity to non-cancer intestinal cells (FHs 74 Int), *M. dodecandrum* and *P. siamensis* did not show inhibitory action at the concentrations tested (IC_{50} > 512 μg/ml) (Table 3). Moderate toxicity was shown by *A. polymorphum, A. grandis, A. blancoi, B. malabarica, E. microphylla, I. nigricans, L. cochinchinensis, M. dodecandrum* (leaves with flower buds), *M. saigonense*, and *P. javanica* at IC_{50} values ranging from 118.76 ± 36.04 to 368.07 ± 30.00 μg/ml. Finally, the extracts of *A. tectorius, A. camansi,* and *B. vitis-idaea* were shown to be cytotoxic (IC_{50} values = 45.5 ± 7.3, 68.2 ± 12.4 and 68.8 ± 8.9 μg/ml, respectively).

The calculated mean values for pathogenic/probiotic bacteria, cancer cells ($\bar{x}$-MIC, $\bar{x}$-IC_{50}, and $\bar{x}$-IC_{80}), and derived SIs are also presented in Table 3. Comparing the concentrations inhibiting 80% of growth for pathogenic bacteria and non-cancer intestinal cells, the antibacterially active extracts were shown to be relatively safe (SIa values = 0.02–0.2; IC_{80} values >512 μg/ml) except *A. camansi* (SIa = −0.49; IC_{80} = 264.6 ± 6.8 μg/ml). Selective antibacterial effect (SIb values = 0.1) with relative safety for probiotic strains was shown by *B. malabarica*, *B. vitis-idaea*, and *P. siamensis* (Table 3). However, none of the selective effects were as significant as in the case of ciprofloxacin (SIb = 1.2). Other extracts did not show any noticeable selectivity or were comparably more harmful to probiotic bacteria, especially *A. blancoi*, and *A. tectorius* (SIb values = −1.6 and −0.6, respectively). Regarding the selective antiproliferative effects against cancer intestinal cells, *A. blancoi, E. microphylla, L. cochinchinensis, M. dodecandrum* (bark), and *M. saigonense* revealed higher selectivity (SIc values = 0.5–0.7) than that of 5-fluorouracil (SIc = 0.4) (Table 3). Other extracts produced either the same or lower degree of selective effects than that of this cytotoxic drug, whereas *A. tectorius*, *B. malabarica*, and *B. vitis-idaea*. were relatively more toxic to non-cancer intestinal cells (SIc values = −0.9 to −0.1). The probiotic strains were not affected by the antiproliferative concentrations of *A. polymorphum* (SId = 0.13), mainly because of moderate inhibition of HT-29 (IC_{80} = 130.5 ± 12 μg/ml) (Table 3). Interestingly, the extract of *P. siamensis* produced noticeable selective actions combining antibacterial and antiproliferative effects on pathogenic bacteria and intestinal cancer cells without affecting probiotic bacteria and non-cancer intestinal cells.

To the best of our knowledge, this is the first study on antibacterial and antiproliferative activities of *A. polymorphum*, *B. vitis-idaea*, *I. nigricans*, *L. cochinchinensis*, *P. siamensis*, and *M. saigonense*. Moreover, there are no previous studies on the cytotoxic effects of *A. blancoi*. Although the cytotoxic effect of products isolated from *B. malabarica* was described previously (Kittakoop et al., 2000), its antibacterial activity is herein reported for the first time. Our results correspond with those of previous studies on antibacterial and antiproliferative activities of *A. grandis* (Bradacs et al., 2009), *D. esculentum* (Mackeen et al., 1997; Rahmat et al., 2003), and *P. javanica* (Khan et al., 2001; Win et al., 2015). The lack of any antibacterial activity found in case of 19 out of 35 tested extracts can be explained by different therapeutic properties of these medicinal plants, especially antidiarrheal mechanisms such as antimotility and antisecretory effects (Palombo 2006; Formiga et al. 2017). In the following paragraphs, seven plant extracts with promising biological activities, thus *A. blancoi*, *A. camansi*, *A. tectorius*, *P. siamensis*, *E. microphylla*, *L. cochinchinensis*, and *M. saigonense* are mainly discussed.

Two of the four tested species of the genus *Artocarpus*, namely, *A. blancoi* and *A. camansi*, exhibited strong antibacterial and antiproliferative activities in our study. *Artocarpus* spp. are rich in phenolic compounds, such as flavonoids, stilbenoids, and arylbenzofurans, which are known to possess a wide range of biological activities, including antibacterial and anticancer effects (Hafid et al., 2017). Our study is the first to report on anticlostridial activities of *Artocarpus* spp. As flavonoids have been reported to have potent *in vitro* inhibitory effect on some clostridia (Wu et al., 2013), these compounds might be responsible for significant antibacterial activities revealed by *A. blancoi* and *A. camansi* against *C. difficile* and *C. perfringens*. Beloy et al. (1976) isolated the flavonoid 5,7,4′-trihydroxyflavanone-3-O-α-L-rhamnopyranoside from the bark extract of *A. blancoi* showing antibacterial activity against *Mycobacterium tuberculosis*. Ante et al. (2016) showed that bark essential oil of *A. camansi* produced antibacterial activity against some diarrheagenic bacteria. Our results show that both of these plants inhibited gram-positive bacteria only. Beside their anticlostridial effect, this selectivity probably also contributed to their relative toxicity to probiotic bacteria. *In vitro* inhibitory effect against lactobacilli was previously reported for *Artocarpus lacucha* (Teanpaisan et al., 2014). An example of a compound isolated from the plant of this genus and showing similar activities is artocarpin. In the study by Sato et al. (1996), this flavonoid exhibited

strong inhibition of all gram-positive bacteria, including *L. casei*, whereas in another study, it produced higher MICs against *E. coli* and *Pseudomonas aeruginosa* (Septama and Panichayupakaranant, 2015). The absence of antibacterial action of *A. odoratissimus* found herein will correlate with rather low levels of phenolic content detected in its fruit methanolic extract (Abu Bakar et al., 2015), compared to antibacterially active species (Jalal et al., 2015). Although hexane bark extract of *A. elasticus* exhibited activity against *B. cereus* and *E. coli* in the study by Ramli et al. (2016), its lack of activity in the present study could be influenced by the use of different extraction procedures. According to our results, *A. blancoi* and *A. camansi* had a selective cytotoxic effect on intestinal cancer cells, whereas the former did not show cytotoxicity to non-cancer cells at the inhibitory concentrations against several pathogens. Various terpenoids and phytosterols were previously isolated from methanolic and dichloromethane extract of stem and leaves of *A. camansi*, respectively. Among them, friedelinol, cycloartenol, and cycloartenol acetate inhibited the growth of HT-29 cells; squalene has profound chemopreventive activity against colon carcinogenesis; and *ß*-sitosterol has been shown to induce apoptosis in human colon tumours (Tsai et al., 2013). Regarding cytotoxic compounds isolated from other *Artocarpus* spp., the prenylated flavone artelastin revealed strong *in vitro* activity against five colon cancer cell lines (COLO 205, HCT 116, HCT 15, HT-29, and SW 620) in the study by Pedro et al. (2005).

Similar to *Artocarpus* spp., the leaf extract of *A. tectorius* exhibited growth-inhibitory effects only against gram-positive bacteria. This corresponds with the study by Wiart et al. (2004), where its methanolic leaf extract produced antibacterial activity against *B. cereus* but not *E. coli*. We also found that the overall cytotoxic effect of this plant was strong. Although the antiproliferative effect on cancer cells was not selective, the extract concentrations inhibiting the pathogens were generally nontoxic to non-cancer intestinal cells. Previous phytochemical analysis of leaf ethanolic/methanolic extracts of this plant showed the presence of various naphthylisoquinoline alkaloids, such as 7-epiancistrobrevine D, ancistrocladinine, ancistrotectoquinone A-B, ancistrotectoriline A–C, and hamatinine (Anh et al., 1997; Tang et al., 2000; Tang et al., 2010; Bringmann et al., 2016). Since these isoquinoline alkaloids are known to possess various biological activities, including antimicrobial and cytotoxic effects, we suspect them to be responsible for the growth-inhibitory effects revealed by *A. tectorius* in the present study. For example, in the study by Mihalyi et al. (2014), michellamine B isolated from

Ancistrocladus korupensis inhibited *B. subtilis*. Jiang et al. (2013) showed that naphthylisoquinolines isolated from *A. tectorius* exhibited cytotoxic effect against three leukemia cells *in vitro*. In another study, 7-epiancistrobrevine and ancistrotectoriline exhibited activity against pancreatic cancer cells (Shang et al., 2020). The present study is the first to report on *in vitro* selective antiproliferative activity of *A. tectorius* against intestinal cells.

Regarding *P. siamensis*, there are no comparable studies dealing with species of the same genus. However, our results showing a noticeable combination of selective antibacterial and cytotoxic effects of its bark extract can be compared to the data available for closely related genus *Shorea*. For example, Marandi et al. (2016) showed that bark ethanolic extract from Indian antidiarrheal and antidysenteric medicinal plant *Shorea robusta* exhibited inhibitory action against *B. cereus*, *B. subtilis*, *E. faecalis*, *E. coli*, *S.* Typhi, and *V. cholerae*. Stilbene derivatives isolated from barks of *Shorea* spp. previously showed strong antibacterial effects against some of these strains (Nitta et al., 2002; Sudto et al., 2019). Some polyphenols, such as stilbenes, can inhibit several nonbeneficial bacteria from the human microbiota, with no noticeable effects on the growth of probiotic bacteria (Requena et al., 2010). Therefore, we suggest that some of these agents could also contribute to the selective antibacterial activities of *P. siamensis* shown in the present study. Regarding cytotoxic effect, oligostilbenoids were usually the constituents derived from *Shorea* spp., with reported antiproliferative action against various cancer cell lines (Rohaiza, 2011; Zawawi et al., 2012; Moriyama et al., 2016). Among them, ampelopsin E exhibited obvious antiproliferative properties on COLO205 and HT-29 cells (Tian et al., 2019), whereas *α*-viniferin showed selective inhibition of colon cancer cells (HCT-116, HT-29, and Caco-2) with twofold lower IC_{50} compared to non-cancer colon cells (CCD-18Co) (Gonzalez-Sarrias et al., 2011). To identify phytochemicals responsible for the *in vitro* selective inhibitory actions shown by *P. siamensis* in the present study, an accurate chemical analysis of this plant is needed.

Finally, *E. microphylla*, *L. cochinchinensis*, and *M. saigonense* revealed a strong selective antiproliferative effect against intestinal cancer lines. It has been reported that triterpenes urs-12-en-24-oic acid, 3-oxo-, methyl ester, and *ß*-amyrin are involved in anticancer activities of products derived from leaves of *E. microphylla* (Rajkumar et al., 2019). Our study corresponds with other studies dealing with these chemicals. For

example, in the study by Kuete et al. (2018), *ß*-amyrin produced a selective cytotoxic effect against Caco-2 compared to that on non-cancer cell line HEK293. In another study, extract of *Alstonia macrophylla* containing *ß*-amyrin produced a selective cytotoxic effect against HT-29 compared to that on non-cancer cell line HDFn (Tan et al., 2019). The present study is the first to report the antiproliferative activities of *E. microphylla* against intestinal cell lines. Compounds such as triterpenes, tannins, ellagic acids, glycosides, and flavones were previously attributed to bioactive properties of *Lagerstroemia* spp. (Chan et al., 2014). In previous studies, triterpenes isolated from species of this genus produced significant *in vitro* activity against colon cancer cells, for instance, betulinic acid and 3*β*-acetoxyolean-12-en-28-acid against HCT15 (Woo et al., 2016) and corosolic acid against HCT116 (Sung et al., 2014). Regarding *M. saigonense* (Kuntze) Merr., there are various previously published studies on related species showing corresponding results. For example, the methanolic leaf extract of *Melastoma malabathricum* L. produced an antiproliferative effect on HT-29 in the study by Kamsani et al. (2019). Asiatic acid, caffeic acid, *p*-coumaric acid, kaempferol, quercetin, rutin, and ursolic acid were isolated compounds with previously profound antiproliferative action to this cell line. In the study by Karakurt et al. (2020), *p*-coumaric acid exhibited selective inhibition of Caco-2 and HT-29 cells compared to that of healthy colon epithelial cells (CCD-18Co). Since the decoction from the leaves of *M. malabathricum* L. is also traditionally consumed to treat diarrhea, we suggest a similar composition of bioactive compounds to be present in *M. saigonense* (Kuntze) Merr. (Ong and Nordiana, 1999). Regarding the moderate selective antiproliferative activities of bark and leaf with flower bud extracts of *M. dodecandrum*, three pentacyclic triterpenoids (ursolic acid, asiatic acid, and terminolic acid) and one tannin (casuarinin) were previously isolated from this plant and found to significantly decrease interleukin-8 production in HT-29 (Yang et al., 2014).

In summary, *A. blancoi*, *A. tectorius*, and *P. siamensis* produced significant growth-inhibitory effects against diarrheagenic bacterial pathogens at concentrations nontoxic to non-cancer intestinal cells. Except the strong anticlostridial actions of *A. blancoi*, the MICs determined for these plant extracts in the present study reflect rather moderate antibacterial activities. However, the discrimination of specific cell toxicity indicates that higher amounts of these products necessary to acquire the appropriate efficiency may still be safe to use (Cos et al., 2006). A long tradition of their use in folk medicinal systems supports this assumption. Moreover, it has been reported that

microorganisms are less likely to develop resistance to phytochemicals with anti-infective potential, mainly because of their high diversity in plants. Some were even considered as antibiotic resistance modifying compounds (Sibanda and Okoh, 2007). Additionally, our study showed that the extract of *P. siamensis* was relatively safe for probiotic bacteria, and together with *A. blancoi*, they exerted selective anticancer activities *in vitro*. Similar to the cytotoxic activities revealed by *E. microphylla*, *L. cochinchinensis*, and *M. saigonense*, the inhibitory effect of *A. blancoi* on cancer cell line Caco-2 and the selectivity of its overall antiproliferative actions were generally higher than those of anticancer drug 5-fluorouracil.

These results suggest that extracts from the above-mentioned Cambodian and Philippine plant species are promising materials for further research focused on the development of new plant-derived selective antibacterial and antiproliferative agents used in the treatment of infectious diarrhoea and associated intestinal cancer diseases. For instance, the combination of strong anticlostridial and anticancer actions of *A. blancoi* may in the future be utilized in the treatment of digestive cancers associated with *C. difficile* infections (Han et al., 2013). However, further phytochemical and pharmacological research is needed for the isolation and proper identification of their bioactive constituents. Referring to studies dealing with taxonomically related plants to estimate the presence of their bioactive principles is a very limited approach as their composition can vary greatly. On the other hand, our results could serve as an indicator of bioactive potentials of products derived from species of the same taxa. This is mainly the case of *P. siamensis* that exhibited selective inhibition of pathogenic bacteria and intestinal cancer cells without affecting probiotic bacteria and non-cancer intestinal cells. Future research combining the ethnomedicinal and chemotaxonomic approaches might help to identify more plants with promising bioactivities (Hao and Xiao, 2020).

7.3 The relationship between chemical structure of (iso)quinoline alkaloids and their effects on human intestinal bacteria and cells

Results of previously described experiments performed with phytochemicals, synthetic phytochemical analogues, and antibiotics indicated that particularly compounds containing quinoline or isoquinoline scaffold as part of their structure, such as chloroxine, 8-hydroxyquinoline, nitroxoline, and sanguinarine and antidiarrheal antibiotic

ciprofloxacin, possess promising bioactive properties in terms of *in vitro* selective antibacterial and anticancer activities against intestinal agents. Also information gained from analysis of phytochemical literature on one antibacterial and anticancer Cambodian plant (i.e., naphthylisoquinolines in *A. tectorius*) indicated that these plant compounds are important for such *in vitro* effects. Due to that, (iso)quinoline alkaloids were identified as the class of plant compounds to be subjected to broader literature review analysis.

As a result of this analysis, 258 plant (iso)quinolines were found to be previously tested for *in vitro* activities against intestinal diarrheagenic/probiotic bacteria and/or cancer/non-cancer cells. All data related to this literature review analysis including the list of references can be found in Appendix 1. Specifically, biological activities expressed by inhibitory concentrations of plant (iso)quinolines against intestinal bacteria and cells are presented in Appendix 1-Table 2. The complete list of plant species containing these chemicals, and ethnobotanical profile of the most significant ones can be found in the respective Appendix 1-Tables 1 and 3. Finally, chemical structures of all (iso)quinoline alkaloids included are presented in Appendix 1-Figures 1-6.

The *in vitro* antimicrobial activities against bacterial agents able to cause infection of human gastrointestinal tract and diarrhoea have been reported for 146 quinoline and isoquinoline alkaloids, especially belonging to structural subclasses furoquinolines, benzophenanthridines, quinolones, aporphines, protoberberines and Amaryllidaceae alkaloids (Appendix 1-Table 2). In total, these reports encompass 26 bacterial species dominated by *Enterococcus faecalis*, *Escherichia coli*, and *Staphylococcus aureus*. According to the available studies, 17 alkaloids were able to produce strong *in vitro* antibacterial actions with minimum inhibitory concentrations (MICs) ranging from 0.49 to 8 μg/ml, especially benzophenanthridines (**145**, **146**, **157**, **163**, **165**, and **167**) and indolo(iso)quinolines (**71**, **76**, **253**, and **254**). Such a low concentration-based effects appeared in about 11-25% of cases the compounds from these two structural classes were tested. Various strains of *E. coli* and *S. aureus* were the most susceptible and frequently reported bacteria followed by *Bacillus cereus*, *E. faecalis*, *Enterococcus faecium*, *Helicobacter pylori*, *Listeria monocytogenes*, *Plesiomonas shigelloides*, and *Shigella dysenteriae*. Aporphines (**202** and **205**), furoquinolines (**6** and **22**), protoberberines (**119**), and simple quinolines (**1**) and benzylisoquinolines (**88**) were the remaining structural groups involved in these strong *in vitro* actions. However, those were rather exceptional

if compared to the overall data on their antipathogenic actions. With the respective six and five diarrheagenic species, 8-hydroxyquinoline (**1**) and cryptolepine (**71**) showed such a low MICs (1–6.25 μg/ml) against the highest number of bacteria. Next, 53 alkaloids, mainly furoquinolines (14), benzophenanthridines (9), indoloquinolines, and protoberberines (5 for each), were reported to produce moderate antimicrobial actions against various numbers of 24 diarrheagenic bacterial species (MICs = 9.3–128 μg/ml). Such moderate antibacterial actions prevailed in overall reports on bisbenzylisoquinolines (60%), simple quinolines, (45%), and indolo(iso)quinolines (40%). From the point of view of number of diarrheagenic species moderately susceptible to (iso)quinoline agents, the highest numbers of moderately susceptible diarrheagenic species (8–11) were reported for **1**, **71,** cocsoline (**104**), and sanguinarine (**163**). Then, 41 alkaloids quantitatively dominated by furoquinolines and protoberberines (8 for each) were claimed to have antibacterial effect on the bases of using some non-quantitative methods. Finally, a weak or no antimicrobial effect (MICs >128 μg/ml) was observed in the case of 97 alkaloids dominated by furoquinolines (25). This also includes those compounds that have not proven any antibacterial effect in non-quantitative *in vitro* assays. Interestingly, berberine (**120**) failed to produce significant inhibitory activity against most of 16 bacterial species tested. It is important to note that such insignificant *in vitro* effects statistically prevailed in majority of the structural classes, especially protoberberines, phthalide isoquinolines (85% for each), Amaryllidaceae alkaloids of phenanthridine structure (80%), quinolones, simple benzylisoquinolines (80% for each), aporphines, furoquinolines (70% for each), and benzophenanthridines (60%). To also summarize the overall susceptibility profile for individual diarrheagenic bacteria to the reported (iso)quinolines, among those most frequently used, the strains of *E. coli*, *Salmonella* spp., and *S. aureus* were resistant or weakly susceptible in the majority of cases, whereas *B. cereus*, clostridia, enterococci, *Shigella* and *Vibrio* spp. were mostly found moderately to weakly resistant.

Narrowing the focus on toxicities of quinoline and isoquinoline alkaloids to some of the human intestinal bacteria with probiotic function, only 14 compounds have been tested against at least one. As seen in Table 2 of Appendix 1, they involved 4 protoberberines (**118-120**, and **122**), 3 simple quinolines (**1**, **3**, and **4**), 3 bisbenzylisoquinolines (**93**, **114**, **115**), 2 benzophenanthridines (**157** and **163**), and one indoloquinoline (**71**) and simple benzylisoquinoline (**88**). The following are bacterial

species that appeared in these reports: *Bacillus subtilis*, *Bifidobacterium adolescentis*, *Bifidobacterium animalis* spp. *lactis*, *Bifidobacterium animalis* subsp. *animalis*, *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium gallinarum*, *Bifidobacterium longum ssp. longum*, *Lacticaseibacillus casei*, *Lactobacillus fermentum*, *Lactobacillus reuteri*, and *Lacticaseibacillus rhamnosus*. The absence of toxicity to some of these bacteria either based on concentration dependency or non-quantitatively was reported in the cases of **1**, **3**, **4**, **119**, and **120** (Appendix 1-Table 2). In the context of overall toxicities to probiotic bacteria reported for the compounds of the two alkaloid groups involved, it accounts for about 50 and 30% of cases for simple quinolines and protoberberines, respectively. However, only **120**, **1** and **119** were tested against at least six strains. Whereas the available data on **1** and **119** indicate these compounds are either nontoxic or just moderately toxic to bifidobacteria and lactobacilli (MICs = 31.25–1024 μg/ml), **120** tends to initiate toxicity at moderately high MICs (MICs = 31.25–128 μg/ml) in nearly all the cases. Although no toxicity was claimed for **3** and **4**, the studies consider only two strains of probiotic bacteria and they are not supported by any quantitative methods defining concentration based toxicity. The studies on the other compounds that were tested against at least two bacteria, thus **122**, jatrorrhizine (**118**), and **163**, were presented as moderately to weakly toxic (MICs = 31.25–1,000 μg/ml) to the probiotic strains used. The remaining six alkaloids were only tested against *B. subtilis* towards which they showed strong to moderate toxicity (MICs = 3.2–20 μg/ml).

The antiproliferative or cytotoxic actions towards intestinal cancer cells have been tested *in vitro* and reported in the cases of 163 quinoline and isoquinoline alkaloids, especially aporphines, bisbenzylisoquinolines, benzophenanthridines, furoquinolines, and Amaryllidaceae alkaloids of phenanthridine structure (Appendix 1-Table 2). Overall, these reports encompass 18 cancer cell lines of colorectal carcinoma including one line of lung metastasis. Additionally, two gastric, and one pancreatic cancer lines have been involved. The most frequently appearing cells were HT-29 and HCT116 followed by HCT15, Caco-2, SW480, LOVO, HCT8, and DLD-1. According to these reports, 36 alkaloids from twelve different structural groups were able to produce strong effects with 50% cytotoxic concentrations (IC_{50}/ED_{50}) ranging from 0.000263 to 2 μg/ml, especially benzophenanthridines (**90**, **91**, **116**, **120**, **139**, **149**, **154**, **158**, **159**, **161-164**, **167**, **172**), furoquinolines (**7**, **15**, **22**, **28**, **38**, **46**), and Amaryllidaceae alkaloids of phenanthridine

structure (**216**, **223**, **226**, **227**). Out of all the reports on benzophenanthridines, such strong activities account for about 40% of cases. It is important to note that the most significant anticancer actions (IC_{50} values ≤0.01 μg/ml) involving five different cell lines (HCT116, HT-29, LS174T, SW620, and T84) were produced by neothalfine (**116**) and **76**, thus representatives of the respective bisbenzylisoquinolines and indoloquinolines. However, in nearly 90% of cases the former structural group produced rather moderate to weak activities (IC_{50} values 2.19–330 μg/ml). Although this is not the case of indoloquinolines, the amount of data is too limited to analyse properly. Considering the reports on moderate cytotoxic activities, 96 compounds dominated by benzophenanthridines, bisbenzylisoquinolines, Amaryllidaceae alkaloids of phenanthridine structure, and furoquinolines were presented accordingly (IC_{50}/ED_{50}/GI_{50} values = 2.1–72.6 μg/ml). Also, the majority of studies dealing with alkaloids of these four groups characterized them as moderately cytotoxic. Next, 40 compounds dominated by aporphines were claimed to have a cytotoxic potential against some intestinal cancer cells based on other non-quantitative methods. No or weak effects were observed while testing 17 alkaloids from five structural (iso)quinoline groups, namely aporphines, simple benzylisoquinolines, protoberberines, furoquinolines bisbenzylisoquinolines, simple (iso)quinolines, and phthalide isoquinolines. The overall susceptibility of the most commonly used cell lines was particularly shown as moderate. Within them, HCT8, HT-29, and DLD-1 appeared as the most susceptible, whereas HCT15 as the most resistant.

Only 18 (iso)quinoline alkaloids were tested for their toxicities to some non-cancer intestinal cells *in vitro* (Appendix 1-Table 2). Majority of these alkaloids were Amaryllidaceae alkaloids of phenanthridine structure (**212-214**, **216**, **218**, **221**, **223**, **226-228**, **230**, **232**, **234**, **236**) that were tested against FHs 74 Int. This line was also used for the toxicity assessment of **1** and **163**. The remaining two protoberberine compounds (**120**, **122**) were tested for their cytotoxic actions towards the respective NCM460 and IEC-6 non-cancer lines. The safety to FHs 74 Int was proven for compounds **232**, **214**, crinine (**221**), and galanthine (**213**) (IC_{50} >27 μg/ml), whereas **120** and **122** were not toxic NCM460 (IC_{50} >67.28 μg/ml) and IEC-6 (IC_{50} >3.2 μg/ml), respectively. Remaining Amaryllidaceae alkaloids and compounds **1**, **120**, and **163** showed strong to moderate toxicities to FHs 74 Int (IC_{50} values = 1–29.7 μg/ml). Generally, the amount of data is too limited to hypothesize which type of (iso)quinoline alkaloids is least toxic to intestinal

non-cancer cells. The differences between toxic actions of **120** also showed that susceptibilities between two different non-cancer cell lines can be significant.

Sixty-six alkaloids were tested for their *in vitro* inhibitory actions against more than one type of bacterial or cellular intestinal agent (Appendix 1-Table 2). Obviously, vast majority of these compounds (50) were tested for antimicrobial and cytotoxic effects against the respective diarrheagenic bacteria and intestinal cancer cells. In that case, strong activities against some agents of both types were reported for **1**, **22**, **76**, **163**, and **167**. Additionally, similar combination of strong to moderate effects were observed in the cases of **15**, **104**, **119**, **120**, **139**, **146**, **154**, and **164**. These data support the suggestion that particularly benzophenanthridine, furoquinoline, and protoberberine alkaloids are potent in terms of producing combined bioactive actions towards diarrheagenic bacteria and intestinal cancer cells *in vitro*. In average, this was proved in about 35% of cases when the compounds from the three structural groups were tested against both such types of agents. Then, there is just a limited number of (iso)quinoline alkaloids involved in the studies on their toxicities to intestinal non-cancer cells. In that manner, no concentration dependent toxicity to at least one line was reported for six compounds (**120**, **122**, **213**, **214**, **221**, **232**). Referring to their anticancer effects, the cytotoxic concentrations of **214** and **221** were nontoxic to non-cancer line FHs 74 Int line (SI values $\geq$ 0.24), and those of **120** were nontoxic to non-cancer line NCM460 (SI = 0.77). Regarding **120**, however, there is no anticancer selective effect if referring to the reported toxicity to FHs 74 Int (SI = -1.06). Although **1**, **216**, and **223** were moderately toxic to FHs 74 Int, the concentrations at which they were active against the cancer lines were still comparably lower (respective SI values = 0.87, 1.32, and 0.52). Next, comparing the toxicities to non-cancer intestinal cells with *in vitro* antibacterial actions, none of the alkaloids involved in both kinds of tests showed any notable selectivity. Only 30% of diarrheagenic bacteria were relatively more susceptible comparing to FHs 74 Int line in the case of the compound **1**, whereas only 11% of these bacteria were proved to be more susceptible than NCM460 in the case of **120**. The concentration dependent toxicity of **122** to non-cancer line IEC-6 was not proven but neither was there any notable activity observed against the diarrheagenic bacteria. Moreover, the highest nontoxic concentration to IEC-6 reported for this compound was very low. Finally, few (iso)quinoline alkaloids were also involved in studies bringing additional information on their toxicities to probiotic bacteria, particularly protoberberines and simple quinolines. In that manner, compound **1** is the

only compound supported by enough of data showing selectivity of its both *in vitro* antibacterial and cytotoxic actions (respective SI values = 0.60 and > 2.5). Then, studies dealing with quinaldic acid (**3**) and quinoline-4-carboxaldehyde (**4**) claimed their anticlostridial effects as selective and relatively harmless to some bifidobacteria and lactobacilli. The data on **163** and **120** indicate that these probiotic bacteria might be relatively resistant at most of their anticancer concentrations (respective SI values = 1.76 and > 1). However, relatively higher inhibitory concentrations against diarrheagenic bacteria prevailing in case of these two chemicals as well as in the case of **122** (SI values < -0.47) suggests that protoberberines are generally not potent selective antimicrobials to these intestinal bacterial agents. Only **119** was found to be relatively nontoxic to probiotic strains if considering its antimicrobial concentrations against about half of the diarrheagenic strains.

The results of quantitative structure-property relationship analysis with identified functional groups of the most effective compounds are displayed in Figure 5. For reference, chemical structures of all (iso)quinoline alkaloids are presented in Appendix 1-Figures 1-6. In this study, 2D structural configuration of the compounds is particularly discussed, however it should be taken into account that each substituent modifies the shape and particular charges of the molecule in the 3D structure, thus the effects of structurally similar compounds to bacteria and cells can differ due to that. The future application of three-dimensional quantitative structure–activity relationships model could unveil some crucial differences between such compounds (Verma et al. 2010).

Generally, benzophenanthridine alkaloids were able to produce strong actions against diarrheagenic bacteria more frequently than other structural classes (Appendix 1-Table 2). However, their efficacy varied greatly depending on the chemical structure of particular agents (Figure 5). Generally, compounds with methyl group bonded to the nitrogen atom of the benzophenanthridine ring tend to produce more significant activities. For example, the inhibitory concentrations against *E. coli* and *S. aureus* are lower in case of 6-methoxydihydrosanguinarine (**167**) (respective MICs = 20 and 2.5 μg/ml) than in case of pancorine (**142**) (respective MICs = 410 and 440 μg/ml) (Xue et al 2017; Hu et al 2014). Similarly, angoline (**157**) produces better activities against *S. aureus* (MIC = 25–33 μg/ml) if compared to 8-methoxynorchelerythrine (**137**) (MIC = 420 μg/ml) (Yu et al. 2014; Hu et al 2014). However, this substitution does not seem to make any difference

between the antibacterial activities of 2,3,13-trimethoxy-[1,3]benzodioxolo[5,6-c]phenanthridine (**141**) and 8-methoxynitidine (**147**) (Hu et al 2014). Next, the substitution of 7, 8 and 9-positions appears to be important. For example, avicine (**145**), a benzophenanthridine most active against *E. coli* (MIC = 1.5 μg/ml), has substituted 8,9-positions by methylenedioxy group. In comparison, nitidine (**144**), which exhibited significantly weaker effect on this bacterium (MIC >100 μg/ml), is structurally same but having the methoxyl groups at 8 and 9-positions instead (Tavares et al., 2014). The substitutions of 7,8-positions by methylenedioxy group seems to be also slightly better than by the two methoxyl groups. This can be observed if we compare the anti-staphylococcal activities of compounds **165**, **167**, **163**, and **164** (MICs = 0.49–100 μg/ml) with the respective **156, 157, 146,** and **154** (MICs = 0.98–320 μg/ml) (Appendix 1-Table 2). Another structural variation that seems to have influence on antibacterial activities take place at the 6-position. For example, comparing susceptibilities of *E. faecium* and *E. coli* to **167** (respective MICs = 5 and 20 μg/ml) with oxysanguinarine (**152**) (respective MICs = 640 and 320–1,200 μg/ml) and dihydrosanguinarine (**164**) (MICs = 80 and 100–320 μg/ml) suggests that methoxyl group at the 6-position correlates with improved activity against these strains (Xue et al. 2017). In case of chelerythrine (**146**) and **144**, on the other hand, this methoxyl groups seems to rather decline the activity if we compare their antistaphylococcal effects (MICs = 1.5–31.3 μg/ml) with 8-methoxynitidine (**147**) and 8-methoxychelerythrine (**148**) (MICs = 410-470 μg/ml) (Kelley et al. 2012; Tavares et al., 2014; Hu et al 2014). Similarly, ketone group at the 6-position generally impedes the antibacterial effects as seen in the cases of oxynitidine (**151**) and **152**. Regarding the activities against *S. aureus*, the substitution of this position by hydroxyl group appears to be more convenient. This is obvious if we compare activities produced by 8-hydroxydihydrosanguinarine (**165**) and 8-hydroxydihydrochelerythrine (**156**) (respective MICs = 0.49 and 0.98 μg/ml) with the remaining alkaloids (Zielinska et al. 2018), especially structurally close dihydrochelerythrine (**154**) and **164** (respective MICs = 18.7– 320 and 9.3–100 μg/ml) (Xue et al. 2017; Zielinska et al. 2018). The differences between activities of **146** and **154** produced against *E. faecalis* (respective MICs = 4–32 and 18.7 μg/ml), *E. coli* (respective MICs = 16–125 and 25–640 μg/ml), and *S. aureus* (respective MICs = 1.5–31.3 and 18.7–320 μg/ml) also indicate that the compound increases its activity in the form of quaternary salt (Wang et al. 2021; Navarro and Delgado 1999).

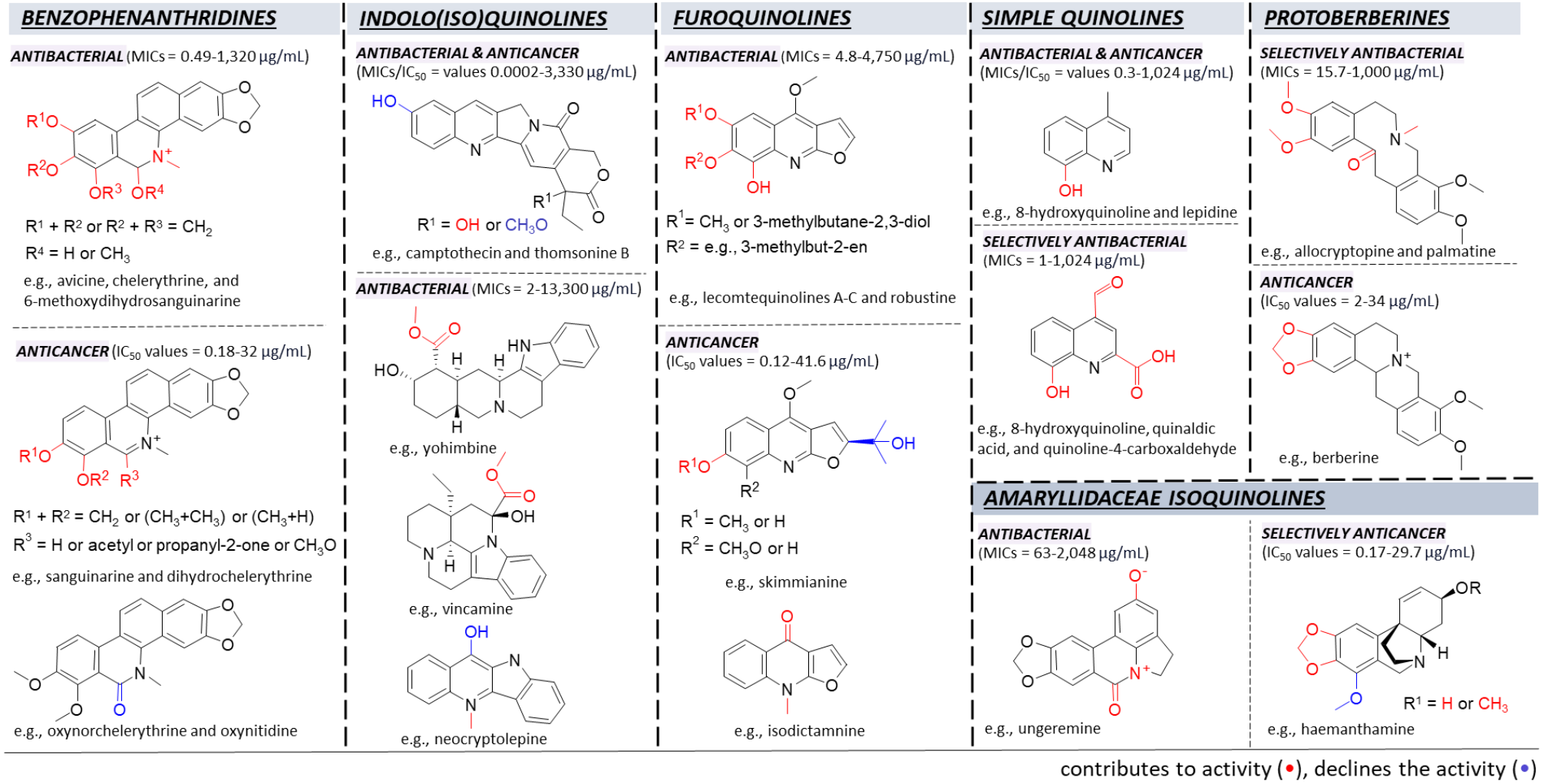


Figure 5 Structure-activity relationship of (iso)quinoline alkaloids on intestinal bacteria and cells *in vitro*

Referring to the antiproliferative activities against intestinal cancer cells, benzophenanthridine alkaloids were shown as strongly active in about 40% of the reported cases (Appendix 1-Table 2). Significant variations in cytotoxicity produced by these compounds to identical cancer lines suggest crucial role of certain differences in their structures (Figure 5). For example, differences in the effects of benzophenanthridines tested against HCT8, HCT116, and SW480 cell lines indicate that those having 7,8-positions substituted by methylenedioxy group (e.g., **163** and **167**) tend to produce slightly stronger cytotoxic effects (IC_{50} values = 0.18–0.84 μg/ml) (Slaninova et al. 2014; Yu 2014), especially in comparison with some of those differing in the substitutions of these positions only (**146** and **154**) (IC_{50} values = 0.48–2.5 μg/ml) (Slaninova et al. 2014; Lin et al. 2018). However, it does not seem to be applicable in the case of HCT15 against which the strongest compound was fagaridine (**149**) (ED_{50} = 0.41 μg/ml) (Cho et al. 1996). Then, it appears that the differences in activities of benzophenanthridines are notably influenced by the substitutions at the 6-position. Dihydrosanguinarine (**164**) and dihydrochelerythrine (**154**), thus compounds that have not substituted this position by any additional groups, produced strong cytotoxic effect on HCT8 (respective IC_{50} values = 0.43 and 0.48 μg/ml). While methoxyl group, only seen in the case of 6-methoxydihydrosanguinarine (**167**), seems to be the only option that contributes to such activity (IC_{50} = 0.18 μg/ml), other substitutions tend to rather lower this effect (**158**, **161**, **162**, **172**) (IC_{50} values = 0.69–1.14 μg/ml) (Lin et al. 2018). This is mainly characteristic for some more complicated ring moieties. Similarly, the alkaloids bearing substitutions of this position by groups like ketone produced worse cytotoxic actions. For example, oxynorchelerythrine (**150**) produced weaker actions against HCT116 (IC_{50} values = 6.46 μg/ml) comparing **146** (IC_{50} = 2.5 μg/ml) (Zdarilova et al. 2006; Wei et al. 2019), whereas 6-oxocorynoline (**153**) and **151** produced weaker actions against HCT15 (respective ED_{50}/IC_{50} values = 2.26 and 14.2 μg/ml) than corynoline (**168**) and **147** (respective ED_{50}/ IC_{50} values = 32.76 and 6.3 μg/ml) (Hu et al. 2014; Choi et al. 2007). Some correlation with slightly improved activities against HCT116 and HCT15 could be only observed in the C6 substitutions by propanyl-2-one (**159**) and acetyl (**139**) groups, respectively (Mansoor et al. 2013; Hu et al. 2014).

The studies showed that more than a half of tested quinolines and isoquinolines bearing fused indole ring as part of their structure produced strong to moderate *in vitro* effects against diarrheagenic bacteria (Appendix 1-Table 2). As seen in the cases of

yohimbine (**253**) and vincamine (**254**) (Figure 5), structural configurations of these indolo(iso)quinolines with carboxylic acid methyl ester bonded to the main ring seems to have a contributing role in the activities exerted against *E. faecalis* (MICs = 2 μg/ml), *E. coli* (respective MICs = 4–250 and 8 μg/ml), and *S. aureus* (MICs = 2–64 μg/ml) (Ozçelik et al. 2011). Then, significantly different susceptibilities of *E. coli* and *S. aureus* to the structurally related **76** (MIC = 16.67 and 4.16 μg/ml) and thomsonine B (**77**) (MIC = 3,330 and 13,330 μg/ml) indicate that either the presence of hydroxyl group instead of methoxyl group at 18-position and/or absence of hydroxyl group at 10-position is important for their *in vitro* effects on these bacteria (Gompe et al. 2018). Similarly, the substitution of cryptolepine (**71**) by the hydroxyl group at the 11-position, as seen in the case of hydroxycryptolepine (**72**), seems to negatively influence the activities against the following bacteria: *E. faecalis* (respective MICs = 12.5 and >100 μg/ml), *E. coli* (respective MICs = 5–80 and >100 μg/ml), *S. aureus* (respective MICs = ≤12.5 and >100 μg/ml), *S. dysenteriae* (respective MICs = 6.25 and >100 μg/ml), and *V. cholerae* (respective MICs = ≤50 and >100 μg/ml) (Appendix 1-Table 2). Then, unlike **71**, structurally similar quindoline (**70**) did not show any activity (MICs >100 μg/ml) (Lavrado et al. 2010). Therefore, methyl group bonded to the nitrogen atom of **71** could play a role in these differences. The data also showed that changes in the structural configuration of **71** to neocryptolepine (**73**) or the creation of bonds with other indoloquinoline ring units (**74** or **75**) correlate with the decrease of antibacterial activities against *B. cereus*, *E. coli*, enterococci, *S. aureus*, *S.* Typhimurium, *S. dysenteriae*, and *V. cholerae* (Lavrado et al. 2010; Cimanga et al. 1998). Although most significant anticancer actions (IC_{50} values ≤0.01 μg/ml) involving five different cell lines (HCT116, HT-29, LS174T, SW620, and T84) were produced by indoloquinoline camptothecin (**76**), the amount of data is too limited to properly analyse structure-activity relationship in terms of antiproliferative actions (Appendix 1-Table 2).

Furoquinoline alkaloids were able to produce strong to moderate actions in about 30 % of cases when they were tested against diarrheagenic bacteria (Appendix 1-Table 2). The simple furoquinoline ring observed in the case of dictamnine (**5**) can produce moderate effect on *E. coli* (MICs ≥100 μg/ml). Regarding that most active compounds against this bacterium were 7-(3-anilino-2-hydroxyprenyloxy)-8-methoxydictamine (**35**) and lecomtequinolines A-C (**19-21**) (MICs = 15.3–18.7 μg/ml), certain ether moieties at the 7-position could be one of the substitutions considerably increasing this *in vitro* effect

(Kouam et al. 2017; Kouam et al. 2019). However, this was not the case of melineurine (**11**) that did not show any activity in the same range of concentrations (MIC >32 μg/ml) (Robertson et al. 2021). Comparing the activities of **5** (respective MICs on enterococci, *E. coli* and *S. aureus* = 25, ≥100, and ≥86 μg/ml) with other furoquinolines such as **21** (MIC on *E. coli* = 15.7 μg/ml) and robustine (**6**) (respective MICs on *E. faecalis* and *S. aureus* = 5.37 and ≥92 μg/ml), suggests that substitution of 8-position by hydroxyl group correlates with the improvement of antibacterial potential against these bacteria (Zhao et al. 2018; Kouam et al. 2017). Finally, oxygen containing groups at both 6 and 7-positions seem to be convenient for the activities of furoquinoline alkaloids against *S.* Typhi (Kuete et al. 2008). Regarding the *in vitro* cytotoxic effect of furoquinolines, these alkaloids produced strong *in vitro* effect on intestinal cancer lines in about 20% of cases, especially on HT-29 (Appendix 1-Table 2). It seems that the substitution of furoquinoline ring's 7-position by the methoxyl group tends to contribute to the effect on this cell line (Figure 5). For example, skimmianine (**15**) was reportedly strongly active against HT-29 (IC_{50} = 0.38 μg/ml; ED_{50} = 0.12 μg/ml) (Rasamison et al. 2016; Chen et al. 2003), whereas γ-fagarine (**8**), that only differs in not having this group, produced moderate activity only (IC_{50} = 24.35 μg/ml) (Chen et al. 2004). The same configuration of moieties where the 7-position is for a change substituted by hydroxyl group showed slightly worse effect on this line as seen in the case of haplopine (**14**) (IC_{50} = 3.3 μg/ml) (Chen et al. 2003). The hydroxyl at the 7-position seems contribute to the activity against HT-29 if only combined with methoxyl group at the 4-position. This is obvious from comparison of the activities of **5** (ED_{50} = 26.7 μg/ml) with confusameline (**7**) (ED_{50} = 0.24 μg/ml) (Chen et al. 2003; Chen et al. 2004). The data also suggest that propan-2,2-olyl at the 2-postion decreases the activity against HT-29 cell line. For example, (S)-(-)-7,8-dimethoxyplatydesmine (**28**) and (+)-7,8-dimethoxymyrtopsine (**29**) produced comparably worse effects (respective ED_{50} values = 1.9 and 41.6 μg/ml) than strongly active **15** (Chen et al. 2003; Chou et al. 2005; Rasamison et al. 2016). Despite the above-described suggestions for structure-activity relationship against HT-29, it does not seem to be applicable for the LOVO and HCT15 cancer lines, against which furoquinolines were reported to be only moderately active (Appendix 1-Table 2).

Generally, alkaloids with simple quinoline structure produced strong or moderate *in vitro* antibacterial effects on diarrheagenic strains (Appendix 1-Table 2). However, a limited number of such alkaloids has previously been tested for this biological action. Out

of them, **1** and **2** produced significant *in vitro* effects on *B. cereus, L. monocytogenes*, and *S.* Typhimurium. (MICs = 2–75 μg/ml) (Yang et al. 2013; Kim et al. 2014). The compound **1** was also moderately active against *C. difficile*, *C. perfringens*, and *E. coli* as a result of our experiments in the present dissertation (MICs = 32–128 μg/ml). The remaining alkaloids, thus **3** and **4** were claimed to be active against clostridia but inactive against *E. coli* (Lee et al. 2009; Cho et al. 2005). Although these two last mentioned alkaloids would need to prove their actions in a concentration dependent manner, the overall data indicate that single substitution of simple quinolines by the carboxyl and carbonyl groups at the respective 2 and 4-positions might not be as effective in terms antimicrobial activity on these bacterial species as the substitution of 8 and 4-positions by the respective hydroxyl and methyl groups (Figure 5). Simple quinolines are one of the two classes presumably less toxic to probiotic bacteria as they showed comparably lower antibacterial effect to several species: *B. adolescentis, B. bifidum, B. longum ssp. longum*, and *L. casei* (MICs ≥512 μg/ml) (Appendix 1-Table 2). If comparing the strong selective anticancer actions of 8-hydroxyquinoline (**1**) determined in this dissertation with weaker activities of quinaldic acid (**3**) reported by Langner et al. (2015), we can suggest that hydroxyl group at C8 position most likely play the contributing role. However, more data on anticancer activities of simple quinolines against intestinal cells is needed.

Regarding protoberberines, it is obvious from the antimicrobial tests using *E. coli* and *S. aureus* that those with ketone group at 13a-position and N-methyl group tend to reveal better activities against these bacteria (Figure 5). Specifically, allocryptopine (**133**) produced lower MICs (125 and 250 μg/ml, respectively) than **120** (respective MICs >512 and =500–1,000 μg/ml), and protopine (**134**) produced lower MICs (≥125 and 80–250 μg/ml, respectively) than coptisine (**122**) (respective MICs = 1000 and >1000 μg/ml) (Appendix 1-Table 2). Differences between antimicrobial effects of palmatine (**119**) and **120** on *C. perfringens* (respective MICs = 15.75–125 and 62.5–256 μg/ml) and *B. cereus* (respective MICs = 400 and >512 μg/ml) signify that presence of methoxyl groups at 2 and 3-positions is more important for the activity against some gram-positive bacteria than methylenedioxy group (Kim et al. 2014; Long et al. 2019). The data on protoberberines indicate that bifidobacteria and lactobacilli might be more susceptible to those with methylenedioxy group at 2,3-positions as observed in the case *L. fermentum* towards which **120** and **122** produced more significant activities (MICs = 250 μg/ml) comparing to **118** and **119** (MICs = 500–1,000 μg/ml). The compound **120** was also more

toxic to *B. adolescentis*, *B. longum* ssp. *longum*, and *L. casei* than the latter two mentioned alkaloids but all three compounds were evenly toxic to *B. bifidum* (MICs = 31.25–62.5 μg/ml) (Lyu et al. 2021). The differences of anticancer effects of protoberberines produced against three cancer lines also bring certain ideas on which functional groups could be important (Figure 5). For example, comparing the reported *in vitro* activities between **119** and **120** against HCT15 (respective ED_{50} values >30 and = 27.2 μg/ml) and HT-29 (respective IC_{50} values = 17.3 and 2.1–5 μg/ml) indicates that the substitution of 2,3-positions by methylenedioxy group might be in this case more convenient for the activity than the two methoxyl groups (Long et al. 2019; Min et al. 2006). Interestingly, the activity of **120** against Caco-2 (IC_{50} = 19.4 μg/ml) is improved if conjugated to a ring-opened isoquinoline as observed in the case of baicalensine A (**136**) (IC_{50} = 6.91 μg/ml) (Xue et al. 2020).

Finally, there are three alkaloids of phenanthridine structure from the plants of Amaryllidaceae family that were able to produce activities against *E. coli* and *S. aureus* at some moderate MICs (25–63 μg/ml) (Appendix 1-Table 2). Ungeremine (**219**) as the most active one is unlike others in the form of quaternary salt. Also, this compound is unique in terms of having a negatively charged oxygen at the 2-position. The remaining two alkaloids, namely buphanidrine (**224**) and distichamine (**231**), have substituted their 3 and 7-positions by methoxyl groups (Figure 5). Although other compounds with these groups were inactive, they never appear in a combination like in the cases of **224** and **231**. Moreover, they bear some additional moieties that might presumably decline the antimicrobial effect. Additionally, hippadine (**220**) that produced rather weak activities but still against *E. coli* and *S.* Typhi (Maroyi et al. 2016), is of simple structure and unlike others it has substituted 7-position by the ketone group. Regarding the antiproliferative activity, Amaryllidaceae isoquinoline alkaloids produced moderate cytotoxic effects in 70% of cases they were tested on intestinal cancer cell lines, whereas in nearly 20% these *in vitro* actions were strong (Appendix 1-Table 2). Therefore, some structural features play a role in these differing activities (Figure 5). For example, the hydroxyl group at 2-position of the pyrrolo[3,2,1-de]phenanthridine structure might be important. This is obvious from the differences between cytotoxic effects of lycorine (**216**) and caranine (**214**) against Caco-2 (respective IC_{50} values = 0.28 and 17.4 μg/ml) and HT-29 (respective IC_{50} values = 0.34 and 12.6 μg/ml). Comparing the activities of these two compounds with actions determined for acetylcaranine (**218**) against the same two lines

(respective IC_{50} values = 9.24 and 6 μg/ml) indicates that if the hydroxyl group at the 2-position is absent, the acetoxyl group comes as better option for the substitution of 1-position rather than another hydroxyl group. For the alkaloids of 5,7-dioxa-12-azapentacyclo[10.5.2.01,13.02,10.04,8]nonadecane structure, the substitutions of 3 and 11-positions by the respective methoxyl and hydroxyl groups appears to be correlated with better cytotoxic activities (Figure 5). For example, in terms of actions produced against Caco-2 and HT-29 cells, haemanthamine (**226**) (respective IC_{50} values = 0.29 and 0.17 μg/ml) was more active than hamayne (**228**) (respective IC_{50} values = 4.9 and 3.55 μg/ml) and buphanisine (**223**) (respective IC_{50} values = 2.45 and 1.51 μg/ml) (Vaneckova et al. 2016; Doskocil et al. 2015). In this context, a weaker activity produced by ambelline (**230**) (respective IC_{50} values = 24.5 and 16.6 μg/ml) suggests that methoxyl group at the 7-position might notably reduce the cytotoxic ability against these two lines. Other alkaloids bearing the same group did not show any strong activity on Caco-2 and HT-29 lines either, namely buphanamine (**232**) (respective IC_{50} values = 16.1 and 14.3 μg/ml) and 1-O-acetylbulbisine (**234**) (respective IC_{50} values = 12 and 17.3 μg/ml) (Doskocil et al. 2015). Considering the variabilities in toxic responses of FHs 74 Int cells to some Amaryllidaceae alkaloids, there are observable structural features within this group that might play a role in terms of their toxicities to non-cancer intestinal cells. Generally, the suggested characteristics of these alkaloids that positively correlate with inhibitory actions to intestinal cancer lines similarly contributed to the toxicities to non-cancer cells (Figure 5). For example, two methoxyl groups or methylenedioxy group at 9,10-positions of pyrrolo[3,2,1-de]phenanthridine structure appears as better for the low toxicity comparing to the combination of methoxyl and hydroxyl groups at C9 and C10, respectively. This is obvious from comparison of toxicities of **214** and **213** (IC_{50} values >27 μg/ml) with 9-O-demethylgalanthine (**212**) (IC_{50} = 23.07 μg/ml). The hydroxyl group at 1-position seems to also be important for lower toxicity as it is present in cases of both **214** and **213**. On the other hand, comparing the toxicities of the former with **216** (IC_{50} = 6.51 μg/ml) and **218** (IC_{50} = 20.7 μg/ml) indicates that hydroxyl group at C2 and acetoxyl group at C1 relatively contribute to the toxicity. For the alkaloids of 5,7-dioxa-12-azapentacyclo[10.5.2.01,13.02,10.04,8]nonadecane structure, the substitutions of hydroxyl group at the 11-position seems to correlate with increased toxicity, whereas the substitution of 3-position by the hydroxyl group seems to lower the toxic effect if compared to the methoxyl group. This is mainly seen if comparing toxicities of **221** (IC_{50}

>27 μg/ml), **228** (IC_{50} = 15.3 μg/ml), and **226** (IC_{50} = 5.8 μg/ml) (Vaneckova et al. 2016; Doskocil et al. 2015).

Although quinoline nucleus has no biological importance, its derivatives have a wide range of biological activities. They either work by killing the living organism's cell or halting its replication by aiming crucial enzymes, which engage in either maintaining its integrity or are involved in its replication (Kumar et al. 2022). The main mechanism of antimicrobial action of quinolines is inhibition of DNA synthesis by promoting cleavage of bacterial DNA gyrase and type IV topoisomerase that leads to rapid bacterial death (Narwal et al. 2017). The inhibition of enterotoxin formation or metal chelating abilities have also been described (Lv et al. 2015; Chobot et al. 2011). The inhibition of cell growth by cycle arrest, apoptosis, and angiogenesis, as well as disruption of cell migration, and modulation of nuclear receptor responsiveness have been attributed to anticancer actions of quinoline alkaloids (Afzal et al. 2015). Since the mutation of DNA gyrase, topoisomerase, and other enzymes has led to development of resistance towards some structurally related antibiotics such as fluroquinolones, it is necessary to search for agents structurally assembled to aim a new enzymatic targets or circumvent their resistance. Among (iso)quinoline alkaloids, several derivatives have been synthesised in that order. For example, series of novel N-methylbenzofuro[3,2-b]quinoline and N-methylbenzoindolo[3,2-b]-quinoline derivatives were found active against several resistant bacteria as they strongly inhibited the GTPase activity of SFtsZ, which is the key molecule in bacterial cell division that polymerizes in the presence of GTP into tubulin-like protofilaments by head-to-tail association. This lead to abnormal bacterial cell division and eventually causing the cell death. Then, series of novel 2-sulfoether-4-quinolone scaffolds were synthetised and shown to cause cell wall destruction facilitating the penetration of the compound into the bacteria, whereas the molecular docking studies showed that the compounds fairly bound to the DNA gyrase complex via more extensive types interactions. Another way how these compounds could combat resistance is the prediction of riboswitch, a regulatory segment of a m-RNA (Kumar et al. 2022). Finally, in study of Osei-Owusu et al. (2021), a synergistic interaction between antibacterial activities of two quinoline derivatives ciprofloxacin and nitroxoline was found and attributed to their abilities to produce different mechanism of action. It has previously been described that the activity of the quinolones is reduced in the presence of divalent cations, such as Mg2+ as metal ion cofactors substantially affect the biological properties

of topoisomerases. Since nitroxoline has been observed to chelate metal ions, it is possible to assume that Mg2+ bonded to these compounds is not available as a cofactor necessary for proper functions of topoisomerases, and, at the same time, it does not affect the activity of ciprofloxacin that targets this enzyme. Therefore, synergistic interactions between these compounds could be another way how to mitigate resistance.

7.4 Chemotaxonomic distribution of (iso)quinoline alkaloids and their ethnopharmacological role in the treatment gastrointestinal infections and cancer

The analysis of the distribution of (iso)quinoline compounds among various plant taxa (Appendix 1-Table 1) showed that certain genera belonging to Rutaceae (*Zanthoxylum*, *Melicope, Haplophyllum, Ruta,* and *Acronychia* spp.) and Papaveraceae (*Corydalis*, *Fumaria*, *Papaver*, *Glaucium*, *Bocconia* spp.) families are containing highest numbers of the most active compounds (Appendix 1-Table 2). From this point of view, other genera that should be highlighted are *Berberis*, *Stephania*, *Thalictrum*, *Annona*, *Sida*, *Centaurea*, *Ophiorrhiza*, and *Tabernaemontana*. Although they belong to different plant families, the most prominent are of Ranunculales order. There is a strong literature evidence that these plants have been ethnobotanically utilized in the treatment of various digestive complaints in traditional folk systems. As summarized in Appendix 1-Table 3, most of the species are reported to be used against diarrhoea (37), stomach-ache and abdominal pain (36), dysentery (25), dyspepsia (12), indigestion (7), anthelmintic/intestinal worms, hepatobiliary disorders, cholera, gastroenteritis (6 for each), digestive infections (3), and haemorrhoids (2). Treatment of gastric, liver and/or colorectal cancers and ulcers have been reported in case of 8 species, whereas 21 were reported as traditional nonspecific anticancer and antiulcer remedies. Interestingly, several plants have been simultaneously involved in therapies of atopic diseases such as asthma and allergy (12), that have been lately discussed as one of the potential outcomes of intestinal dysbiosis (Li et al. 2021).

In present review, 62 rutaceous plant genera were identified to contain 105 (iso)quinoline alkaloids, particularly furoquinolines and quinolones. However, the benzophenanthridines and protoberberines present in these plants generally proved their

activities against higher amounts of intestinal agents. Forty four different (iso)quinoline compounds have been isolated from 56 species of *Zanthoxylum* genus and tested against 23 diarrheagenic (MICs = 1.5–1,240 μg/ml) and 10 probiotic bacteria (MICs = 8.27–1,000 μg/ml), and 9 cancer (IC_{50} values = 0.12–100 μg/ml) and 2 non-cancer intestinal cells (IC_{50} values = 1–>3.2 μg/ml) (Appendix 1-Table 1 and 2). *Zanthoxylum* is a genus of over 200 species, shrubs sometimes scrambling, trees, or woody climbers, primarily pantropical, but extending into the North Temperate Zone in eastern Asia and North America (World Flora Online 2022). At least 19 species have been recorded as traditional medicines used for the digestive issues (Appendix 1-Table 3). Most of these plants occur in China, Korea, and Japan and are utilized by Traditional Chinese Medicine. Specifically, *Z. armatum* [syn. *Z. planispinum*], *Z. bungeanum, Z. myriacanthum, Z. nitidum, Z. piperitum, Z. rhetsa, Z. schinifolium,* and *Z. simulans* were reported to be traditionally used for diarrhoea, abdominal pain, stomach ache, enteritis, colitis, and/or gastritis. In South Asia, *Z. armatum* [syn. *Z. alatum*] and *Z. rhetsa* have been used for cholera, diarrhoea, dysentery, indigestion, dyspepsia, stomach disorders, and gas problems (Aziz et al. 2022; Kanwal et al. 2015). In North America, a tea or tincture of the bark of *Z. americanum* and *Z. clava-herculis* have been used in the treatment of dyspepsia and dysentery (Fern 2023), whereas in Central and West African countries similar conditions have been treated by Z. *leprieurii* and Z. *zanthoxyloides* (Ngoumfo et al. 2010; Kassim et al. 2015). Six species of the genus have been involved in the herbal therapies of digestive cancers and ulcers, namely *Z. armatum* [syn. *Z. alatum*], Z. *gilletii* [syn. Z. *tessmannii*], Z. *nitidum*, Z. *oxyphyllum*, and *Z. piperitum* (Appendix 1-Table 3). Interestingly, Z. *leprieurii*, and *Z. rhetsa* have also been recorded to be used for asthma (Aziz et al. 2022; Kuete et al. 2011).

Thirty alkaloids found in 11 *Melicope* species were tested against 8 diarrheagenic bacteria (MICs = 4.88–≥1,240 μg/ml), and 4 intestinal cancer lines (IC_{50} values = 0.12–≥41.6 μg/ml) (Appendix 1-Table 1 and 2). *Melicope* is a genus of nearly 250 shrubs and trees occurring from the Hawaiian Islands across the Pacific Ocean to tropical Asia, Australia and New Zealand (World Flora Online 2022). At least three species have traditionally been used for a digestive ailments such as diarrhoea, intestinal worms, or stomach ache, namely *M. madagascariensis*, *M. pteleifolia*, and *M. triphylla* (Appendix 1-Table 3). Another genus *Haplophyllum* consists of about 160 herbs and low shrubs native from Mediterranean basin to Southern Siberia and South Asia (Royal Botanic

Gardens 2017). There are 18 species bearing 20 (iso)quinolines that were tested against 8 diarrheagenic bacteria (MICs = 4.88–≥1000 μg/ml), and 4 intestinal cancer lines (IC_{50} values = 0.12–≥36.6 μg/ml) (Appendix 1-Table 1 and 2). *H. tuberculatum* has been reported to be traditionally used in East Africa and West Asia for gastric disorders such as dyspepsia but also atopic diseases like asthma (Fern 2014; Awaad and Alothman 2017). Next, *H. dauricum* and *H. acutifolium* [syn. *H. perforatum*] have supposedly been involved in nonspecific anticancer therapies in Temperate Asian countries (Kang et al. 2014; Ea et al. 2008). *Ruta* is another rather smaller genus of about 23 species of evergreen subshrubs native to the Mediterranean basin and mainly found in temperate and tropical regions (Coimbra et al. 2020). Six species provided 11 alkaloids that were tested against 9 diarrheagenic (MICs = 4.88–≥1000 μg/ml) and 2 probiotic bacteria (not active at 0.25 mg/disk), and 3 intestinal cancer cells (IC_{50} values = 0.12–36.6 μg/ml) (Appendix 1-Table 1 and 2). *R. angustifolia*, *R. chalepensis*, and *R. graveolens* have been involved in European, East African, South and/or Southeast Asian countries as traditional remedies of diarrhoea, dysentery, indigestion, intestinal worms, and/or stomach-ache (Appendix 1-Table 3). The genus *Acronychia* is comprising 44 species of shrubs and small trees distributed in Southern and eastern parts of Asia and the islands of the western Pacific Ocean (Epifano et al. 2013). Five compounds found in 3 species of this genus were tested against 8 diarrheagenic bacteria (MICs = 4.88–≥512 μg/ml) and 3 intestinal cancer lines (IC_{50} values = 0.12–36.6 μg/ml) (Appendix 1-Table 1 and 2). In the above-mentioned regions, *A. pedunculata* has been ethnobotanically utilized as a remedy for stomach-ache (Fern 2014).

Thirty-five plant genera of the poppy family provided 52 (iso)quinoline alkaloids, most of which were benzophenanthridines that also showed the most significant activities *in vitro*. Twenty-seven different (iso)quinoline compounds have been isolated from 39 species of *Corydalis* genus and tested against 22 diarrheagenic (MICs = 1.5–≥1,320 μg/ml) and 10 probiotic bacteria (MICs = 16–1,000 μg/ml), and 12 cancer (IC_{50} values = 0.43–100 μg/ml) and 3 non-cancer intestinal cells (IC_{50} values = 1–>67.28 μg/ml) (Appendix 1-Table 1 and 2). The genus *Corydalis* consists of more than 400 species of annual and perennial herbaceous plants native to the temperate Northern Hemisphere (Iranshahy et al. 2014). At least ten species are known for their ethnopharmacological utilization in the treatment of various digestive issues. Many of them (e.g., *C. govaniana*, *C. heterocarpa*, *C. incisa*, *C. turtschaninovii*, *C. saxicola*, *C. ternata*, and *C. yanhusuo*)

are involved in the treatment of diarrhoea, dysentery, abdominal pain, haemorrhoids, rectal collapse, and allergies in East Asia (Appendix 1-Table 3). Two other species, namely *C. crispa*, and *C. dubia*, have been used in South Asia against liver, pancreatic, and bile infections (Wangchuk et al. 2011). Additionally, *C. yanhusuo* is used in Traditional Chinese Medicine against digestive ulcers and cancers. Although it has not been confirmed that *C. aurea* contains any of the herein presented alkaloids, it has been reported to be traditionally used in North America against diarrhoea and stomach-ache (Fern 2023). Twenty (iso)quinoline compounds identified in 20 species of the genus *Fumaria* have been tested against 22 diarrheagenic (MICs = 1.56–1,320 μg/ml) and 10 probiotic bacteria (MICs = 16–1,000 μg/ml), and 10 cancer (IC_{50} values = 0.43–100 μg/ml) and 2 non-cancer intestinal cells (IC_{50} values = 1–>3.2 μg/ml) (Appendix 1-Table 1 and 2). The genus comprises about 60 species with native range from Europe to central Asia and North Africa (Zhang et al. 2020). Two species, namely *F. indicia* and *F. parviflora* were reported to be used in South and/or West Asian countries for treatment of diarrhoea, abdominal pain, indigestion, helminths, and asthma (Appendix 1-Table 3). Finally, *F. bastardi*, *F. capreolata*, and *F. officinalis* have been reported as remedies against various hepatobiliary and digestive disorders, particularly in countries of Mediterranean Basin (Fadila et al. 2007; Orhan et al. 2012). The temperate and cooler regions of Eurasia, Africa and North America are native habitats of the genus *Papaver* that consists of about 100 annual, biennial, and perennial species (World Flora Online 2022). Twenty-three (iso)quinoline compounds found in 28 *Papaver* species have been tested against 22 diarrheagenic (MICs = 1.56–1,320 μg/ml) and 10 probiotic bacteria (MICs = 16–1,000 μg/ml), and 12 cancer (IC_{50} values = 0.43–100 μg/ml) and 3 non-cancer intestinal cells (IC_{50} values = 1–>67.28 μg/ml) (Appendix 1-Table 1 and 2). Despite the richness of this genus in terms of number of species and biologically active (iso)quinoline alkaloids, there is a little evidence on their utilization in herbal systems for the treatment of digestive disorders. The most well-known species *P. somniferum* has been globally used as a medicine for centuries. It has been used for the treatment of diarrhoea, poor digestion, and some nervous digestive disorders in Europe, South America, and South Asia (Fern 2023). Although the anticancer potency of opium alkaloids have been discussed extensively (DeBono et al. 2012; Mello et al. 2022), reports on *Papaver* species to be utilized in such a way in folk medicinal systems are rather scarce.

Total of 19 alkaloids detected in five species of the *Glaucium* genus were tested against 22 diarrheagenic (MICs = 1.5–1,000 μg/ml) and 10 probiotic bacteria (MICs = 16–1,000 μg/ml), and 13 cancer (IC_{50} = 0.43–100 μg/ml) and 3 non-cancer intestinal cells (IC_{50} = 1–>67.28 μg/ml) (Appendix 1-Table 1 and 2). *Glaucium* includes about 25 species of annual, biennial or perennial herbaceous flowering plants that are distributed throughout Western, Northern and Eastern Asia, Europe, Northern Africa, and Australia (Feng and Noedoost 2022). Although there are reports on the traditional uses of *Glaucium* spp. (e.g. *G. grandiflorum* and *G. vitellinum*) as anti-inflammatory and antidiabetic remedies in West Asia (Bozkurt et al. 2022; Morteza-Semnani et al. 2002; Rangriz et al. 2016), there is no information on their use against digestive disorders like diarrhoea and cancer. *Bocconia* genus consists of about 10 species of small trees or shrubs growing in the montane rain forests from southern Mexico and the Caribbean islands to western South America (World Flora Online 2022). Six of these species provided 9 (iso)quinoline compounds that were tested against 18 diarrheagenic (MICs = 1.5–1,320 μg/ml) and 9 probiotic bacteria (MICs = 8.27–64 μg/ml), and 7 cancer (IC_{50} = 0.43–14.5 μg/ml) and 1 non-cancer intestinal cells (IC_{50} = 1 μg/ml) (Appendix 1-Table 1 and 2). Two species, namely *B. arborea,* and *B. frutescens*, have been reported to be used internally as medicines for various gastrointestinal complaints such as diarrhoea. The former has also been utilized for its antitumor properties (Yu et al. 2014; Lunagomez et al. 2020).

As far as other plant taxa are considered, there are 71 *Berberis* (Berberidaceae) species bearing 24 (iso)quinoline compounds tested *in vitro* against 20 diarrheagenic (MICs = 3.12–≥1,000 μg/ml) and 9 probiotic bacteria (MICs = 31.25–1,000 μg/ml), and 10 cancer (IC_{50} values = 0.8–100 μg/ml) and 3 non-cancer intestinal cells (IC_{50} = 1–>67.28 μg/ml). Most of these quinolines were in both cases protoberberines that also revealed the most significant bioactivities. Aporphines and bisbenzylisoquinolines were other structural groups showing similar antibacterial and anticancer effects, respectively (Appendix 1-Table 1 and 2). This genus is represented by around 500 species distributed all over the world mainly in India, Pakistan, West and Central Asia, China, Japan, Southeast Asia, Europe, East Africa, North America and South America (Khan et al. 2016). There are 10 species reported to be involved in traditional herbal systems and used for the digestive issues. Most of them occur in the mountainous East Asia and are used for diarrhoea, dysentery, gastroenteritis, and intestinal colic, namely *B. amurensis, B. aristata, B. bealei, B. chitria, B. heteropoda,* and *B. lyceum*. Then, conditions such as

diarrhoea, dysentery, dyspepsia, and stomach infections were reported to be traditionally cured by *B. canadensis*, *B. hispanica* [*B. vulgaris* subsp. *australis*], *B. vulgaris*, and *B. wallichiana* in herbal systems of North America, North Africa, Europe, and Southeast Asia, respectively. Additionally, *B. amurensis*, *B. aristata*, *B. chitria*, *B. hispanica*, and *B. vulgaris* were reported as remedies for various types of cancers and ulcerations including stomachic and colorectal (Appendix 1-Table 3). Twenty-seven (iso)quinoline compounds found in 34 species of the genus *Thalictrum* (Ranunculaceae) have been tested against 20 diarrheagenic (MICs = 3.12–1,000 μg/ml) and 10 probiotic bacteria (MICs = 32–1,000 μg/ml), and 11 cancer (IC_{50} values = 0.0038–100 μg/ml) and 3 non-cancer intestinal cells (IC_{50} values = 1–>67.28 μg/ml). In case of the antibacterial actions, protoberberines prevailed quantitatively but aporphines were generally more active. Interestingly, bisbenzylisoquinolines dominated as anticancer agents from the point of their amounts and degree of activities (Appendix 1-Table 1 and 2). *Thalictrum* is a genus of 120–200 species of herbaceous perennial plants distributed throughout most of the Northern Hemisphere, especially North America. However, there are also species in southern parts of Africa and tropical South America (World Flora Online 2022; Royal Botanic Gardens 2017). There are 4 species with the existing reports on their uses against gastrointestinal disorders (Appendix 1-Table 3). Three of them, namely *T. foliolosum, T. fortunei,* and *T. minus* have been used in East Asia for the treatment of dysentery, dyspepsia, stomach-ache, intestinal obstruction, indigestion, and/or haemorrhoids. Additionally, *T. foliolosum* and *T. fortunei* have also been considered as effective agents against tumours and peptic ulcers (Mishra et al. 2021; Zhang et al. 2013; Badamjav et al. 2021). In Europe, *T. collinum* [*T. minus* subsp. *saxatile*] is then valued as stomachic agent (Fern 2023). Thirty-four (iso)quinoline compounds identified in the 24 species of *Stephania* genus (Menispermaceae) were tested against 19 diarrheagenic (MICs = 3.12–≥1,000 μg/ml) and 10 probiotic bacteria (MICs = 31.25–1,000 μg/ml), and 12 cancer (IC_{50} values = 0.8–330.15 μg/ml) and 2 non-cancer intestinal cells (IC_{50} values = 1–>67.28 μg/ml). Considering the quantities of these alkaloids and degree of bioactivities produced, aporphines and bisbenzylisoquinolines significantly dominated in both aspects in terms of antibacterial and anticancer actions, respectively (Appendix 1-Table 1 and 2). *Stephania* is a genus of about 45 flowering plant species native to eastern and southern Asia and Australia. They are herbaceous perennial vines typically bearing a large tuber (Forman 1988). There are four species that have been reported to be used for some

digestive complains, especially in Southeast and East Asia (Appendix 1-Table 3). Namely, *S. glabra, S. japonica, S. rotunda, S. tetrandra* have been used for diarrhoea, dysentery, gastritis, and/or dyspepsia. *S. glabra* and *S. tetrandra* were also recorded as traditional anticancer herbal agents. Except *S. japonica*, the plants have been used as anti-asthmatics as well (Desgrouas et al. 2014; Semwal et al. 2015; Bokshi et al. 2013; Bun et al. 2009).

Nineteen (iso)quinoline compounds detected in 21 *Annona* spp. (Annonaceae) were tested against 19 diarrheagenic (MICs = 3.12–≥1,000 μg/ml) and 10 probiotic bacteria (MICs = 32–1,000 μg/ml), and 10 cancer (IC_{50} values = 0.8–100 μg/ml) and 2 non-cancer intestinal cells (IC_{50} values = 1–>67.28 μg/ml). Aporphines were the most common bioactive compounds among those isolated from this genus. Only protoberberines showed similar cytotoxic actions against the cancer cells (Appendix 1-Table 1 and 2). The genus *Annona* comprises approximately 162 species of trees and shrubs distributed in tropical and subtropical regions around the world (de Oliveira et al. 2014). There are six species reported for their traditional use in the treatment of diarrhoea, dysentery, and other digestive disorders. Most of them are particularly used in South and Central American countries, namely *A. cherimola, A. dioica, A. muricata, A. squamosa,* and *A. crassiflora*. *A. muricata* has also become a plant that is almost pantropically valued as an anticancer agent that is used in therapies of gastric, liver, and colon cancer (Appendix 1-Table 3). The involvement in anticancer treatment was also reported in the cases of *A. cherimola* and *A. squamosa* (Calzada et al. 2020; Soni et al. 2013). Finally, *A. senegalensis* is the purely African plant utilized in countries like Nigeria and Senegal for the treatment of diarrhoea and other gastrointestinal troubles (Suleiman et al. 2008).

Remaining five taxonomically diverse genera are represented by rather low number of species containing limited number (iso)quinoline alkaloids that have been tested against intestinal bacteria and cells *in vitro* (Appendix 1-Table 1 and 2). However, the ethnopharmacological background of these plants is significant, the same as are the bioactivities produced by the isolated compounds (Appendix 1-Table 3). Moreover, relatively large number of species existing per each of these genera indicates they could potentially become a source of more of such bioactive compounds. First, there is an ethnomedicinally important genus *Sida* (Malvaceae) that is represented by about 200 species of herbaceous plants widely distributed as weeds in pasture and waste lands of

tropical and subtropical regions of the world (Dinda et al. 2015). In present review, three indoloquinoline and one benzophenanthridine alkaloids were isolated from *Sida acuta*, *S. cordifolia*, *S. rhombifolia*, and *S. veronicaefolia* and tested against 10 diarrheagenic bacteria [MICs = (<1.5) 5–1,210 μg/ml]. Two compounds were then tested against 2 cancer lines (IC_{50} = 11.1 μg/ml and proved induction of cell cycle arrest), and one against probiotic bacterium (MIC = 10–20 μg/ml) (Appendix 1-Table 1 and 2). *Sida* species have been used for centuries in traditional medicines in different countries for the prevention and treatment of different diseases such as diarrhoea, dysentery, gastrointestinal infections, and asthma (Dinda et al. 2015). The treatment of these ailments has particularly been adopted in South Asian countries where three of the above mentioned species plus *S. cordata* and *S. spinosa* have been used (Gulnaz and Savitha 2013; Shahed-Al-Mahmud et al. 2018; Mah et al. 2017; Tirkey 2019). *Centaurea calcitrapa* and *C. diffusa* are the only representatives of the genus bearing one benzophenanthridine (**174**) and simple quinoline (**1**), respectively (Appendix 1-Table 1). However, the latter is the only compound that showed selectivity of its both *in vitro* antibacterial and cytotoxic actions (Appendix 1-Table 2). *Centaurea* (Asteraceae) is represented by more than 500 species of perennial or annual herbs and shrubs mostly located in the Mediterranean region and Western Asia which have been widely used as herbal remedies in folk medicine for their antidiarrheic, anti-inflammatory, choleretic, diuretic, digestive, stomachic, astringent, antipyretic, cytotoxic, and antibacterial properties (World Flora Online 2022; Sokovic et al. 2017; Kose et al. 2016). For example, *C. benedicta*, *C. cyanus*, and *C. jacea* have been used in Europe for various stomach infections and digestive issues. Moreover, *C. benedicta* has been highlighted as a remedy of stomach-related diseases without having any harmful side effects against beneficial gut bacteria (Fern 2023; Ghiasy-Oskoee et al. 2020). There is a little evidence for (iso)quinolines to be common in *Centaurea* spp. and rather some phenolic compounds have been discussed (Kubik et al. 2022). Several indole alkaloids have been detected in *C. cyanus* and some simple quinolines found in the honey produced from that plant (Sarker et al. 2001; Oelschlaegel et al. 2012). Therefore, it is left to be investigated how much exceptional the presence of such compounds is if referring to this the genus. Finally, there are some significant genera from which the indoloquinoline compound **76** has been isolated, namely *Ophiorrhiza*, *Rinorea*, and *Tabernaemontana* (Appendix 1-Table 1). Its anticancer activities have been broadly researched but the literature suggests its

antimicrobial potential as well (Appendix 1-Table 2). *Ophiorrhiza* (Rubiaceae) is one of the Indo-Malaysian genera consisting of about 321 species widely spread in the wet forests across tropical and subtropical Asia, Australia, New Guinea, and the Pacific Islands (Taher et al. 2020). *O. rugosa* and *O. mungos* have been reported to be traditionally used for the treatment of dysentery and stomach-ache in South and Southeast Asian countries, whereas the anticancer utilization of *O. mungos* has also been recorded. Then there is *O. leptantha* apparently used as antidiarrheagenic agent on some Pacific Islands (Fern 2014; Adnan et al. 2019). However, this species has not yet been appropriately studied for its phytochemical profile. Next genus *Rinorea* (Violaceae) is pantropically distributed with 206 species, especially in Central and West Africa (Achoundong et al. 2021). These plants are known as a valuable source of traditional medicines, and some have been used internally as stomachic agents. Although such specific report is missing in case of the herein presented *R. anguifera*, it exists for other species like *R. oblongifolia* and *R. subintegrifolia* (Munvera et al. 2020; Agnaniet et al. 2003). The last genus *Tabernaemontana* [syn. *Ervatamia*] (Apocynaceae) comprises about 100 shrub or small tree species distributed throughout the tropics, mainly in South America and Africa (World Flora Online 2022). There are at least 9 species particularly from Southern and Eastern parts of Asia and Tropical Africa that have been involved in traditional therapies of digestive disorders, namely *T. corymbosa, T. divaricata* [syn. *T. coronaria*], *T. elegans, T. alternifolia* [syn. *T. heyneana*, *E. heyneana*], *T. pachysiphon, T. pandacaqui, T. persicariifolia, T. rostrata,* and *T. stapfiana*. Three of the species have been proven to contain some of the presented alkaloids including **76**, **197**, **253**, and/or **254** (Appendix 1-Table 1). Most of them are used for diarrhoea, dysentery, and stomach-ache, whereas five are reported as remedies for abdominal tumours, ulcers, or even asthma (Appendix 1-Table 3).

8. Conclusions

In this dissertation thesis, *in vitro* inhibitory effects of various plant-derived products such as plant extracts, compounds, and their synthetic analogues were studied against intestinal bacteria and cells with aim of identifying a sources of potential chemical candidates employed as scaffolds in future development of a new therapeutic drugs used for the treatment of infectious diarrhoea and associated intestinal cancer diseases that are less disruptive for human intestinal environment and microbial ecology. Since both international and local markets already provide multiple over-the-counter pharmaceuticals, dietary supplements, and herbal medicines recommended for the support and maintenance of gastrointestinal health containing significantly bioactive plant compounds and their derivatives, the first section was dedicated to examination and identification of those that appear to be most prominent. For appropriate comparison of these features to the currently used therapeutic drugs, several standard antidiarrheal antibiotics were also included. As a result of these experiments, 8-hydroxyquinoline alkaloids (chloroxine and nitroxoline) and metal-pyridine derivative complex (zinc pyrithione) together with antibiotics ciprofloxacin and tetracycline showed significant selective growth-inhibitory activity against diarrheagenic bacteria with lowered toxicity to probiotic intestinal bacteria. Quinoline and isoquinoline alkaloids (8-hydroxyquinoline, chloroxine, nitroxoline, sanguinarine) together with zinc pyrithione were also found to exhibit strong cytotoxic effects that were in the cases of 8-hydroxyquinoline and sanguinarine selective to cancer intestinal cells. Therefore, in correspondence with the first hypothesis of this work, these findings indicated that particularly compounds containing quinoline scaffold as part of their structure, such as the phytochemicals and phytochemical analogues chloroxine, 8-hydroxyquinoline, nitroxoline, and sanguinarine and antidiarrheal antibiotic ciprofloxacin, possess promising bioactive properties in terms of *in vitro* selective antibacterial and anticancer activities against intestinal agents.

Regarding that majority of useful drugs derived from plants have been discovered by follow-up of ethnomedical use and that examination of plants traditionally used for the treatment of gastrointestinal complaints has led to the discovery of several bioactive compounds including those tested in the first part of this study, the second section of the dissertation was focused on assessing the same *in vitro* dual and selective properties of

extracts derived from the selection of ethnobotanically important but pharmacologically unrecognized antidiarrheal medicinal plants from Southeast Asia, specifically Cambodia and the Philippines. Out of 35 extracts prepared from 32 medicinal plants, 16 showed some antibacterial properties against the diarrheagenic bacteria *in vitro*. Although it indicates that a high percentage of plants are employed as antidiarrheal medicines due to other properties, the second hypothesis was still shown to be valid. *A. tectorius*, *A. blancoi*, and *P. siamensis* produced significant inhibitory actions against several diarrheagenic bacteria at the concentration nontoxic to intestinal non-cancer cells. *A. tectorius*, *A. blancoi*, *E. microphylla*, and *L. cochinchinensis* then revealed strong antiproliferative effects to intestinal cancer cell lines that were in majority of the cases relatively harmless to the non-cancer cells. With exception of *A. tectorius*, chemical composition of biologically active species has not been previously studied. Literature data on chemical composition of *A. tectorius* revealed the presence of isoquinoline alkaloids, which suggests this class of compounds as agents potentially producing selective inhibitory action against intestinal pathogenic bacteria and cancer cells.

Based on the results obtained from *in vitro* experiments focused on biological activities of phytochemicals indicating that quinoline and isoquinoline alkaloids are classes of compounds producing selective antimicrobial and cytotoxic properties, the analysis of literature data on their quantitative structure-property relationship and chemotaxonomic distribution was performed as the last step of the research. The results suggested benzophenanthridine, indolo(iso)quinoline, and furoquinoline as the structures most potent to show strong activities against diarrhoea-causing bacteria and intestinal cancer cells. Amaryllidaceae isoquinolines, simple quinolines, and protoberberines appeared to have the highest tendency to produce antibacterial and/or anticancer activities at concentrations nontoxic to non-cancer cells and/or probiotic bacteria. In correspondence with the third hypothesis, quantitative structure-property relationship analysis lead to the identification of functional groups that potentially play a role in these activities. Investigation of chemotaxonomic distribution of (iso)quinoline alkaloids in relation to ethnobotanical profile (plants used for the treatment of various digestive complaints) identified several genera belonging to Rutaceae, Papaveraceae and other mainly Ranunculales families as prospective taxa worth further phytochemical and pharmacological research. Therefore, even the last hypothesis has been proved to valid. Nevertheless, future research will be needed to verify that combining chemotaxonomic

and ethnobotanical procedures will lead to the discovery of new pharmacologically important plants.

This dissertation identified structural classes of phytochemicals and plant taxa that are worth further research focused on development of a new efficient and safer antibacterial and anticancer drugs employed in antidiarrheal and anticancer therapies. Generally, (iso)quinoline alkaloids and the plant species containing these constituents were found as the most prominent from this point of view. However, Cambodian and Philippine medicinal plants that showed combination of bioactivities await for phytochemical analysis that might reveal other class of plant compounds possessing similar kind of qualities. In order to establish safety and efficacy of a newly developed drugs in humans, it is necessary to take into account the limitations of herein presented *in vitro* data and consider strategies used to transit these findings into *in vivo* assays and eventually clinical trials. Prior to it, the selected compounds and extracts should be studied for their effect on complex microbial cultures that better imitate human gut microbiota, such as the batch incubation assays with human stool in tandem with rRNA sequencing methods. Utilization of a dynamic computer controlled multi-compartmental systems mimicking the digestive tract with adjustable parameters for the physiological conditions of the stomach and intestines (e.g., TNO (gastro-) Intestinal Models) would also be convenient. Candidates for *in vivo* tests should be supported by appropriate amount of *in vitro* data indicating their lack of cytotoxic, mutagenic, and oncogenic properties to mammalian cell lines. *In vivo* tests should mainly consist of a standard animal models (e.g., mice and rats) concerning mucosal toxicity performed by histology examination of the intestinal epithelium. Systemic toxicity determining dose dependent manifestation of specific side-effects after the exposure to the drug including the lethal dose should be also involved. Then, spontaneous or induced intestinal cancer animal models (rats, mouse, and rodents) should verify the anticancer therapeutic properties of the drugs. In order to mimic the effect of the tested drugs on intestinal microorganisms in *in vivo* models, stool cultures' of the pigs, that share similarities to humans in intestinal microbiota and gastrointestinal anatomy and physiology, would be prioritized. Finally, only the compounds passing the *in vivo* toxicity tests would be included in human clinical trials. Blind and double-blind studies would be performed with humans suffering from chronic diarrhoea, dysbiosis or late stage of cancer with palliative care. On top of the single drug treatment trials, antibiotic combination therapy trials using the test drugs with

standard antibiotics would be involved. Together with the assessment of effectiveness of the therapy, side-effects and toxicity, stool examination of the patients would determine how the drug affects intestinal microbiota and survival rates of supplemented probiotics.

Then, a strategies for integration of a newly developed plant-derived compounds into current treatment protocols for diarrheal diseases and colorectal cancer should be considered. Since the stool examination is impossible to perform for every diarrhoeal patient for whom antimicrobial therapy is recommended, a proper choice of drugs allowing maximized effect on broad spectrum of possible pathogens with limited risks for side-effects and antibiotic resistance growth would be important. Also, specific anticancer properties of such drugs could help to prevent oligosymptomatic intestinal carcinogenesis associated with dysbiosis and chronic diarrhoea. In case of such therapy, the survival rates of supplemented probiotics would be increased as well. In this study, several structural features of plant-derived compounds were identified to correlate with these biological actions. This could assist future research dealing with synthetic chemistry in the process of modifying natural compounds to improve their biological activities and the development of a new antibiotic/anticancer drugs used for the empiric treatment of bacterial diarrhoea. Obviously, as in other pharmaceuticals, the main challenge would be a high risk of bacterial and cancer resistance development. In that case, antibiotic combination therapy would be useful in case that two or more drugs of the same class but with different mechanisms of biological action would be identified. Also, considering synergistic or additive effect of quinoline alkaloids, their use in form of cheaper and more available products like dietary supplements containing mixtures of compounds such as extracts and tinctures could be a reasonable choice for the prevention and treatment of diarrheal episodes. Taking into account that bacterial diarrhoea is the main issue in developing countries with limited access to modern pharmaceuticals, education in terms of prioritizing some herbal products derived from identified plant species containing bioactive (iso)quinoline alkaloids could also be included into current treatment and prevention protocols for diarrheal and colorectal cancer diseases.

In summary, the results of this dissertation thesis can be used by life science researches, especially those working in the areas of pharmacy, pharmacology, and medicinal and natural product chemistry. For example, the selection of phytochemicals to be tested in the future *in vitro* and *in vivo* experiments can be made on that basis. It

could be useful for the researchers modifying natural compounds to synthetic analogues with improved biological activities. With the support of findings obtained from the literature review analysis, this work could also assist future scientific community to build up an improved research concept combining ethnobotanical and chemotaxonomic approaches to identify a new pharmacologically important plant species.

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10. Appendices

List of the Appendices:

Appendix 1: Antimicrobial and anticancer (iso)quinoline alkaloids in plants with antidiarrheal ethnobotanical use: a review of *in vitro* effects on intestinal bacteria and cells (Tables 1-3 + References & Figures 1-7)

Table 1 Plant taxa containing antibacterial and cytotoxic (iso)quinolines

No.	Compound	Species	Family	References
SIMPLE QUINOLINES				
1	8-Hydroxyquinoline (quinolin-8-ol or 8-quinolinol or oxyquinoline)	*Centaurea diffusa*	Asteraceae	**1**
		Microstachys corniculata	Euphorbiaceae	**2**
2	Lepidine (4-methylquinoline or 4-methyl-quinoline)	*Citrullus colocynthis*	Cucurbitaceae	**3**
		Lepidium sativum	Brassicaceae	**4**
3	Quinaldic acid (Quinoline-2-carboxylic acid or 2-Quinolinecarboxylic-acid or quinaldinic-acid)	*Ephedra pachyclada*	Ephedraceae	**5**
4	Quinoline-4-carboxaldehyde (4-Quinolinecarboxaldehyde or 4-Quinolinecarbaldehyde)	*Ruta chalepensis*	Rutaceae	**6**
FUROQUINOLINES				
5	Dictamnine (syn. Dictamine)	*Acronychia pedunculata, A. pubescens*	Rutaceae	**7,8**
		Andreadoxa flava	Rutaceae	**7**
		Balfourodendron riedelianum	Rutaceae	**7**
		Boronia inornata, B. pinnata	Rutaceae	**7,11,12**
		Bouchardatia neurococca	Rutaceae	**7**
		Clausena vestita	Rutaceae	**7**
		Chorilaena quercifolia	Rutaceae	**7**
		Comptonella sessilifoliola	Rutaceae	**7**

Dictamnus albus	Rutaceae	**8**
Drummondita calida	Rutaceae	**7**
Esenbeckia berlandieri, E. febrifuga, E. leiocarpa	Rutaceae	**7,19-21**
Euodia spp.	Rutaceae	**7**
Glycosmis mauritiana, G. pentaphylla	Rutaceae	**7**
Halfordia kendack	Rutaceae	**7**
Haplophyllum acutifolium, H. bucharicum, H. bungei, H. buxbaumii, H. cappadocicum, H. dauricum, H. griffithianum, H. myrtifolium, H. obtusifolium	Rutaceae	**7,10,25-33**
Helietta apiculata	Rutaceae	**9**
Hortia longifolia	Rutaceae	**7**
Leionema spp.	Rutaceae	**7**
Medicosma cunninghamii	Rutaceae	**7**
Melicope pteleifolia, M. semecarpifolia, M. triphylla,	Rutaceae	**7,10,11**
Myrtopsis macrocarpa	Rutaceae	**7**
Phebalium spp.	Rutaceae	**7**
Phellodendron amurense	Rutaceae	**7**
Pitavia punctata	Rutaceae	**7**
Raputia praetermissa	Rutaceae	**7**
Ruta corsica, R. graveolens, R. chalepensis, R. montana	Rutaceae	**7,10,44-46**
Sarcomelicope argyrophylla	Rutaceae	**7**
Skimmia japonica, S. laureola	Rutaceae	**7**
Teclea natalensis, T. trichocarpa	Rutaceae	**7**
Tetradium glabrifolium, T. trichotomum	Rutaceae	**7**
Vepris lecomteana, V. trichocarpa	Rutaceae	**7,12**
Zanthoxylum ailanthoides, Z. armatum, Z. austrosinense, Z. avicennae, Z. beecheyanum, Z. dimorphophyllum, Z. ekmanii, Z. mayu, Z. pistaciiflorum, Z. rhetsa, Z. scandens, Z. schinifolium, Z. simulans, Zanthoxylum wutaiense	Rutaceae	**7,13,14,37**

6	Robustine	*Dictamnus albus*	Rutaceae	**15**
		Haplophyllum acutifolium, H. bucharicum, H. cappadocicum, H. dauricum, H. myrtifolium, H. obtusifolium, H. ramosissimum,	Rutaceae	**7**
		Raputia praetermissa	Rutaceae	**7**
		Ruta graveolens	Rutaceae	**7**
		Tetradium glabrifolium	Rutaceae	**7**
		Thamnosma montana	Rutaceae	**7**
		Zanthoxylum ailanthoides, Z. avicennae, Z. beecheyanum, Z. nitidum, Z. schinifolium, Z. simulans, Z. wutaiense	Rutaceae	**7,37,16**
7	Confusameline (7-hydroxydictamnine)	*Dictamnus albus*	Rutaceae	**8**
		Melicope elleryana, M. lasioneura, M. pteleifolia, M. semecarpifolia	Rutaceae	**7,10,11**
		Pitaviaster haplophyllus	Rutaceae	**17**
		Zanthoxylum ailanthoides	Rutaceae	**7**
8	γ-Fagarine	*Dictamnus albus*	Rutaceae	**8**
		Helietta apiculata	Rutaceae	**9**
		Peltostigma guatemalense	Rutaceae	**18**
		Zanthoxylum pistaciiflorum	Rutaceae	**13**
9	Evolitrin	*Acronychia pedunculata, A. pubescens*	Rutaceae	**7**
		Almeidea rubra	Rutaceae	**7**
		Balfourodendron riedelianum	Rutaceae	**7**
		Boronia inornata, B. pancheri, B. pinnata	Rutaceae	**7**
		Comptonella sessilifoliola	Rutaceae	**7**
		Dictamnus albus	Rutaceae	**8**
		Drummondita calida	Rutaceae	**7**
		Esenbeckia berlandieri	Rutaceae	**7**
		Euodia spp.	Rutaceae	**7**
		Haplophyllum acutifolium	Rutaceae	**7**
		Melicope lunu-ankenda, M.pteleifolia, M. semecarpifolia, M. triphylla	Rutaceae	**7,10**

		Nematolepis phebalioides	Rutaceae	**7**
		Phebalium spp.	Rutaceae	**7**
		Pitaviaster haplophyllus	Rutaceae	**17**
		Raputia praetermissa	Rutaceae	**7**
		Ruta montana	Rutaceae	**7**
		Sarcomelicope argyrophylla	Rutaceae	**7**
		Zanthoxylum ailanthoides	Rutaceae	**7**
10	Pteleine	*Acronychia baeuerlenii*	Rutaceae	**7**
		Comptonella sessilifoliola	Rutaceae	**7**
		Drummondita calida	Rutaceae	**7**
		Dutaillyea spp.	Rutaceae	**7**
		Haplophyllum thesioides	Rutaceae	**7**
		Medicosma cunninghamii	Rutaceae	**7**
		Melicope semecarpifolia, M. triphylla	Rutaceae	**11**
		Pitaviaster haplophyllus	Rutaceae	**17**
		Ruta chalepensis	Rutaceae	**7**
		Vepris nobilis	Rutaceae	**43**
		Zanthoxylum ailanthoides	Rutaceae	**7**
11	Melineurine	*Evodia lepta*	Rutaceae	**19**
		Pitaviaster haplophyllus	Rutaceae	**17**
12	Leptanoine D	*Melicope pteleifolia*	Rutaceae	**10**
13	Confusadine	*Melicope semecarpifolia*	Rutaceae	**20**
14	Haplopine	*Dictamnus albus*	Rutaceae	**8**
		Dutaillyea spp.	Rutaceae	**7**
		Haplophyllum acutifolium, H. bucharicum, H. cappadocicum, H. dauricum, H. latifolium, H. obtusifolium, H. patavinum, H. ramosissimum, H. robustum, H. thesioides	Rutaceae	**7**
		Helietta spp.	Rutaceae	**7**

		Melicope semecarpifolia	Rutaceae	**11**
		Skimmia reevesiana	Rutaceae	**7**
		Vepris suaveolens	Rutaceae	**7**
		Zanthoxylum ailanthoides, Z. beecheyanum, Z. nitidum, Z. rhoifolium, Z. scandens, Z. simulans	Rutaceae	**7**
15	Skimmianine	*Acronychia pedunculata*	Rutaceae	**7**
		Adiscanthus fusciflorus	Rutaceae	**7**
		Aegle marmelos	Rutaceae	**7**
		Agathosma bisulca, A. capensis	Rutaceae	**7**
		Almeidea rubra	Rutaceae	**7**
		Balfourodendron riedelianum	Rutaceae	**7**
		Boronia ternata	Rutaceae	**7**
		Casimiroa edulis	Rutaceae	**7**
		Clausena dunniana	Rutaceae	**7**
		Choisya ternata	Rutaceae	**35**
		Chorilaena quercifolia	Rutaceae	**7**
		Dictamnus albus	Rutaceae	**8**
		Drummondita calida, D. hassellii	Rutaceae	**7**
		Esenbeckia berlandieri, E. febrifuga, E. grandiflora, E. leiocarpa	Rutaceae	**7**
		Flindersia bennettiana, F. laevicarpa, F. maculosa	Rutaceae	**7**
		Geijera salicifolia	Rutaceae	**7**
		Glycosmis citrifolia, G. macrophylla, G. mauritiana, G.parviflora, G. pentaphylla, G.trichanthera	Rutaceae	**7**
		Haplophyllum acutifolium, H. bucharicum, H. bungei, H. buxbaumii, H. cappadocicum, H. dauricum, H. griffithianum, H. latifolium, H. myrtifolium, H. obtusifolium, H. patavinum, H. popovii, H. ramosissimum, H. robustum, H. thesioides, H. tuberculatum	Rutaceae	**7**
		Helietta apiculata	Rutaceae	**9**
		Hortia longifolia	Rutaceae	**7**

Leionema spp.	Rutaceae	**7**
Melicope madagascariensis, M. pteleifolia, M. quadrilocularis, M. semecarpifolia, M. triphylla, M. xanthoxyloides	Rutaceae	**7,10,11,21**
Metrodorea nigra	Rutaceae	**7**
Myrtopsis macrocarpa	Rutaceae	**7**
Nematolepis phebalioides	Rutaceae	**7**
Orixa japonica	Rutaceae	**7**
Peltostigma guatemalense	Rutaceae	**18**
Phebalium spp.	Rutaceae	**7**
Phellodendron amurense	Rutaceae	**7**
Philotheca brucei, P. thryptomenoides	Rutaceae	**7**
Pitavia punctata	Rutaceae	**7**
Pitaviaster haplophyllus	Rutaceae	**17**
Ptelea crenulata	Rutaceae	**7**
Raputia praetermissa	Rutaceae	**7**
Ruta angustifolia, R. chalepensis, R. corsica, R. graveolens, R. macrophylla	Rutaceae	**7,22**
Sarcomelicope simplicifolia	Rutaceae	**7**
Skimmia japonica	Rutaceae	**7**
Skimmia reevesiana	Rutaceae	**7**
Teclea afzelii, T. simplicifolia, T. trichocarpa	Rutaceae	**7**
Tetradium glabrifolium, T. ruticarpum	Rutaceae	**7**
Thamnosma montana	Rutaceae	**7**
Vepris lecomteana, V. nobilis, V. soyauxii, V. suaveolens	Rutaceae	**7**
Zanthoxylum ailanthoides, Z. asiaticum, Z. avicennae, Z. beecheyanum, Z. capense, Z. caribaeum, Z. coco, Z. culantrillo, Z. delagoense, Z. dimorphophyllum, Z. ekmanii, Z. fagara, Z. gilletii, Z. leprieurii, Z. mayu, Z. nitidum, Z. pistaciiflorum, Z. rhetsa, Z.	Rutaceae	**7,13,14,24,25,37**

		rhoifolium, Z. scandens, Z. schinifolium, Z. simulans, Z. tragodes, Z. viride, Z. wutaiense, Z. zanthoxyloides		
16	7-O-Isopentenyl-γ-fagarine	*Peltostigma guatemalense*	Rutaceae	**18**
17	Evoxine	*Dictamnus albus*	Rutaceae	**7**
		Dutaillyea spp.	Rutaceae	**7**
		Haplophyllum acutifolium, H. dubium, H. latifolium, H. obtusifolium, H. popovii, H. ramosissimum, H. suaveolens, H. tuberculatum	Rutaceae	**7**
		Choisya ternata	Rutaceae	**35**
		Orixa japonica	Rutaceae	**7**
		Peltostigma guatemalense	Rutaceae	**18**
		Skimmia reevesiana	Rutaceae	**7**
		Teclea gerrardii	Rutaceae	**7**
		Vepris lecomteana	Rutaceae	**12**
18	Anhydroevoxine	*Haplophyllum acutifolium*	Rutaceae	**7**
		Peltostigma guatemalense	Rutaceae	**18**
		Vepris lecomteana, V. nobilis	Rutaceae	**7**
19	Lecomtequinoline A	*Vepris lecomteana*	Rutaceae	**7**
20	Lecomtequinoline B	*Vepris lecomteana*	Rutaceae	**7**
21	Lecomtequinoline C	*Vepris lecomteana*	Rutaceae	**7**
22	Kokusaginine	*Acronychia baeuerlenii, A. pedunculata, A. pubescens*	Rutaceae	**7**
		Balfourodendron riedelianum	Rutaceae	**7**
		Clausena dunniana	Rutaceae	**7**
		Dictamnus albus	Rutaceae	**8**
		Esenbeckia almawillia, E. berlandieri, E. febrifuga, E. grandifolia, E. leiocarpa	Rutaceae	**7,23**
		Euodia spp.	Rutaceae	**7**
		Flindersia maculosa	Rutaceae	**7**
		Glycosmis mauritiana, G. pentaphylla	Rutaceae	**7**
		Halfordia kendack	Rutaceae	**7**

		Haplophyllum buxbaumii, H. obtusifolium, H. suaveolens, H. thesioides	Rutaceae	**7**
		Helietta apiculata	Rutaceae	**9**
		Choisya ternata	Rutaceae	**35**
		Melicope pteleifolia, M. semecarpifolia, M. triphylla	Rutaceae	**7,10,11**
		Peltostigma guatemalense	Rutaceae	**18**
		Phebalium spp.	Rutaceae	**7**
		Pitaviaster haplophyllus	Rutaceae	**17**
		Ptelea trifoliata	Rutaceae	**7**
		Ruta graveolens, R. chalepensis	Rutaceae	**7**
		Sarcomelicope simplicifolia	Rutaceae	**7**
		Teclea afzelii	Rutaceae	**23**
		Tinospora crispa, T. malabarica	Menispermaceae	**7**
		Vepris nobilis, V. suaveolens	Rutaceae	**7,26**
23	Nkolbisine (montrifoline)	*Haplophyllum thesioides*	Rutaceae	**7**
		Oricia suaveolens	Rutaceae	**27**
		Teclea nobilis, T. simplicifolia	Rutaceae	**7,23**
		Vepris nobilis, V. simplicifolia, V. suaveolens	Rutaceae	**7**
24	Acronycidine	*Medicosma fareana, M. semecarpifolia,*	Rutaceae	**7,11**
		Sarcomelicope argyrophylla, S. megistophylla, S. simplicifolia	Rutaceae	**7,8,28**
25	Platydesmine	*Dictamnus albus*	Rutaceae	**8**
		Geijera salicifolia	Rutaceae	**7**
		Haplophyllum griffithianum	Rutaceae	**7**
		Melicope semecarpifolia	Rutaceae	**11**
		Zanthoxylum ailanthoides, Z. schinifolium, Z. simulans	Rutaceae	**7**
26	N-Methylplatydesminium	*Pitaviaster haplophyllus*	Rutaceae	**17**
		Ruta graveolens	Rutaceae	**29**
27	(+-)-8-Methoxyplatydesmine	*Melicope semecarpifolia*	Rutaceae	**30**

28	(S)-(-)-7,8-Dimethoxyplatydesmine	*Dictamnus albus*	Rutaceae	**8**
		Melicope semecarpifolia	Rutaceae	**11**
29	(+)-7,8-Dimethoxymyrtopsine	*Dictamnus albus*	Rutaceae	**8**
		Melicope semecarpifolia	Rutaceae	**11**
30	Melicarpinone	*Melicope semecarpifolia*	Rutaceae	**31**
31	5-Hydroxy-4,8-dimethoxy furoquinoline	*Dictamnus albus*	Rutaceae	**8**
		Melicope semecarpifolia	Rutaceae	**11**
32	Megistoquinone I	*Sarcomelicope megistophylla*	Rutaceae	**28**
33	Maculine	*Esenbeckia berlandieri, E. grandifolia, E. leiocarpa*	Rutaceae	**7,23**
		Flindersia bennettiana, F. dissosperma, F. maculosa, F. xanthoxyla	Rutaceae	**7**
		Helietta apiculata	Rutaceae	**9**
		Vepris nobilis, V. soyauxii, V. suaveolens	Rutaceae	**7,43**
34	Flindersiamine	*Balfourodendron riedelianum*	Rutaceae	**7**
		Esenbeckia berlandieri, E. febrifuga, E. grandiflora, E. leiocarpa, E. leiocarpa	Rutaceae	**7**
		Flindersia bennettiana, F. collina, F. dissosperma, F. maculosa, F. xanthoxyla	Rutaceae	**7**
		Helietta apiculata	Rutaceae	**9**
		Metrodorea flavida	Rutaceae	**7**
		Nematolepis phebalioides	Rutaceae	**7**
		Raulinoa echinata	Rutaceae	**7**
		Teclea afzelii, T. natalensis	Rutaceae	**7**
		Vepris nobilis, V. suaveolens, V. uguenensis	Rutaceae	**7,43**
35	7-(3-Anilino-2-hydroxyprenyloxy)-8-methoxydictamine	*Vepris lecomteana*	Rutaceae	**32**
36	5-Methoxydictamnine	*Toddalia asiatica*	Rutaceae	**33**
37	Dimethyl rhoifolinate	*Melicope semecarpifolia*	Rutaceae	**34**
38	Dutadrupine	*Almeidea coerulea*	Rutaceae	**7**
		Comptonella sessilifoliola	Rutaceae	**7**

		Dutaillyea spp.	Rutaceae	**7**
		Melicope semecarpifolia	Rutaceae	**7**
39	Semecarpine	*Melicope semecarpifolia*	Rutaceae	**7**
40	Choisyine	*Choisya ternata*	Rutaceae	**35**
41	Melicarpine	*Melicope semecarpifolia*	Rutaceae	**34**
42	Megistoquinone II	*Sarcomelicope megistophylla*	Rutaceae	**28**
43	Zanthonitidine A	*Zanthoxylum nitidum*	Rutaceae	**16**
44	Isodictamnine	*Boronia inornata*	Rutaceae	**7**
		Dictamnus albus	Rutaceae	**15**
		Glycosmis pentaphylla	Rutaceae	**7**
		Zanthoxylum avicennae	Rutaceae	**37**
45	Acrophylline	*Pitaviaster haplophyllus*	Rutaceae	**17**
		Sarcomelicope simplicifolia	Rutaceae	**7**
46	(S)-(+)-Isoplatydesmine	*Boronia pancheri*	Rutaceae	**7**
		Haplophyllum patavinum	Rutaceae	**7**
		Melicope barbigera, M. semecarpifolia	Rutaceae	**7**
		Teclea simplicifolia	Rutaceae	**7**
		Vepris nobilis, V. simplicifolia, V. soyauxii	Rutaceae	**7,43**
		Zanthoxylum nitidum, Z. tingoassuiba	Rutaceae	**7**
47	Balfouridine	*Buxus sempervirens*	Buxaceae	**36**
48	Lemobiline	*Flindersia ifflaiana*	Rutaceae	**36**
QUINOLONES				
49	4-methoxy-N-methyl-2- quinolone	*Andreadoxa flava*	Rutaceae	**7**
		Casimiroa edulis	Rutaceae	**7**
		Clausena vestita	Rutaceae	**7**
		Drummondita calida	Rutaceae	**7**
		Euodia spp.	Rutaceae	**7**
		Haplophyllum dauricum	Rutaceae	**7**

		Helietta apiculata	Rutaceae	**9**
		Hortia longifolia	Rutaceae	**7**
		Limonia acidissima	Rutaceae	**7**
		Melicope lunu-ankenda	Rutaceae	**7**
		Naringi crenulata	Rutaceae	**7**
		Raputia praetermissa	Rutaceae	**7**
		Ruta chalepensis, R. montana	Rutaceae	**7**
		Tetradium glabrifolium	Rutaceae	**7**
		Toddalia spp.	Rutaceae	**7**
		Zanthoxylum ailanthoides, Z. avicennae, Z. nitidum, Z. schinifolium, Z. wutaiense	Rutaceae	**7,16**
50	Edulitine	*Angelica edulis*	Apiaceae	**7**
		Casimiroa edulis	Rutaceae	**7**
		Cnidium monnieri	Apiaceae	**7**
		Glycosmis pentaphylla	Rutaceae	**7**
		Haplophyllum bungei, H. dauricum, H. griffithianum, H.robustum	Rutaceae	**7**
		Limonia acidissima	Rutaceae	**7**
		Murraya exotica, M. paniculata	Rutaceae	**7**
		Zanthoxylum ailanthoides, Z. avicennae, Z. simulans	Rutaceae	**7,37**
51	Lunacridine	*Lunasia amara*	Rutaceae	**36**
52	2′-O-trifluoroacetyl lunacridine	*Lunasia amara*	Rutaceae	**38**
53	Glycocitridine	*Glycosmis citrifolia, G. parviflora*	Rutaceae	**7**
		Melicope semecarpifolia	Rutaceae	**34**
54	Melisemine	*Melicope semecarpifolia*	Rutaceae	**34**
55	Edulinine	*Boronia pancheri*	Rutaceae	**7**
		Haplophyllum griffithianum, H. patavinum	Rutaceae	**7**
		Melicope semecarpifolia	Rutaceae	**34**
		Teclea simplicifolia	Rutaceae	**7**

		Vepris nobilis, V. simplicifolia	Rutaceae	**7**
		Zanthoxylum mayu, Z. nitidum	Rutaceae	**7**
56	Flindersine	*Flindersia australis*	Rutaceae	**7**
		Glycosmis parviflora	Rutaceae	**7**
		Haplophyllum acutifolium, H. bucharicum, H. suaveolens, H. thesioides, H. tuberculatum	Rutaceae	**7**
		Helietta apiculata	Rutaceae	**7**
		Micromelum minutum	Rutaceae	**7**
		Toddalia asiatica	Rutaceae	**39**
		Zanthoxylum beecheyanum, Z. coco, Z. holtzianum, Z. chalybeum, Z. nitidum, Z. simulans, Z. zanthoxyloides	Rutaceae	**7**
57	Veprisine	*Pitaviaster haplophyllus*	Rutaceae	**17**
		Rauia resinosa	Rutaceae	**7**
		Vepris louisii, V. soyauxii, V. stolzii	Rutaceae	**7**
58	Zanthodioline	*Zanthoxylum beecheyanum, Z. nitidum, Z. rhetsa, Z. simulans*	Rutaceae	**7,14,16**
59	Melicodenine C	*Melicope denhamii*	Rutaceae	**40**
60	Melicodenine F	*Melicope denhamii*	Rutaceae	**40**
61	Melicodenine G	*Melicope denhamii*	Rutaceae	**40**
62	Vepridimerine A	*Oricia renieri*	Rutaceae	**41**
		Vepris louisii	Rutaceae	**41**
63	Melicodenine H	*Melicope denhamii*	Rutaceae	**40**
64	Evocarpine	*Tetradium ruticarpum*	Rutaceae	**42**
65	Graveoline (graveolinine)	*Haplophyllum acutifolium, H. dubium, H. griffithianum*	Rutaceae	**7**
		Lunasia amara	Rutaceae	**7**
		Ruta angustifolia, R. graveolens, R. chalepensis	Rutaceae	**7,22**
66	Ribalinine	*Balfourodendron riedelianum*	Rutaceae	**7**
		Haplophyllum bucharicum, H. patavinum	Rutaceae	**7**
		Teclea simplicifolia	Rutaceae	**7**

		Vepris nobilis, V. simplicifolia, V. soyauxii	Rutaceae	**7,43**
		Zanthoxylum mayu, Z. nitidum	Rutaceae	**7**
67	Rutaecarpine	*Bouchardatia neurococca*	Rutaceae	**7**
		Hortia oreadica	Rutaceae	**7**
		Phellodendron amurense, P. chinense	Rutaceae	**7**
		Rutaceae spp.	Rutaceae	**7**
		Tetradium glabrifolium, T. ruticarpum, Z. dimorphophyllum, Z. pistaciiflorum, Z. wutaiense	Rutaceae	**7,13,42**
68	1-Hydroxyrutaecarpine	*Bouchardatia neurococca*	Rutaceae	**7**
		Tetradium glabrifolium	Rutaceae	**7**
		Zanthoxylum dimorphophyllum, Z. pistaciiflorum	Rutaceae	**7,13**
69	Evodiamine	*Euodia spp.*	Rutaceae	**7**
		Phellodendron chinense	Rutaceae	**7**
		Tetradium ruticarpum	Rutaceae	**42**
INDOLOQUINOLINES				
70	Quindoline	*Cryptolepis sanguinolenta*	Apocynaceae	**44**
		Justicia betonica	Acanthaceae	**7**
		Sida acuta, S. rhombifolia	Malvaceae	**45**
71	Cryptolepine	*Cryptolepis sanguinolenta*	Apocynaceae	**47**
		Micropholis guyanensis	Sapotaceae	**7**
		Sida acuta, S. cordifolia, S. rhombifolia	Malvaceae	**7**
72	Hydroxycryptolepine	*Cryptolepis sanguinolenta*	Apocynaceae	**44**
		Sida acuta	Malvaceae	**7**
73	Neocryptolepine	*Cryptolepis sanguinolenta*	Apocynaceae	**47**
74	Biscryptolepine	*Cryptolepis sanguinolenta*	Apocynaceae	**47**
75	Cryptoquindoline	*Cryptolepis sanguinolenta*	Apocynaceae	**44**
76	Camptothecin	*Camptotheca acuminata*	Cornaceae	**48**
		Didymochlaena truncatula	Hypodematiaceae	**7**

		Ervatamia heyneana	Apocynaceae	**48**
		Mappia foetida	Icacinaceae	**7**
		Merrilliodendron megacarpum	Icacinaceae	**48**
		Mostuea thomsonii	Loganiaceae	**49**
		Nothapodytes foetida, N. nimmoniana	Icacinaceae	**7,48**
		Ophiorrhiza kuroiwae, O. liukiuensis, O. mungos, O. pumila, O. rugosa	Rubiaceae	**7,48**
		Pyrenacantha klaineana	Icacinaceae	**7**
		Rinorea anguifera	Violaceae	**7**
		Tabernaemontana divaricata	Apocynaceae	**50**
77	Thomsonine B	*Mostuea thomsonii*	Loganiaceae	**49**
SIMPLE ISOQUINOLINES				
78	Thalifoline	*Hernandia nymphaezfoli*	Hernandiaceae	**51**
79	Northalifoline	*Hernandia nymphaezfoli*	Hernandiaceae	**51**
SIMPLE BENYZLISOQUINOLINES				
80	Coclaurine	*Aniba canelilla*	Lauraceae	**7**
		Annona muricata	Annonaceae	**52**
		Aristolochia gigantea	Aristolochiaceae	**7**
		Cissampelos pareira	Menispermaceae	**53**
		Clematis parviloba	Ranunculaceae	**7**
		Cocculus hirsutus, C. laurifolius	Menispermaceae	**7**
		Coptis japonica	Ranunculaceae	**7**
		Cryptocarya concinna	Lauraceae	**7**
		Cyclea barbata	Menispermaceae	**7**
		Damburneya salicifolia	Lauraceae	**7**
		Delphinium pentagynum	Ranunculaceae	**7**
		Erythrina crista-galli	Fabaceae	**7**
		Fumaria parviflora, F. vaillantii	Papaveraceae	**7,155,156**

		Gnetum montanum	Gnetaceae	**7**
		Magnolia salicifolia	Magnoliaceae	**7**
		Monodora junodii	Annonaceae	**7**
		Monoon borneense	Annonaceae	**7**
		Ocotea fasciculata	Lauraceae	**7**
		Pachygone ovata	Menispermaceae	**7**
		Phaeanthus ophthalmicus	Annonaceae	**7**
		Roemeria refracta	Papaveraceae	**7**
		Romneya coulteri	Papaveraceae	**7**
		Stephania excentrica, S. pierrei	Menispermaceae	**7**
		Xylopia parviflora	Annonaceae	**7**
		Ziziphus jujuba, Z. mauritiana	Rhamnaceae	**7**
81	Reticuline	*Aconitum seravschanicum*	Ranunculaceae	**7**
		Aniba canelilla	Lauraceae	**7**
		Annona emarginata, A.glabra, A.cherimola, A. muricata, A. purpurea, A. reticulata, A. salzmannii	Annonaceae	**7,52,54**
		Argemone albiflora, A. mexicana, A. ochroleuca, A. platyceras	Papaveraceae	**7,55,56**
		Aristolochia gigantea	Aristolochiaceae	**7**
		Artabotrys hexapetalus, A. monteiroae, A. venustus	Annonaceae	**7,57**
		Berberis aristata, B. heteropoda, B. integerrima, B. nummularia, B. petiolaris, B. stolonifera	Berberidaceae	**7,58,59**
		Bongardia chrysogonum	Berberidaceae	**7**
		Ceratocapnos claviculata	Papaveraceae	**7**
		Cissampelos capensis	Menispermaceae	**7**
		Clematis parviloba	Ranunculaceae	**7**
		Coptis japonica	Ranunculaceae	**7**
		Corydalis taliensis	Papaveraceae	**7**
		Croton celtidifolius, C. hemiargyreus, C. linearis	Euphorbiaceae	**7,60**

Cymbopetalum brasiliense	Annonaceae	**7**
Damburneya salicifolia	Lauraceae	**7**
Dehaasia hainanensis	Lauraceae	**7**
Delphinium pentagynum	Ranunculaceae	**7**
Dicentra peregrina	Papaveraceae	**7**
Erythrina variegata	Fabaceae	**7**
Eschscholzia californica	Papaveraceae	**7**
Fumaria capreolata, F. vaillantii	Papaveraceae	**7,156**
Glaucium corniculatum, G. fimbrilligerum, G. flavum	Papaveraceae	**7**
Glossocalyx brevipes	Siparunaceae	**7**
Greenwayodendron oliveri	Annonaceae	**7**
Guatteria juruensis	Annonaceae	**7**
Gyrocarpus americanus	Hernandiaceae	**7**
Hernandia cordigera, H. nymphaeifolia	Hernandiaceae	**7,51**
Hypserpa nitida	Menispermaceae	**7**
Isopyrum thalictroides	Ranunculaceae	**7**
Laureliopsis philippiana	Atherospermataceae	**7**
Laurus nobilis	Lauraceae	**7**
Leontice leontopetalum	Berberidaceae	**7**
Leptadenia reticulata	Apocynaceae	**7**
Lindera aggregata, L. glauca, L. megaphylla, L. cubeba, L. elliptica, L. lancifolia	Lauraceae	**7**
Magnolia biondii	Magnoliaceae	**7**
Magnolia obovata, M. officinalis, M. salicifolia	Magnoliaceae	**7**
Miliusa velutina	Annonaceae	**7**
Monocyclanthus vignei	Annonaceae	**7**
Monodora junodii	Annonaceae	**7**
Neolitsea aciculata, N. acuminatissima, N. konishii	Lauraceae	**7**

		Ocotea velloziana	Lauraceae	**7**
		Pachygone ovata	Menispermaceae	**7**
		Papaver somniferum	Papaveraceae	**7**
		Peumus boldus	Monimiaceae	**7**
		Phoebe formosana	Lauraceae	**7**
		Siparuna brasiliensis	Siparunaceae	**7**
		Stephania cephalantha, S. pierrei, S. venosa, S. viridiflavens	Menispermaceae	**7**
		Thalictrum foliolosum	Ranunculaceae	**7**
		Uvaria dulcis	Annonaceae	**7**
		Xylopia parviflora	Annonaceae	**7**
		Zanthoxylum rhetsa	Rutaceae	**14**
82	Laudanosine	*Berberis heteropoda, B. nummularia*	Berberidaceae	**7**
		Cissampelos pareira	Menispermaceae	**7**
		Croton linearis	Euphorbiaceae	**60**
		Glaucium flavum	Papaveraceae	**7**
		Guatteria amplifolia	Papaveraceae	**7**
		Hazomalania voyronii	Hernandiaceae	**7**
		Papaver macrostomum, P. somniferum	Papaveraceae	**7**
83	Papaverine	*Papaver somniferum, P. armeniacum, P. commutatum, P. rhoeas, P. triniifolium*	Papaveraceae	**7,61**
		Sauropus androgynus	Phyllanthaceae	**7**
84	Oblongine	*Cissampelos pareira*	Menispermaceae	**53**
		Berberis petiolaris, B. heteropoda, B. integerrima	Berberidaceae	**7,59**
		Cyrtanthus obliquus	Amaryllidaceae	**7**
		Leontice leontopetalum	Berberidaceae	**7**
		Stephania cephalantha, S. tetrandra	Menispermaceae	**7**
		Tiliacora funifera	Menispermaceae	**7**
		Xylopia parviflora	Annonaceae	**7**

		Zanthoxylum gilletii, Z. chalybeum, Z. usambarense	Rutaceae	**7**
85	Hexapetaline A	*Artabotrys hexapetalus*	Annonaceae	**57**
86	Hexapetaline B	*Artabotrys hexapetalus*	Annonaceae	**57**
87	Cularine	*Ceratocapnos claviculata*	Papaveraceae	**7**
		Ceratocapnos heterocarpa [*Corydalis*]	Papaveraceae	**7**
		Croton linearis	Euphorbiaceae	**60**
		Papaver rhoeas	Papaveraceae	**7**
		Sarcocapnos baetica, S. crassifolia, S. enneaphylla, S. saetabensis	Papaveraceae	**7**
88	Thalicfoetine	*Thalictrum foetidum*	Ranunculaceae	**62**
BISBENZYLISOQUINOLINES				
89	Costaricine	*Damburneya salicifolia*	Lauraceae	**7**
		Lindera aggregata	Lauraceae	**63**
90	Neferine	*Nelumbo nucifera*	Nelumbonaceae	**64**
91	O-Methylneferine	*Nelumbo nucifera*	Nelumbonaceae	**64**
92	Isoliensinine	*Nelumbo nucifera*	Nelumbonaceae	**65**
93	Cycleanine	*Albertisia villosa*	Menispermaceae	**66**
		Chondrodendron tomentosum	Menispermaceae	**7**
		Cissampelos capensis, C. pareira	Menispermaceae	**7,67**
		Cyclea tonkinensis	Menispermaceae	**7**
		Epinetrum villosum	Menispermaceae	**68**
		Heracleum wallichii	Apiaceae	**7**
		Stephania cephalantha, S. elegans, S. pierrei, S. rotunda, S. tetrandra	Menispermaceae	**7,69**
94	N-Desmethylcycleanine	*Albertisia villosa*	Menispermaceae	**66**
		Stephania glabra, S. pierrei, S. rotunda	Menispermaceae	**7,70**
95	Isochondodendrine	*Chondrodendron tomentosum*	Menispermaceae	**7**
		Cissampelos pareira	Menispermaceae	**67**
		Curarea candicans, C. tecunarum, C. toxicofera	Menispermaceae	**7**
		Cyclea barbata	Menispermaceae	**7**

		Epinetrum villosum	Menispermaceae	**68**
		Isolona ghesquierei	Annonaceae	**7**
		Stephania elegans	Menispermaceae	**7**
96	Cycleanine N-oxide	*Epinetrum villosum*	Menispermaceae	**68**
97	Tetrandrine	*Cissampelos pareira*	Menispermaceae	**53**
		Cocculus pendulus	Menispermaceae	**7**
		Cyclea barbata	Menispermaceae	**7**
		Isopyrum thalictroides	Ranunculaceae	**7**
		Menispermum dauricum	Menispermaceae	**7**
		Pachygone dasycarpa	Menispermaceae	**7**
		Stemona japonica	Stemonaceae	**7**
		Stephania tetrandra	Menispermaceae	**71**
		Strychnopsis thouarsii	Menispermaceae	**7**
		Thalictrum spp.	Ranunculaceae	**7**
		Triclisia subcordata	Menispermaceae	**7**
98	Isotetrandrine	*Atherosperma moschatum*	Atherospermataceae	**7**
		Berberis aquifolium, B. bealei, B. crataegina, B. duclouxiana, B. japonica, B. napaulensis, B. stolonifera, B. vulgaris	Berberidaceae	**7**
		Stephania erecta, S. pierrei	Menispermaceae	**7**
		Xylopia aethiopica	Annonaceae	**72**
99	Berbamine	*Atherosperma moschatum*	Atherospermataceae	**7**
		Berberis amurensis, B. angulosa, B. aquifolium, B. aristata, B. bealei, B. brachypoda, B. canadensis, B. circumserrata, B. crataegina, B. cretica, B. dasystachya, B. diaphana, B. dubia, B. empetrifolia, B. ferdinandi-coburgii, B. gyalaica, B. heteropoda, B. integerrima, B. japonica, B. julianae, B. kansuensis, B. lycium, B. nummularia, B. orthobotrys, B. poiretii, B. prattii, B. sargentiana, B. sibirica, B. silva-taroucana, B. soulieana, B. stolonifera, B. thunbergii, B. vernae, B. virgetorum, B. vulgaris	Berberidaceae	**7,58,73**

		Dehaasia incrassata	Lauraceae	**7**
		Pycnarrhena novoguineensis	Menispermaceae	**7**
		Stephania cephalantha	Menispermaceae	**7**
		Thalictrum spp.	Ranunculaceae	**7**
100	Fangchinoline	*Cyclea barbata*	Menispermaceae	**7**
		Isopyrum thalictroides	Ranunculaceae	**7**
		Pachygone dasycarpa	Menispermaceae	**7**
		Stephania hernandifolia	Menispermaceae	**7**
		Stephania japonica	Menispermaceae	**7**
		Stephania rotunda	Menispermaceae	**7**
		Stephania tetrandra	Menispermaceae	**74**
		Strychnopsis thouarsii	Menispermaceae	**7**
101	Obaberine	*Berberis cretica*	Berberidaceae	**7**
		Berberis fendleri	Berberidaceae	**7**
		Berberis iliensis	Berberidaceae	**7**
		Berberis integerrima	Berberidaceae	**7**
		Berberis laurina	Berberidaceae	**7**
		Berberis nummularia	Berberidaceae	**7**
		Berberis repens	Berberidaceae	**7**
		Berberis vulgaris	Berberidaceae	**7**
		Cissampelos pareira	Menispermaceae	**53**
		Daphnandra johnsonii	Atherospermataceae	**7**
		Dehaasia incrassata	Lauraceae	**7**
		Laurelia sempervirens	Atherospermataceae	**7**
		Pycnarrhena longifolia	Menispermaceae	**7**
		Stephania cephalantha	Menispermaceae	**7**
		Stephania corymbosa	Menispermaceae	**7**
		Stephania erecta	Menispermaceae	**7**

		Stephania pierrei	Menispermaceae	**7**
		Thalictrum cultratum	Ranunculaceae	**7**
		Thalictrum lucidum	Ranunculaceae	**7**
		Thalictrum minus	Ranunculaceae	**7**
102	Homoaromoline	*Abuta rufescens*	Menispermaceae	**7**
		Berberis laurina	Berberidaceae	**7**
		Cissampelos pareira	Menispermaceae	**53**
		Cyclea barbata	Menispermaceae	**7**
		Dehaasia incrassata	Lauraceae	**7**
		Pycnarrhena longifolia	Menispermaceae	**7**
		Stephania cephalantha	Menispermaceae	**7**
		Stephania erecta	Menispermaceae	**7**
		Stephania excentrica	Menispermaceae	**7**
		Stephania pierrei	Menispermaceae	**7**
		Stephania venosa	Menispermaceae	**7**
		Thalictrum foliolosum	Ranunculaceae	**7**
		Thalictrum minus	Ranunculaceae	**7**
103	Thalrugosaminine	*Thalictrum minus*	Ranunculaceae	**75**
104	Cocsoline	*Albertisia villosa*	Menispermaceae	**66**
		Cocculus pendulus	Menispermaceae	**7**
		Epinetrum villosum	Menispermaceae	**68**
105	Thalmidine (O-Methylthalicberine)	*Thalictrum aquilegiifolium*	Ranunculaceae	**7**
		Thalictrum cultratum	Ranunculaceae	**7**
		Thalictrum foetidum	Ranunculaceae	**7**
		Thalictrum lucidum	Ranunculaceae	**7**
		Thalictrum minus	Ranunculaceae	**75**
106	5′-Hydroxythalidasine	*Thalictrum cultratum*	Ranunculaceae	**7**
		Thalictrum minus	Ranunculaceae	**75**

107	Thalrugosidine	*Thalictrum rugosum*	Ranunculaceae	**76**
108	Northalrugosidine	*Thalictrum alpinum*	Ranunculaceae	**76**
109	Thalidasine	*Thalictrum dasycarpum*	Ranunculaceae	**76**
110	Bersavine	*Berberis vulgaris*	Berberidaceae	**73**
111	Cepharanthine	*Stephania cephalantha*	Menispermaceae	**7**
		Stephania corymbosa	Menispermaceae	**7**
		Stephania epigaea	Menispermaceae	**77**
		Stephania erecta	Menispermaceae	**7**
		Stephania pierrei	Menispermaceae	**7**
		Stephania sinica	Menispermaceae	**7**
		Stephania suberosa	Menispermaceae	**7**
112	(+)-2-Norcepharanthine	*Stephania epigaea*	Menispermaceae	**77**
113	Fangchinoline	*Stephania epigaea*	Menispermaceae	**77**
114	Tiliarine	*Tiliacora racemosa*	Menispermaceae	**78**
115	2′-nortiliacorinine	*Tiliacora racemosa*	Menispermaceae	**78**
116	Neothalfine	*Thalictrum delavayi*	Ranunculaceae	**79**
PROTOBERBERINES				
117	Columbamine	*Anamirta cocculus*	Menispermaceae	**7**
		Berberis aggregata, B. amurensis, B. aquifolium, B. bealei, B. brevissima, B. canadensis, B. crataegina, B. cretica, B. gagnepainii, B. heteropoda, B. integerrima, B. japonica, B. nummularia, B. parkeriana, B. petiolaris, B. poiretii, B. pruinosa, B. repens, B. sibirica, B. stolonifera, B. thunbergii, B. vulgaris, B. wilsoniae	Berberidaceae	**7,59**
		Burasaia madagascariensis	Menispermaceae	**7**
		Chasmanthera dependens	Menispermaceae	**7**
		Coptis chinensis, C. deltoidea, C. japonica, C. quinquefolia, C. teeta	Ranunculaceae	**7,81,82**
		Corydalis ophiocarpa, C. turtschaninovii, C. yanhusuo	Papaveraceae	**7**
		Dioscoreophyllum cumminsii	Menispermaceae	**7**
		Fibraurea chloroleuca, F. tinctoria	Menispermaceae	**7**

		Glaucium fimbrilligerum	Papaveraceae	**7**
		Haematocarpus subpeltatus	Menispermaceae	**7**
		Isopyrum thalictroides	Ranunculaceae	**7**
		Nandina domestica	Berberidaceae	**7**
		Ranunculus serbicus	Ranunculaceae	**7**
		Stephania glabra	Menispermaceae	**70**
		Thalictrum alpinum, T. cultratum, T. foliolosum, T. javanicum, T. lankesteri, T. lucidum, T. minus, T. podocarpum, T. revolutum	Ranunculaceae	**7**
		Thalictrum tuberosum	Ranunculaceae	**7**
		Tinospora capillipes	Menispermaceae	**7**
		Zanthoxylum rhetsa	Rutaceae	**14**
118	Jatrorrhizine	*Stephania glabra*	Menispermaceae	**70**
		Coptis japonica, C. chinensis, C. deltoidea, C. teeta	Ranunculaceae	**81,82**
		Berberis iliensis, B. aristata, B. brevissima, B. parkeriana	Berberidaceae	**58,80,83**
		Tinospora capillipes	Menispermaceae	**84**
119	Palmatine	*Albizia adianthifolia*	Fabaceae	**85**
		Anamirta cocculus	Menispermaceae	**7**
		Annickia affinis, A. chlorantha	Annonaceae	**7**
		Annona glabra	Annonaceae	**7**
		Arcangelisia flava	Menispermaceae	**7**
		Berberis aggregata, B. amurensis, B. aquifolium, B. aristata, B. asiatica, B. barandana, B. bealei,,B. bodinieri, B. canadensis, B. chitria, B. crataegina, B. cretica, B. diaphana, B. dubia, B. empetrifolia, B. fendleri, B. fortunei, B. gagnepainii, B. gracilipes, B. heteropoda, B. ilicifolia, B. iliensis, B. integerrima, B. japonica, B. julianae, B. laurina, B. lycium, B. morrisonensis, B. nummularia, B. poiretii, B. polyodonta, B. pruinose, B. repens, B. sibirica, B. silva-taroucana, B. stolonifera, B. thunbergia, B. vernae, B. vulgaris, B. wallichiana, B. wilsoniae	Berberidaceae	**7,58,83**
		Burasaia madagascariensis	Menispermaceae	**7**

Cocculus carolinus	Menispermaceae	**7**
Coptis deltoidea, C. chinensis, C. deltoidea, C. japonica, C. omeiensis, C. quinquefolia, C. teeta	Ranunculaceae	**7,86**
Corydalis balansae, C. cava, C. decumbens, C. intermedia, C. nobilis, C. pallida, C. solida, C. speciosa, C. turtschaninovii, C. yanhusuo	Papaveraceae	**7,87,88**
Dioscoreophyllum cumminsii	Menispermaceae	**7**
Enantia chlorantha	Annonaceae	**89**
Fibraurea chloroleuca, F. recisa, F. tinctoria, F. parviflora	Menispermaceae	**7,89**
Glaucium arabicum	Papaveraceae	**7**
Goniothalamus amuyon	Annonaceae	**7**
Guatteria citriodora	Annonaceae	**71**
Haematocarpus subpeltatus	Menispermaceae	**7**
Hydrastis canadensis	Ranunculaceae	**7**
Isopyrum thalictroides	Ranunculaceae	**7**
Mahonia bealei	Berberidaceae	**91**
Meconopsis cambrica	Papaveraceae	**7**
Nandina domestica	Berberidaceae	**7**
Papaver atlanticum, P. bracteatum, P. nudicaule, P. orientale, P. tatricum	Papaveraceae	**7**
Parabaena sagittata	Menispermaceae	**7**
Penianthus zenkeri	Menispermaceae	**7**
Phellodendron amurense, P. chinense	Rutaceae	**7,88**
Ranunculus serbicus	Ranunculaceae	**7**
Rhigiocarya racemifera	Menispermaceae	**7**
Sphenocentrum jollyanum	Menispermaceae	**7**
Stephania cephalantha, S. glabra, S. lincangensis, S. rotunda, S. yunnanensis	Menispermaceae	**7,69,70,88**
Thalictrum alpinum, T. atriplex, T. cultratum, T. foliolosum, T. javanicum, T. lankesteri, T. minus, T. petaloideum, T. podocarpum, T. simplex	Ranunculaceae	**7**

		Tinospora baenzigeri, T. capillipes, T. cordifolia, T. crispa, T. glabra, T. malabarica, T. sagittata, T. sinensis, T. smilacina	Menispermaceae	**7,88**
		Xylopia parviflora	Annonaceae	**7**
		Zanthoxylum chalybeum, Z. coco	Rutaceae	**7**
120	Berberine	*Achyranthes bidentata, A. japonica*	Amaranthaceae	**7**
		Anamirta cocculus	Menispermaceae	**7**
		Andira inermis	Fabaceae	**7**
		Annickia spp.	Annonaceae	**7**
		Annona mucosa	Annonaceae	**7**
		Aquilegia alpina, A. atrata, A. buergeriana, A. canadensis, A. chrysantha, A. coerulea, A. eximia, A. formosa, A. jonesii, A. oxysepala, A. skinneri, A. viridiflora	Ranunculaceae	**7**
		Arcangelisia flava, A. gusanlung	Menispermaceae	**7**
		Argemone albiflora, A. grandiflora, A. mexicana, A. ochroleuca, A. platyceras, A. subfusiformis	Papaveraceae	**7,56,92**
		Berberis aetnensis, B. aggregata, B. amurensis, B. aquifolium, B. aristata, B. barandana, B. bealei, B. bodinieri, B. brevissima, B. buxifolia, B. canadensis, B. candidula, B. chitria, B. crataegina, B. cretica, B. darwinii, B. diaphana, B. dictyophylla, B. dubia, B. duclouxiana, B. empetrifolia, B. fendleri, B. fortunei, B. gagnepainii, B. gracilipes, B. heteropoda, B. ilicifolia, B. iliensis, B. ntegerrima, B. japonica, B. julianae, B. kawakamii, B. laurina, B. lycium, B. microphylla, B. mingetsensis, B. morrisonensis, B. napaulensis, B. nervosa, B. nummularia, B. parkeriana, B. philippinensis, B. poiretii, B. polyodonta, B. pruinosa, B. repens, B. sibirica, B. silva-taroucana, B. soulieana, B. stolonifera, B. swaseyi, B. thunbergii, B. vernae, B. verruculosa, B. virgetorum, B. vulgaris, B. wilsoniae	Berberidaceae	**7,80,83,93,94**
		Burasaia madagascariensis	Menispermaceae	**7**
		Capnoides sempervirens	Papaveraceae	**7**
		Chelidonium majus	Papaveraceae	**95**
		Cissampelos pareira	Menispermaceae	**67**

Coptis chinensis, C. deltoidea, C. japonica, C. omeiensis, C. quinquefolia, C. teeta	Ranunculaceae	**7,82,86**
Corydalis cheilanthifolia, C. intermedia, C. pallida, C. solida, C. speciosa, C. turtschaninovii, C. yanhusuo	Papaveraceae	**7,87**
Coscinium fenestratum	Menispermaceae	**7**
Dicranostigma lactucoides	Papaveraceae	**7**
Eschscholzia caespitosa, E. californica, E. lobbii	Papaveraceae	**7,96**
Festuca ovina, F. pratensis, F. rubra	Poaceae	**7**
Fibraurea tinctoria	Menispermaceae	**7**
Glaucium arabicum, G. corniculatum, G. squamigerum	Papaveraceae	**7**
Haematocarpus subpeltatus	Menispermaceae	**7**
Hunnemannia fumariifolia	Papaveraceae	**7**
Hydrastis canadensis	Ranunculaceae	**97**
Mahonia aquifolium	Berberidaceae	**98**
Meconopsis cambrica	Papaveraceae	**7**
Nandina domestica	Berberidaceae	**7**
Orixa japonica	Rutaceae	**7**
Papaver bracteatum, P. dubium, P. lapponicum, P. radicatum, P. rhoeas, P. somniferum	Papaveraceae	**7**
Parabaena sagittata	Papaveraceae	**7**
Penianthus zenkeri	Menispermaceae	**7**
Phellodendron amurense, P. chinense	Rutaceae	**97**
Pseudofumaria lutea	Papaveraceae	**7**
Sanguinaria canadensis	Papaveraceae	**7**
Stephania cephalantha, S. tetrandra	Menispermaceae	**7**
Stylophorum diphyllum, S. lasiocarpum	Papaveraceae	**7**
Thalictrum alpinum, T. aquilegiifolium, T. atriplex, T. baicalense, T. calabricum, T. cultratum, T. dasycarpum, T. delavayi, T. dioicum, T. elegans, T. fendleri, T. flavum, T. foetidum, T. foliolosum, T.	Ranunculaceae	**7**

		hernandezii, T. javanicum, T. lankesteri, T. lucidum, T. minus, T. petaloideum, T. podocarpum, T. przewalskii, T. revolutum, T. sachalinense, T. simplex, T. tuberosum		
		Tinospora baenzigeri, T. cordifolia, T. crispa, T. glabra, T. sinensis, T. smilacina	Menispermaceae	**7**
		Xanthorhiza simplicissima	Ranunculaceae	**99**
		Zanthoxylum coco, Z. monophyllum	Ranunculaceae	**7**
121	Dehydrocheilanthifoline	*Berberis brevissima, B. parkeriana*	Berberidaceae	**80**
122	Coptisine	*Aquilegia* spp.	Ranunculaceae	**7**
		Argemone albiflora, A. grandiflora, A. mexicana, A. ochroleuca, A. platyceras	Papaveraceae	**7,100**
		Berberis bealei, B. japonica	Berberidaceae	**7**
		Capnoides sempervirens	Papaveraceae	**7**
		Chelidonium majus	Papaveraceae	**95**
		Coptis chinensis, C. deltoidea, C. japonica, C. omeiensis, C. quinquefolia, C. teeta, C. trifolia	Ranunculaceae	**7,71,82**
		Corydalis adunca, C. cava, C. cheilanthifolia, C. dasyptera, C. decumbens, C. fumariifolia, C. incisa, C. intermedia, C. ledebouriana, C. nobilis, C. ophiocarpa, C. pallida, C. remota, C. repens, C. solida, C. turtschaninovii, C. yanhusuo	Papaveraceae	**7,87**
		Dicranostigma lactucoides	Papaveraceae	**7**
		Eschscholzia californica	Papaveraceae	**7**
		Fumaria agraria, F. barnolae, F. capreolata, F. densiflora, F. indica, F. judaica, F. muralis, F. officinalis, F. parviflora, F. petteri, F. sepium, F. vaillantii	Papaveraceae	**7,152,154,155,**
		Glaucium arabicum, G. squamigerum	Papaveraceae	**7**
		Hunnemannia fumariifolia	Papaveraceae	**7**
		Hypecoum erectum, H. leptocarpum, H. procumbens	Papaveraceae	**7**
		Meconopsis cambrica, M. robusta	Papaveraceae	**7**
		Nandina domestica	Berberidaceae	**7**

		Papaver alpinum, P. argemone, P. atlanticum, P. bracteatum, P. dubium, P. glaucum, P. kerneri, P. nudicaule, P. orientale, P. pavoninum, P. pygmaeum, P. rhoeas, P. rupifragum, P. somniferum, P. tatricum	Papaveraceae	**7**
		Platycapnos spicata	Papaveraceae	**7**
		Pseudofumaria lutea	Papaveraceae	**7**
		Sanguinaria canadensis	Papaveraceae	**7**
		Stylophorum diphyllum, S. lasiocarpum	Papaveraceae	**7**
		Thalictrum minus	Ranunculaceae	**7**
		Zanthoxylum nitidum	Rutaceae	**7**
123	Scoulerine	*Annona squamosa*	Annonaceae	**7**
		Argemone ochroleuca	Papaveraceae	**56**
		Berberis aquifolium, B. bealei	Berberidaceae	**7**
		Coptis japonica	Ranunculaceae	**7**
		Corydalis bungeana, C. caseana, C. cava, C. dubia, C. incisa, C. intermedia, C. nobilis, C. pallida, C. scouleri, C. solida, C. turtschaninovii, C. yanhusuo	Papaveraceae	**7,101**
		Fumaria densiflora, F. officinalis, F. vaillantii	Papaveraceae	**7,156**
		Lamprocapnos spectabilis	Papaveraceae	**7**
		Macleaya cordata	Papaveraceae	**7**
		Meconopsis cambrica	Papaveraceae	**7**
		Papaver armeniacum, P. bracteatum, P. orientale, P. rhoeas, P. somniferum, P. triniifolium	Papaveraceae	**7**
		Sarcocapnos saetabensis	Papaveraceae	**7**
124	Cyclanoline (syn. cissamine)	*Cissampelos pareira*	Menispermaceae	**53**
		Cyclea tonkinensis	Menispermaceae	**7**
		Macleaya cordata	Papaveraceae	**7**
		Stephania cephalantha, S. elegans, S. japonica, S. tetrandra	Menispermaceae	**7**
125	Isocoreximine	*Annona cherimola*	Annonaceae	**7**

		Guatteria blepharophylla, G. hispida	Annonaceae	**7,102**
126	11-Hydroxy-10-methoxy-(2,3)-methylenedioxytetrahydroprotoberberine	*Toddalia asiatica*	Rutaceae	**33**
127	(2,3,10,11)-Dimethylenedioxytetrahydroprotoberberine	*Toddalia asiatica*	Rutaceae	**33**
128	Pendulamine A	*Polyalthia longifolia var. pendula*	Annonaceae	**103**
129	Pendulamine B	*Polyalthia longifolia var. pendula*	Annonaceae	**103**
130	8-Oxoberberine (oxyberberine)	*Arcangelisia gusanlung*	Menispermaceae	**7**
		Berberis actinacantha, B. amurensis, B. aquifolium, B. bealei, B. brevissima, B. buxifolia, B. cretica, B. darwinii, B. empetrifolia, B. japonica, B. lycium, B. microphylla, B. parkeriana, B. petiolaris, B. vulgaris	Berberidaceae	**7,80**
		Coptis japonica, C. teeta	Ranunculaceae	**7,80**
		Coscinium fenestratum	Menispermaceae	**7**
		Glaucium arabicum	Papaveraceae	**7**
		Thalictrum acutifolium, T. alpinum, T. foliolosum, T. javanicum, T. lucidum, T. minus, T. podocarpum	Ranunculaceae	**7**
131	8-Oxo-epiberberine	*Coptis japonica*	Ranunculaceae	**86**
132	8-Oxocoptisine	*Ceratocapnos claviculata*	Papaveraceae	**7**
		Coptis japonica	Ranunculaceae	**86**
		Corydalis turtschaninovii, C. yanhusuo	Papaveraceae	**7**
		Fumaria indica, F. parviflora, F. vaillantii	Papaveraceae	**7,155**
		Thalictrum delavayi	Ranunculaceae	**7**
133	Allocryptopine	*Aegle marmelos*	Rutaceae	**7**
		Arctomecon humilis, A. merriamii	Papaveraceae	**7**
		Argemone albiflora, A. grandiflora, A. mexicana, A. munita, A. platyceras	Papaveraceae	**7**
		Berberis buxifolia, B. microphylla, B.petiolaris	Berberidaceae	**7,59**
		Bocconia frutescens	Papaveraceae	**7**
		Caltha palustris	Ranunculaceae	**7**

	Chelidonium majus	Papaveraceae	**95**
	Corydalis bulleyana, C. caseana, C. decumbens, C. fumariifolia, C. intermedia, C. ledebouriana, C. nobilis, C. ophiocarpa, C. pallida, C. remota, C. solida, C. turtschaninovii, C. yanhusuo	Papaveraceae	**7**
	Dicentra peregrina	Papaveraceae	**7**
	Eschscholzia californica	Papaveraceae	**7**
	Eschscholzia lobbii	Papaveraceae	**7**
	Glaucium arabicum, G. corniculatum, G. fimbrilligerum, G. flavum, G. squamigerum	Papaveraceae	**7**
	Haplophyllum bucharicum, H. robustum	Rutaceae	**7**
	Hunnemannia fumariifolia	Papaveraceae	**7**
	Hypecoum erectum, H. leptocarpum, H. procumbens	Papaveraceae	**7**
	Macleaya cordata, M. microcarpa	Papaveraceae	**7,104**
	Meconopsis cambrica, M.s robusta	Papaveraceae	**7**
	Papaver alpinum, P. argemone, P. atlanticum, P. dubium, P. glaucum, P. kerneri, P. lapponicum, P. nudicaule, P. orientale, P. pavoninum, P. pseudo-orientale, P. pygmaeum, P. radicatum, P. rhoeas, P. somniferum, P. tatricum	Papaveraceae	**7**
	Ruta corsica	Rutaceae	**7**
	Sanguinaria canadensis	Papaveraceae	**7**
	Stylophorum diphyllum, S. lasiocarpum	Papaveraceae	**7**
	Thalictrum atriplex, T. foliolosum, T. minus, T. petaloideum, T. revolutum, T. simplex	Ranunculaceae	**7**
	Zanthoxylum avicennae, Z. beecheyanum, Z. brachyacanthum, Z. coco, Z. nitidum, Z. zanthoxyloides	Rutaceae	**7**
134 Protopine (macleyine)	*Arctomecon humilis, A. merriamii*	Papaveraceae	**7**
	Argemone albiflora, A. grandiflora, A. mexicana, A. munita, A. ochroleuca, A. platyceras, A. subfusiformis	Papaveraceae	**7**
	Berberis buxifolia, B. darwinii, B. empetrifolia, B. laurina, B. microphylla	Berberidaceae	**7**
	Bocconia frutescens, B. latisepala	Papaveraceae	**7**

Caltha palustris	Ranunculaceae	**7**
Capnoides sempervirens	Papaveraceae	**7**
Ceratocapnos claviculata, C. heterocarpa	Papaveraceae	**7**
Chelidonium majus	Papaveraceae	**105**
Corydalis adunca, C. ambigua, C. balansae, C. bulleyana, C. bungeana, C. cava, C. cheilanthifolia, C. crispa, C. govaniana, C. decumbens, C. dubia, C. esquirolii, C. fumariifolia, C. heterocarpa, C. incisa, C. intermedia, C. ledebouriana, C. nobilis, C. ophiocarpa, C. pallida, C. racemosa, C. remota, C. repens, C. saxicola, C. sheareri, C. solida, C. speciosa, C. ternata, C. turtschaninovii, C. yanhusuo	Papaveraceae	**7,101**
Cyclea atjehensis	Menispermaceae	**7**
Dactylicapnos torulosa	Papaveraceae	**7**
Dicentra formosa, D. peregrina	Papaveraceae	**7**
Dicranostigma lactucoides	Papaveraceae	**7**
Eschscholzia californica	Papaveraceae	**7**
Fumaria agraria, F. asepala, F. barnolae, F. bastardii, F. bracteosa, F. capreolata, F. densiflora, F. gaillardotii, F. indica, F. judaica, F. kralikii, F. macrosepala, F. muralis, F. officinalis, F. parviflora, F. petteri, F. rostellata, F. sepium, F. vaillantii	Papaveraceae	**7,151,153-156**
Galanthus trojanus	Amaryllidaceae	**7**
Glaucium arabicum, G. corniculatum, G. fimbrilligerum, G. flavum, G. squamigerum	Papaveraceae	**7**
Hunnemannia fumariifolia	Papaveraceae	**7**
Hylomecon japonica, H. erectum, H. imberbe, H. leptocarpum, H. pendulum, H. procumbens	Papaveraceae	**7,106**
Ichtyoselmis macrantha	Papaveraceae	**7**
Lamprocapnos spectabilis	Papaveraceae	**7**
Macleaya cordata	Papaveraceae	**104**
Meconopsis cambrica, M. napaulensis, M. paniculata, M. robusta	Papaveraceae	**7**

		Nandina domestica	Berberidaceae	**7**
		Papaver alpinum, P. argemone, P. armeniacum, P. atlanticum, P. bracteatum, P. californicum, P. canescens, P. dubium, P. glaucum, P. heterophyllum, P. kerneri, P. lapponicum, P. lateritium, P. macrostomum, P. nudicaule, P. orientale, P. pavoninum, P. pseudo-orientale, P. pygmaeum, P. radicatum, P. rhoeas, P. somniferum, P. tatricum	Papaveraceae	**7**
		Platycapnos saxicola, P. spicata, P. californicus	Papaveraceae	**7**
		Roemeria refracta	Papaveraceae	**7**
		Rupicapnos africana	Papaveraceae	**7**
		Sanguinaria canadensis	Papaveraceae	**7**
		Sarcocapnos baetica, S. crassifolia, S. enneaphylla, S. saetabensis	Papaveraceae	**7**
		Stylophorum diphyllum, S. lasiocarpum	Papaveraceae	**7**
		Thalictrum delavayi, T. foetidum, T. lucidum, T. minus, T. revolutum, T. simplex	Ranunculaceae	**7**
135	Cheilanthifoline	*Ceratocapnos claviculata*	Papaveraceae	**7**
		Corydalis dubia, C. saxicola	Papaveraceae	**7,101**
		Dactylicapnos torulosa	Papaveraceae	**7**
		Fumaria judaica, F. parviflora, F. vaillantii	Papaveraceae	**7,156**
		Menispermum dauricum	Menispermaceae	**7**
		Papaver armeniacum, P. macrostomum, P. triniifolium	Papaveraceae	**7**
136	Baicalensine A	*Thalictrum baicalense*	Ranunculaceae	**107**
BENZOPHENANTHRIDINES				
137	8-Methoxynorchelerythrine	*Toddalia asiatica*	Rutaceae	**33**
138	11-Demethylrhoifoline B	*Toddalia asiatica*	Rutaceae	**33**
139	8-Acetylnorchelerythrine	*Toddalia asiatica*	Rutaceae	**33**
140	8,9,10,12-tetramethoxynorchelerythrine	*Toddalia asiatica*	Rutaceae	**33**
141	2,3,13-Trimethoxy-[1,3]benzodioxolo[5,6-c]phenanthridine	*Toddalia asiatica*	Rutaceae	**33**

		Zanthoxylum rhoifolium	Rutaceae	**7**
142	Pancorine	*Toddalia asiatica*	Rutaceae	**33**
143	Decarine (syn. Zanthoxyline, Rutaceline)	*Aralia bipinnata*	Araliaceae	**7**
		Tetradium glabrifolium	Rutaceae	**7**
		Turraeanthus africanus	Rutaceae	**7**
		Zanthoxylum ailanthoides, Z. beecheyanum, Z. capense, Z. fagara, Z. leprieurii, Z. nitidum, Z. rhoifolium, Z. simulans, Z. tingoassuiba, Z. viride, Z. madagascariense	Rutaceae	**7,25,108,118**
144	Nitidine	*Toddalia asiatica*	Rutaceae	**109**
		Zanthoxylum ailanthoides, Z. americanum, Z. avicennae, Z. bungeanum, Z. chalybeum, Z. clava-herculis, Z. coco, Z. dipetalum, Z. dissitum, Z. echinocarpum, Z. fagara, Z. flavum, Z. gilletii, Z. myriacanthum, Z. nitidum, Z. rhetsa, Z. rhoifolium, Z. rubescens, Z. scandens, Z. usambarense, Z. zanthoxyloides	Rutaceae	**7,14,25**
145	Avicine	*Zanthoxylum rhoifolium*	Rutaceae	**25**
		Zanthoxylum simulans	Rutaceae	**7**
146	Chelerythrine	*Argemone mexicana*	Papaveraceae	**55**
		Argemone ochroleuca	Papaveraceae	**56**
		Bocconia frutescens, B. latisepala	Papaveraceae	**7**
		Chelidonium majus	Papaveraceae	**95**
		Corydalis incisa, C. ophiocarpa	Papaveraceae	**7**
		Dicranostigma lactucoides	Papaveraceae	**7**
		Eschscholzia californica	Papaveraceae	**110**
		Glaucium flavum, G. squamigerum	Papaveraceae	**7**
		Hylomecon japonica, H. leptocarpum, H. procumbens	Papaveraceae	**7**
		Macleaya cordata, M. microcarpa	Papaveraceae	**7,56,111**
		Sanguinaria canadensis	Papaveraceae	**112**
		Zanthoxylum coco, Z. coriaceum, Z. gilletii, Z. martinicense, Z. rhetsa, Z. rhoifolium, Z. rubescens, Z. zanthoxyloides	Rutaceae	**7,14,25**

147	8-Methoxynitidine	*Toddalia asiatica*	Rutaceae	**33**
148	8-Methoxychelerythrine	*Toddalia asiatica*	Rutaceae	**33**
149	Fagaridine	*Zanthoxylum nitidum, Z. gilletii*	Rutaceae	**113**
150	Oxynorchelerythrine	*Portulaca oleracea*	Convolvulaceae	**114**
151	Oxynitidine	*Aralia bipinnata*	Araliaceae	**7**
		Melicope semecarpifolia	Rutaceae	**7**
		Papaver somniferum	Papaveraceae	**7**
		Toddalia asiatica	Rutaceae	**33**
		Turraeanthus africanus	Meliaceae	**7**
		Zanthoxylum ailanthoides, Z. asiaticum, Z. beecheyanum, Z. gilletii, Z. nitidum, Z. rhoifolium, Z. schinifolium	Rutaceae	**7**
152	Oxysanguinarine	*Bocconia arborea*	Papaveraceae	**7**
		Chelidonium majus	Papaveraceae	**7**
		Corydalis balansae, C. ledebouriana, C. pallida	Papaveraceae	**7**
		Dactylicapnos torulosa	Papaveraceae	**7**
		Fumaria indica, F. parviflora, F. vaillantii	Papaveraceae	**156**
		Hylomecon japonica	Papaveraceae	**106**
		Ichtyoselmis macrantha	Papaveraceae	**7**
		Papaver bracteatum, P. nudicaule, P. somniferum	Papaveraceae	**7**
		Pteridophyllum racemosum	Papaveraceae	**7**
		Sanguinaria canadensis	Papaveraceae	**7**
		Sarcocapnos crassifolia, S. enneaphylla	Papaveraceae	**7**
		Toddalia asiatica	Rutaceae	**33**
153	6-Oxocorynoline	*Corydalis incisa*	Papaveraceae	**115**
154	Dihydrochelerythrine	*Arctomecon humilis*	Papaveraceae	**7**
		Bocconia arborea, B. integrifolia, B. pearcei	Papaveraceae	**111**
		Chelidonium majus	Papaveraceae	**95**
		Corydalis saxicola	Papaveraceae	**7**

		Eschscholzia californica	Papaveraceae	**7**
		Fagaropsis glabra	Rutaceae	**7**
		Garcinia lucida	Clusiaceae	**7**
		Glaucium flavum	Papaveraceae	**7**
		Hylomecon japonica	Papaveraceae	**106**
		Macleaya cordata, M. microcarpa	Papaveraceae	**111**
		Tetradium glabrifolium	Rutaceae	**7**
		Zanthoxylum ailanthoides, Z. asiaticum, Z. chalybeum, Z. coriaceum, Z. gilletii, Z. kauaense, Z. leprieurii, Z. madagascariense, Z. nitidum, Z. rhetsa, Z. rhoifolium, Z. simulans, Z. zanthoxyloides	Rutaceae	**7,14,25,108**
155	12-Methoxydihydrochelerythrine (6-methoxydihydrochelerythrine)	*Bocconia integrifolia*	Papaveraceae	**111**
155	12-Methoxydihydrochelerythrine (6-methoxydihydrochelerythrine)	*Hylomecon japonica*	Papaveraceae	**106**
155	12-Methoxydihydrochelerythrine (6-methoxydihydrochelerythrine)	*Macleaya microcarpa*	Papaveraceae	**111**
156	8-Hydroxydihydrochelerythrine	*Chelidonium majus*	Papaveraceae	**95**
		Macleaya spp.	Papaveraceae	**116**
157	6-Methoxyldihydrochelerythrine (Angoline)	*Bocconia arborea*	Papaveraceae	**7**
		Chelidonium majus	Papaveraceae	**7**
		Macleaya cordata	Papaveraceae	**117**
		Zanthoxylum zanthoxyloides	Rutaceae	**7**
158	6-Butoxydihydrochelerythrine	*Macleaya microcarpa*	Papaveraceae	**111**
159	6-Acetonyldihydrochelerythrine	*Chelidonium majus*	Papaveraceae	**7**
		Garcinia lucida	Clusiaceae	**7**
		Macleaya cordata	Papaveraceae	**117**
		Zanthoxylum capense, Z. nitidum	Rutaceae	**7**
160	Zanthocapensine	*Zanthoxylum capense*	Rutaceae	**119**

161	(2′,6′-epoxy-1′,2′α,3′β,4′α,5′α - pentahydroxy)hexane-(1′ → 6)-dihydrochelerythrine	*Macleaya spp.*	Papaveraceae	**116**
162	Bis[6-(5,6-dihydrochelerythrinyl)]ether	*Macleaya spp.*	Papaveraceae	**116**
163	Sanguinarine	*Ammodendron* spp.	Fabaceae	**7**
		Arctomecon humilis	Papaveraceae	**7**
		Argemone albiflora, A. grandiflora, A. mexicana, A. ochroleuca, A. platyceras, A. subfusiformis	Papaveraceae	**7,104**
		Bocconia arborea, B. cordata, B. frutescens, B. frutescens, B. latisepala	Papaveraceae	**7,112**
		Capnoides sempervirens	Papaveraceae	**7**
		Chelidonium majus	Papaveraceae	**7,95**
		Coptis japonica	Ranunculaceae	**7**
		Corydalis cava, C. cheilanthifolia, C. ledebouriana, C. remota, C. turtschaninovii	Papaveraceae	**7**
		Dicentra peregrina	Papaveraceae	**7**
		Dicranostigma lactucoides	Papaveraceae	**7**
		Eschscholzia californica	Papaveraceae	**110**
		Fumaria asepala, F. barnolae, F. capreolata, F. kralikii, F. officinalis, F. parviflora	Papaveraceae	**7,151,154**
		Glaucium corniculatum, G. fimbrilligerum, G. flavum, G. squamigerum	Papaveraceae	**7**
		Hylomecon japonica, H. leptocarpum, H. procumbens	Papaveraceae	**7,106**
		Lamprocapnos spectabilis	Papaveraceae	**7**
		Macleaya cordata, M. microcarpa	Papaveraceae	**111**
		Meconopsis cambrica	Papaveraceae	**7**
		Papaver atlanticum, P. bracteatum, P. glaucum, P. nudicaule, P. somniferum	Papaveraceae	**7**
		Sanguinaria canadensis	Papaveraceae	**120**
		Stylophorum diphyllum, S. lasiocarpum	Papaveraceae	**7**

		Zanthoxylum nitidum, Z. rhoifolium	Rutaceae	**7,117**
164	Dihydrosanguinarine	*Arctomecon humilis*	Papaveraceae	**7**
		Argemone mexicana, A.ochroleuca	Papaveraceae	**7,104**
		Bocconia arborea, B. integrifolia	Papaveraceae	**7**
		Ceratocapnos claviculata, C. heterocarpa	Papaveraceae	**7**
		Chelidonium majus	Papaveraceae	**95**
		Coreanomecon hylomeconoides	Papaveraceae	**7**
		Corydalis balansae, C. bulleyana, C. bungeana, C. cava, C. ledebouriana, C. pallida, C. remota, C. saxicola, C. solida, C. turtschaninovii	Papaveraceae	**7**
		Dicentra peregrina	Papaveraceae	**7**
		Eschscholzia californica	Papaveraceae	**7**
		Fumaria agraria, F. barnolae, F. macrosepala, F. officinalis, F. parviflora, F. sepium, F. vaillantii	Papaveraceae	**7,155,156**
		Glaucium fimbrilligerum, G. flavum	Papaveraceae	**7**
		Hylomecon hylomeconoides, H. japonica, H. imberbe, H. leptocarpum, H. procumbens	Papaveraceae	**7,106**
		Lamprocapnos spectabilis	Papaveraceae	**7**
		Macleaya cordata, M. microcarpa	Papaveraceae	**7,111**
		Papaver bracteatum, P. somniferum	Papaveraceae	**7**
		Platycapnos saxicola, P. spicata	Papaveraceae	**7**
		Pteridophyllum racemosum	Papaveraceae	**7**
		Romneya coulteri	Papaveraceae	**7**
		Rupicapnos africana	Papaveraceae	**7**
		Sarcocapnos baetica, S. crassifolia, S. enneaphylla, S. saetabensis	Papaveraceae	**7**
		Zanthoxylum rhoifolium	Rutaceae	**117**
165	8-Hydroxydihydrosanguinarine	*Macleaya spp.*	Papaveraceae	**116**
		Chelidonium majus	Papaveraceae	**95**
		Stylophorum diphyllum	Papaveraceae	**7**

166	10-Methoxydihydrosanguinarine	*Hylomecon japonica*	Papaveraceae	**106**
		Macleaya microcarpa	Papaveraceae	**111**
167	6-Methoxydihydrosanguinarine	*Hylomecon japonica*	Papaveraceae	**106**
		Macleaya microcarpa	Papaveraceae	**111**
168	Corynoline	*Corydalis bulleyana, C. bungeana, C. conspersa, C. incisa, C. remota, C. taliensis, C. turtschaninovii*	Papaveraceae	**7,115**
169	Chelidonine	*Chelidonium majus*	Papaveraceae	**105**
		Glaucium corniculatum, G. fimbrilligerum, G. flavum	Papaveraceae	**7**
		Haplophyllum acutifolium	Rutaceae	**7**
		Macleaya spp.	Papaveraceae	**116**
		Sarcocapnos baetica, S. crassifolia, S. enneaphylla, S. saetabensis	Papaveraceae	**7**
		Stylophorum diphyllum, S. lasiocarpum	Papaveraceae	**7**
		Symphoricarpos albus	Caprifoliaceae	**7**
170	Corynoloxine	*Corydalis ambigua, C. bungeana, C. incisa*	Papaveraceae	**7,115**
171	Maclekarpine C	*Macleaya microcarpa*	Papaveraceae	**111**
172	(5′R)-3′-Methyl-2′(5′H)-furanone-(5′ → 6)-(6R)-dihydrosanguinarine	*Macleaya spp.*	Papaveraceae	**116**
173	Isointegriamide	*Toddalia asiatica*	Rutaceae	**33**
174	Arnottianamide	*Alchornea cordifolia*	Euphorbiaceae	**7**
		Alexandrium excavatum, A. hiranoi	Aizoaceae	**7**
		Amomum daniellii	Zingiberaceae	**7**
		Angelica taiwaniana	Apiaceae	**7**
		Aralia bipinnata	Araliaceae	**7**
		Argemone mexicana	Papaveraceae	**7**
		Artemisia austriaca	Asteraceae	**7**
		Aspergillus fischeri	Asparagaceae	**7**
		Atalantia wightii	Rutaceae	**7**
		Balanophora japonica	Balanophoraceae	**7**

Bellium bellidioides	Asteraceae	**7**
Canarina canariensis	Campanulaceae	**7**
Centaurea calcitrapa	Asteraceae	**7**
Chrysolaena propinqua	Asteraceae	**7**
Coleus esquirolii	Lamiaceae	**7**
Commiphora erlangeriana	Burseraceae	**7**
Consolida hohenackeri	Ranunculaceae	**7**
Coprinellus flocculosus	Polypodiaceae	**7**
Corydalis persica	Papaveraceae	**7**
Corynanthe pachyceras	Rubiaceae	**7**
Cota tinctoria	Asteraceae	**7**
Crambe fruticosa	Brassicaceae	**7**
Cryptocarya canelilla	Lauraceae	**7**
Cynara humilis	Asteraceae	**7**
Cynoglossum amabile	Boraginaceae	**7**
Daphne blagayana	Thymelaeaceae	**7**
Diabelia spathulata	Caprifoliaceae	**7**
Didymium bahiense	Araceae	**7**
Digitalis obscura	Plantaginaceae	**7**
Echinosophora koreensis	Fabaceae	**7**
Elegia deusta	Restionaceae	**7**
Erica glauca	Ericaceae	**7**
Erythrina orientalis	Fabaceae	**7**
Garcinia intermedia, G. xanthochymus	Clusiaceae	**7**
Glycosmis pseudoracemosa	Rutaceae	**7**
Inula grantioides	Asteraceae	**7**
Jacobaea vulgaris	Asteraceae	**7**
Juniperus horizontalis	Cupressaceae	**7**

Kitagawia praeruptora	Apiaceae	**7**
Lathyrus tingitanus (Tangier pea)	Fabaceae	**7**
Leptochilus pothifolius	Polypodiaceae	**7**
Leucas neufliseana	Lamiaceae	**7**
Liatris aspera	Asteraceae	**7**
Lithospermum officinale	Boraginaceae	**7**
Litsea glutinosa	Lauraceae	**7**
Lotus villosus	Fabaceae	**7**
Macleaya microcarpa	Papaveraceae	**7**
Matricaria suffruticosa	Asteraceae	**7**
Mesua elegans	Calophyllaceae	**7**
Michelia rajaniana	Magnoliaceae	**7**
Nicotiana plumbaginifolia	Solanaceae	**7**
Onychopetalum amazonicum	Annonaceae	**7**
Orobanche caerulescens	Orobanchaceae	**7**
Peucedanum oroselinum	Apiaceae	**7**
Pimpinella diversifolia	Apiaceae	**7**
Platonia insignis	Clusiaceae	**7**
Plectranthus caninus	Lamiaceae	**7**
Pueraria tuberosa	Fabaceae	**7**
Rauvolfia salicifolia	Apocynaceae	**7**
Salvia munzii	Lamiaceae	**7**
Sarcococca vagans	Buxaceae	**7**
Senecio densiflorus	Asteraceae	**7**
Sida veronicaefolia	Melastomataceae	**7**
Solanum transcaucasicum	Solanaceae	**7**
Stevia serrata	Asteraceae	**7**
Strychnos spinosa	Loganiaceae	**7**

	Tecoma pentaphylla	Bignoniaceae	**7**
	Tetradium glabrifolium	Rutaceae	**7**
	Toddalia asiatica	Rutaceae	**33**
	Trachelospermum lucidum	Apocynaceae	**7**
	Ulmus americana	Ulmaceae	**7**
	Vitex divaricata	Lamiaceae	**7**
	Wedelia prostrata	Asteraceae	**7**
	Wikstroemia chamaedaphne	Thymelaeaceae	**7**
	Wilcoxia viperina	Cactaceae	**7**
	Zanthoxylum ailanthoides, Z. arnottianum, Z. arnottianum Maxim., Z. asiaticum, Z. beecheyanum, Z. bungeanum, Z. chalybeum, Z. cuspidatum Champ., Z. gilletii, Z. heitzii, Z. nitidum, Z. planispinum, Z. rubescens, Z. rubescers, Z. scandens, Z. schinifolium, Z. simulans	Rutaceae	**7**
APORPHINES			
175 Nornuciferine	*Annickia polycarpa*	Annonaceae	**7**
	Annona glabra, A. muricata	Annonaceae	**7,121**
	Artabotrys hexapetalus, A. venustus	Annonaceae	**7,57**
	Chelonanthus albus	Gentianaceae	**7**
	Duguetia flagellaris	Annonaceae	**7**
	Greenwayodendron oliveri	Annonaceae	**7**
	Guatteria amplifolia, G. blepharophylla, G. diospyroides, G. punctata	Annonaceae	**7,122**
	Liriodendron tulipifera	Magnoliaceae	**7**
	Magnolia obovata	Magnoliaceae	**7**
	Monodora junodii	Annonaceae	**7**
	Nelumbo lutea, Nelumbo nucifera	Nelumbonaceae	**7**
	Neolitsea konishii	Lauraceae	**7**
	Oxandra xylopioides	Annonaceae	**7**
	Ziziphus jujuba, Z. mauritiana	Rhamnaceae	**7**

176	Asimilobine	*Annona cherimola, A. emarginata, A. glabra, A. muricata, A. salzmannii*	Annonaceae	**7,54,102**
		Aristolochia cucurbitifolia	Aristolochiaceae	**7**
		Artabotrys brachypetalus, A. hexapetalus, A. monteiroae, A. venustus	Annonaceae	**7**
		Asimina triloba	Annonaceae	**7**
		Beilschmiedia alloiophylla	Lauraceae	**7**
		Cardiopetalum calophyllum	Annonaceae	**7**
		Chelonanthus albus	Gentianaceae	**7**
		Cymbopetalum brasiliense	Annonaceae	**7**
		Disepalum pulchrum	Annonaceae	**7**
		Fissistigma glaucescens, F. oldhamii	Annonaceae	**7**
		Glossocalyx brevipes, G. longicuspis	Siparunaceae	**7**
		Greenwayodendron oliveri	Annonaceae	**7**
		Hexalobus crispiflorus, H. monopetalus	Annonaceae	**7**
		Huberantha pendula	Annonaceae	**7**
		Laureliopsis philippiana	Atherospermataceae	**7**
		Liriodendron tulipifera	Magnoliaceae	**7**
		Magnolia kobus, M. obovata, M. officinalis	Magnoliaceae	**7**
		Meiogyne monosperma, M. virgata	Annonaceae	**7**
		Monocyclanthus vignei	Annonaceae	**7**
		Monodora junodii	Annonaceae	**7**
		Nelumbo nucifera	Nelumbonaceae	**7**
		Phoebe formosana	Lauraceae	**7**
		Polyalthia insignis, Polyalthia stenopetala	Annonaceae	**7**
		Siparuna brasiliensis	Siparunaceae	**7**
		Stephania pierrei, S. venosa	Menispermaceae	**7**
		Uvaria dulcis	Annonaceae	**7**

177	Anonaine	*Annona cherimola, A. crassiflora, A. emarginata, A. glabra, A. hypoglauca, A. mucosa, A. muricata, A. purpurea, A. salzmannii, A. senegalensis, A. squamosa*	Annonaceae	**7,54,121,123**
		Artabotrys brachypetalus, A. hexapetalus, A. maingayi, A. monteiroae, A. venustus	Annonaceae	**7,57**
		Cardiopetalum calophyllum	Annonaceae	**7**
		Chelonanthus albus	Gentianaceae	**7**
		Dasymaschalon yunnanense	Annonaceae	**7**
		Disepalum pulchrum	Annonaceae	**7**
		Goniothalamus amuyon	Annonaceae	**7**
		Greenwayodendron oliveri	Annonaceae	**7**
		Guatteria oliviformis	Annonaceae	**7**
		Hexalobus crispiflorus	Annonaceae	**7**
		Huberantha pendula	Annonaceae	**7**
		Isolona congolana, Isolona maitlandii	Annonaceae	**7**
		Laureliopsis philippiana	Atherospermataceae	**7**
		Licaria triandra	Lauraceae	**7**
		Liriodendron tulipifera	Magnoliaceae	**7**
		Magnolia compressa, M. grandiflora, M. kobus, M. liliifera, M. obovata, M. officinalis	Magnoliaceae	**7**
		Meiogyne monosperma, M. virgata	Annonaceae	**7**
		Monodora junodii, M. tenuifolia	Annonaceae	**7**
		Nelumbo nucifera	Nelumbonaceae	**7**
		Neolitsea acuminatissima, N. sericea	Lauraceae	**7**
		Oxandra xylopioides	Annonaceae	**7**
		Stephania cephalantha, S. pierrei, S. venosa	Menispermaceae	**7**
		Uvaria dulcis	Annonaceae	**7**
		Xylopia emarginata, X. parviflora	Annonaceae	**7**
178	Roemerine	*Annona cherimola, A. squamosa*	Annonaceae	**7**

		Artabotrys hexapetalus	Annonaceae	**7**
		Chelonanthus albus	Gentianaceae	**7**
		Cryptocarya angulata	Lauraceae	**7**
		Desmos chinensis	Annonaceae	**7**
		Guatteria oliviformis	Annonaceae	**7**
		Liriodendron tulipifera	Magnoliaceae	**7**
		Magnolia grandiflora, M. kobus, M. obovata	Magnoliaceae	**7**
		Nelumbo lutea, N. nucifera	Nelumbonaceae	**7**
		Neolitsea dealbata, N. parvigemma, N. sericea	Lauraceae	**7**
		Papaver armeniacum, P. dubium, P. pilosum, P. rhoeas	Papaveraceae	**7**
		Phoebe formosana	Lauraceae	**7**
		Roemeria refracta	Papaveraceae	**7**
		Stephania abyssinica, S. corymbosa, S. excentrica, S. glabra, S. lincangensis, S. yunnanensis	Menispermaceae	**7,70**
		Uvaria dulcis, U. rufa	Annonaceae	**7**
		Xylopia aethiopica	Annonaceae	**7**
179	Xylopine	*Annona cherimola, A. crassiflora, A. muricata, A. reticulata*	Annonaceae	**7,52**
		Chasmanthera dependens	Menispermaceae	**7**
		Dasymaschalon longiflorum	Annonaceae	**7**
		Desmos chinensis	Annonaceae	**7**
		Duguetia yeshidan	Annonaceae	**7**
		Fissistigma glaucescens, F. oldhamii	Annonaceae	**7**
		Guatteria amplifolia, G. punctata	Annonaceae	**7**
		Magnolia liliifera	Magnoliaceae	**7**
		Monodora junodii	Annonaceae	**7**
		Stephania pierrei	Menispermaceae	**7**
		Xylopia parviflora	Annonaceae	**7**

180	Dehydrocrebanine	*Stephania cephalantha, S. corymbosa, S. delavayi, S. glabra, S. hainanensis, S. venosa*	Menispermaceae	**7,124**
181	Crebanine	*Fissistigma oldhamii*	Annonaceae	**7**
		Stephania abyssinica, S. cephalantha, S. glabra, S. venosa	Menispermaceae	**7,124**
182	Actinodaphnine	*Actinodaphne acuminata*	Lauraceae	**7**
		Annona hypoglauca	Annonaceae	**123**
		Cassytha filiformis	Lauraceae	**7**
		Illigera luzonensis, I. pentaphylla	Hernandiaceae	**7**
		Laurus nobilis	Lauraceae	**7**
		Licaria triandra	Lauraceae	**7**
		Litsea glutinosa, L. lancifolia, L. polyantha, L. sericea, L. wightiana	Lauraceae	**7,124**
		Neolitsea acuminatissima, N. dealbata, N. konishii, N. parvigemma, N. sericea	Lauraceae	**7**
183	Laurolitsine	*Actinodaphne pruinosa*	Lauraceae	**7**
		Alseodaphne perakensis	Lauraceae	**7**
		Berberis stolonifera	Berberidaceae	**7**
		Cinnamomum camphora	Lauraceae	**7**
		Damburneya salicifolia	Lauraceae	**7**
		Dehaasia hainanensis	Lauraceae	**7**
		Huberantha pendula	Annonaceae	**7**
		Lindera aggregata, L. chunii, L. glauca, L. umbellata	Lauraceae	**7,63**
		Litsea glutinosa, L. japonica, L. lancifolia	Lauraceae	**7**
		Nectandra grandiflora	Lauraceae	**7**
		Neolitsea acuminatissima, N. buisanensis, N. dealbata, N. konishii, N. sericea	Lauraceae	**7**
		Peumus boldus	Monimiaceae	**7**
		Phoebe formosana, Phoebe grandis	Lauraceae	**7**
		Sassafras albidum	Lauraceae	**7**
		Siparuna pauciflora	Siparunaceae	**7**

		Xylopia parviflora	Annonaceae	**7**
184	(+)-Laurotetanine	*Actinodaphne acuminata*	Lauraceae	**7**
		Annona cherimola	Annonaceae	**7**
		Beilschmiedia alloiophylla	Lauraceae	**7**
		Corydalis turtschaninovii	Papaveraceae	**7**
		Cyclea atjehensis	Menispermaceae	**7**
		Damburneya salicifolia	Lauraceae	**7**
		Dehaasia hainanensis	Lauraceae	**7**
		Desmos chinensis	Annonaceae	**7**
		Glossocalyx brevipes, G. longicuspis	Siparunaceae	**7**
		Hedycarya angustifolia	Monimiaceae	**7**
		Hernandia guianensis, H. nymphaeifolia, H. ovigera	Hernandiaceae	**7,51**
		Illigera pentaphylla	Hernandiaceae	**7**
		Laurelia sempervirens	Atherospermataceae	**7**
		Lindera angustifolia, L. benzoin, L. erythrocarpa, L. glauca, L. umbellata	Lauraceae	**7**
		Litsea cubeba, L. glutinosa, L. sericea, L. wightiana	Lauraceae	**7**
		Nectandra grandiflora	Lauraceae	**7**
		Neolitsea aciculata, N. konishii	Lauraceae	**7**
		Ocotea lancifolia	Lauraceae	**7**
		Peumus boldus	Monimiaceae	**7**
		Phoebe formosana, P. grandis	Lauraceae	**7**
		Siparuna brasiliensis, S. pauciflora	Siparunaceae	**7**
		Xylopia parviflora	Annonaceae	**7**
185	Isoboldine	*Aconitum karakolicum, A. nemorum, A. sanyoense*	Ranunculaceae	**7**
		Actinodaphne acuminata	Lauraceae	**7**
		Aniba canelilla	Lauraceae	**7**
		Annickia polycarpa	Annonaceae	**7**

Annona cherimola, A. hypoglauca, A. senegalensis	Annonaceae	**7,123**
Beilschmiedia alloiophylla	Lauraceae	**7**
Berberis cretica, B. integerrima, B. nummularia, B. petiolaris	Berberidaceae	**7,59**
Cardiopetalum calophyllum	Annonaceae	**7**
Cassytha filiformis	Lauraceae	**7**
Ceratocapnos claviculata	Papaveraceae	**7**
Cocculus laurifolius, C. trilobus	Menispermaceae	**7**
Corydalis bulleyana, C. bungeana, C. cava, C. intermedia, C. nobilis, C. solida	Papaveraceae	**7**
Croton celtidifolius, C. lechleri	Euphorbiaceae	**7**
Cryptocarya chinensis	Lauraceae	**7**
Damburneya salicifolia	Lauraceae	**7**
Dehaasia incrassata	Lauraceae	**7**
Dicentra peregrina	Papaveraceae	**7**
Erythrina abyssinica	Fabaceae	**7**
Fissistigma oldhamii	Annonaceae	**7**
Fumaria agraria, F. barnolae, F. capreolata, F. parviflora, F. vaillantii	Papaveraceae	**7,152,155,156**
Glaucium arabicum, G. fimbrilligerum, G. flavum	Papaveraceae	**7**
Glossocalyx brevipes, G. longicuspis	Siparunaceae	**7**
Greenwayodendron oliveri	Annonaceae	**7**
Guatteria megalophylla	Annonaceae	**7**
Lindera aggregata, L. angustifolia, L. erythrocarpa, L. glauca, L. sericea, L. umbellata	Lauraceae	**7**
Litsea cubeba, L. sericea, L. wightiana	Lauraceae	**7**
Monodora junodii	Annonaceae	**7**
Nandina domestica	Berberidaceae	**7**
Nectandra grandiflora, N. membranacea	Lauraceae	**7**
Neolitsea konishii	Lauraceae	**7**

		Ocotea glaziovii, O. lancifolia	Lauraceae	**7**
		Pachygone dasycarpa, P. ovata	Menispermaceae	**7**
		Papaver bracteatum, P. orientale, P. rhoeas, P. somniferum	Papaveraceae	**7**
		Phoebe formosana	Lauraceae	**7**
		Sarcocapnos crassifolia	Papaveraceae	**7**
		Sassafras albidum	Lauraceae	**7**
		Schefferomitra subaequalis	Annonaceae	**7**
		Stephania cephalantha, S. excentrica	Menispermaceae	**7**
		Stylophorum diphyllum, S. lasiocarpum	Papaveraceae	**7**
		Thalictrum alpinum, T. aquilegiifolium, T. foetidum, T. isopyroides	Ranunculaceae	**7**
		Uvaria dulcis	Annonaceae	**7**
		Xylopia parviflora	Annonaceae	**7**
186	Laurelliptinhexadecan-1-one	*Cocculus orbiculatus*	Menispermaceae	**126**
187	Laurelliptinoctadecan-1-one	*Cocculus orbiculatus*	Menispermaceae	**126**
188	d-Dicentrine	*Breynia officinalis, B. vitis-idaea*	Phyllanthaceae	**7**
		Cassytha filiformis	Lauraceae	**7**
		Cissampelos capensis, C. pareira	Menispermaceae	**7**
		Dicentra eximia, D. formosa, D. peregrina	Papaveraceae	**7**
		Fumaria barnolae	Papaveraceae	**7**
		Glaucium corniculatum	Papaveraceae	**7**
		Illigera luzonensis	Hernandiaceae	**7**
		Lamprocapnos spectabilis	Papaveraceae	**7**
		Lindera megaphylla, L. megaphylla	Lauraceae	**7,127**
		Ocotea leucoxylon, O. velloziana	Lauraceae	**7**
		Protea eximia	Proteaceae	**7**
		Scolopia chinensis	Salicaceae	**7**
		Stephania abyssinica	Menispermaceae	**7**
189	Glaucine	*Annona mucosa, A. purpurea, A. reticulata*	Annonaceae	**7**

Berberis canadensis, B. cretica, B. heteropoda, B. integerrima, B. nummularia, B. repens, B. thunbergii	Berberidaceae	**7**
Ceratocapnos claviculata, C. heterocarpa	Papaveraceae	**7**
Cocculus laurifolius	Menispermaceae	**7**
Codiaeum variegatum	Euphorbiaceae	**102**
Corydalis cava, C. solida, C. turtschaninovii, C. yanhusuo	Papaveraceae	**7,87**
Croton draco, C. draconoides, C. hemiargyreus, C. lechleri, C. linearis	Euphorbiaceae	**7,60**
Cryptocarya chinensis	Lauraceae	**7**
Desmos chinensis	Annonaceae	**7**
Dicentra formosa	Papaveraceae	**7**
Eschscholzia californica	Papaveraceae	**7**
Fissistigma oldhamii	Annonaceae	**7**
Fumaria barnolae, F. macrosepala	Papaveraceae	**7**
Glaucium corniculatum, G. flavum	Papaveraceae	**7**
Hedycarya angustifolia	Monimiaceae	**7**
Hypecoum procumbens	Monimiaceae	**7**
Lamprocapnos spectabilis	Papaveraceae	**7**
Liriodendron tulipifera	Magnoliaceae	**7**
Litsea wightiana	Lauraceae	**7**
Magnolia obovata	Magnoliaceae	**7**
Neolitsea parvigemma	Lauraceae	**7**
Ocotea macrophylla, O. quixos, O. velloziana	Lauraceae	**7,128**
Papaver pilosum	Papaveraceae	**7**
Phoenicanthus obliquus	Annonaceae	**7**
Platycapnos saxicola, P. spicata, P. tenuiloba	Papaveraceae	**7**
Pseudofumaria alba	Papaveraceae	**7**
Rupicapnos africana	Papaveraceae	**7**

		Sarcocapnos baetica, S. crassifolia, S. enneaphylla, S. saetabensis	Papaveraceae	**7**
		Thalictrum baicalense, T. flavum, T. foetidum, T. hernandezii, T. ichangense, T. minus	Ranunculaceae	**7**
		Xylopia parviflora	Annonaceae	**7**
		Zanthoxylum ailanthoides	Rutaceae	**7**
190	(+)-N-(methoxycarbonyl)-N-norpredicentrine	*Litsea cubeba*	Lauraceae	**129**
191	(+)-N-(methoxycarbonyl)- N-norglaucine	*Litsea cubeba*	Lauraceae	**129**
192	(+)-N-(methoxycarbonyl)-N-nordicentrin	*Litsea cubeba*	Lauraceae	**129**
193	(+)-Hernovine	*Hernandia nymphaezfoli*	Hernandiaceae	**51**
		Illigera luzonensis	Hernandiaceae	**7**
194	(+)-N-Methylhernovine	*Hernandia nymphaezfoli*	Hernandiaceae	**51**
195	(+)-N-Hydroxyhernangerine	*Hernandia nymphaezfoli*	Hernandiaceae	**51**
196	Corydine	*Aconitum leucostomum, A. orientale*	Ranunculaceae	**7**
		Annona reticulata, A. squamosa	Annonaceae	**7**
		Berberis actinacantha, B. repens	Berberidaceae	**7**
		Chelidonium majus	Papaveraceae	**95**
		Cissampelos fasciculata	Menispermaceae	**7**
		Consolida hellespontica	Ranunculaceae	**7**
		Corydalis cava, C.decumbens, C. solida	Papaveraceae	**7**
		Croton hemiargyreus	Euphorbiaceae	**7**
		Damburneya salicifolia	Lauraceae	**7**
		Dehaasia hainanensis	Lauraceae	**7**
		Dicentra peregrina	Papaveraceae	**7**
		Fumaria barnolae	Papaveraceae	**7**
		Glaucium corniculatum, G. fimbrilligerum, G. flavum, G. squamigerum	Papaveraceae	**7**
		Guatteria amplifolia	Annonaceae	**7**
		Hedycarya angustifolia	Monimiaceae	**7**

		Hypecoum leptocarpum, H. procumbens	Papaveraceae	**7**
		Lamprocapnos spectabilis	Papaveraceae	**7**
		Laurelia novae-zelandiae	Atherospermataceae	**7**
		Neolitsea konishii	Lauraceae	**7**
		Ocotea velloziana	Lauraceae	**7**
		Papaver argemone, P. bracteatum, P. dubium, P. glaucum, P. nudicaule, P. pavoninum, P. tatricum	Papaveraceae	**7**
		Pseudofumaria lutea	Papaveraceae	**7**
		Stephania abyssinica, S. cephalantha, S. lincangensis, S. pierrei, S. tetrandra	Menispermaceae	**7**
		Stylophorum diphyllum	Papaveraceae	**7**
		Thalictrum dioicum, T. tuberiferum, T. urbainii	Ranunculaceae	**7**
		Zanthoxylum oxyphyllum	Rutaceae	**7**
197	Magnoflorine	*Aconitum lycoctonum, A. plicatum*	Ranunculaceae	**7**
		Actaea spicata	Ranunculaceae	**7**
		Adonis aestivalis, A. vernalis	Ranunculaceae	**7**
		Anamirta cocculus	Menispermaceae	**7**
		Aquilegia alpina, A. atrata, A. buergeriana, A. canadensis, A. chrysantha, A. coerulea, A. eximia, A. formosa, A. jonesii, A. oxysepala, A. skinneri, A. viridiflora	Ranunculaceae	**7**
		Aristolochia baetica, A. bracteolata, A. clematitis, A. cymbifera, A. elegans, A. gigantea, A. indica, A. littoralis	Aristolochiaceae	**7**
		Berberis actinacantha, B. aquifolium, B. canadensis, B. crataegina, B. cretica, B. darwinii, B. heteropoda, B. iliensis, B. integerrima, B. nummularia, B. petiolaris, B. repens, B. vulgaris	Berberidaceae	**7,59,83**
		Caltha palustris	Ranunculaceae	**7**
		Caulophyllum thalictroides	Berberidaceae	**7**
		Cissampelos glaberrima, C. pareira	Menispermaceae	**7,67**
		Clematis parviloba, C. recta, C. vitalba	Ranunculaceae	**7**
		Cocculus carolinus, C. hirsutus	Menispermaceae	**7**

Consolida regalis	Ranunculaceae	**7**
Coptis chinensis, C. deltoidea, C. japonica, C. quinquefolia	Ranunculaceae	**7,81**
Croton lechleri, C. menthodorus	Euphorbiaceae	**7**
Cunila spp.	Lamiaceae	**7**
Cymbopetalum brasiliense	Annonaceae	**7**
Delphinium pentagynum	Ranunculaceae	**7**
Dioscoreophyllum cumminsii	Menispermaceae	**7**
Eschscholzia californica	Papaveraceae	**7**
Fumaria capreolata	Papaveraceae	**7**
Glaucium arabicum, G. fimbrilligerum, G. squamigerum	Papaveraceae	**7**
Helleborus orientalis, H.viridis	Ranunculaceae	**7**
Hernandia nymphaeifolia	Hernandiaceae	**51**
Hypecoum leptocarpum, H. procumbens	Papaveraceae	**7**
Hypserpa nitida	Menispermaceae	**7**
Isopyrum thalictroides	Ranunculaceae	**7**
Liriodendron tulipifera	Magnoliaceae	**7**
Magnolia acuminata, M. grandiflora, M. kobus, M. obovata	Magnoliaceae	**7**
Meconopsis cambrica, M. robusta, M. canadense	Papaveraceae	**7**
Monodora tenuifolia	Annonaceae	**7**
Nandina domestica	Berberidaceae	**7**
Pachygone ovata	Menispermaceae	**7**
Papaver argemone, P. atlanticum, P. bracteatum, P. glaucum, P. orientale, P. pavoninum, P. rhoeas, P. somniferum	Papaveraceae	**7**
Phellodendron amurense, P. chinense	Rutaceae	**7**
Ranunculus serbicus	Ranunculaceae	**7**
Rhigiocarya racemifera	Menispermaceae	**7**
Semiaquilegia adoxoides	Ranunculaceae	**7**
Stephania cephalantha, S. elegans, S. glabra, S. pierrei, S. tetrandra	Menispermaceae	**7,70**

		Stylophorum diphyllum, S. lasiocarpum	Papaveraceae	**7**
		Tabernaemontana corymbosa	Apocynaceae	**7**
		Thalictrum aquilegiifolium, T. baicalense, T. calabricum, T. cultratum, T. dasycarpum, T. delavayi, T. elegans, T. fendleri, T. foetidum, T. foliolosum, T. isopyroides, T. javanicum, T. lucidum, T. minus, T. petaloideum, T. podocarpum, T. przewalskii, T. sachalinense, T. simplex, T. thalictroides, T. tuberiferum, T. urbainii	Ranunculaceae	**7**
		Tinospora capillipes, T. cordifolia	Menispermaceae	**7**
		Xylopia parviflora	Annonaceae	**7**
		Zanthoxylum austrosinense, Z. chalybeum, Z. gilletii, Z. mayu, Z. mollissimum, Z. myriacanthum, Z. nitidum, Z. piperitum, Z. rhoifolium, Z. scandens, Z. usambarense	Rutaceae	**7**
		Ziziphus jujuba	Rhamnaceae	**7**
198	(+)-8-methoxyisolaurenine-N-oxide	*Litsea cubeba*	Lauraceae	**129**
199	(+)-N-(methoxycarbonyl)-N-norisocorydione	*Litsea cubeba*	Lauraceae	**129**
200	(+)-N-(methoxycarbonyl)-N-norbulbodione	*Litsea cubeba*	Lauraceae	**129**
201	3-Methoxy-nordomesticine	*Ocotea macrophylla*	Lauraceae	**128**
202	Dasymaroine	*Dasymaschalon rostratum*	Annonaceae	**130**
203	N-Formyldehydroovigerine	*Hernandia nymphaezfoli*	Hernandiaceae	**51**
204	Lysicamine	*Abuta rufescens*	Menispermaceae	**131**
		Annickia polycarpa	Annonaceae	**7**
		Annona acuminata, A. cherimola, A. glabra, A. papilionella, A. purpurea, A. vepretorum	Annonaceae	**7,132**
		Aquilegia oxysepala	Ranunculaceae	**7**
		Aristolochia elegans, A. littoralis	Aristolochiaceae	**7**
		Artabotrys maingayi	Annonaceae	**7**
		Cananga odorata	Annonaceae	**7**
		Cassytha filiformis	Lauraceae	**7**

		Chasmanthera dependens	Menispermaceae	**7**
		Chelonanthus albus	Gentianaceae	**7**
		Friesodielsia velutina	Annonaceae	**7**
		Goniothalamus amuyon	Annonaceae	**7**
		Greenwayodendron suaveolens	Annonaceae	**7**
		Guatteria amplifolia, G. blepharophylla, G. citriodora, G. guianensis, G. hispida, G. lehmannii, G. multivenia, G. saffordiana	Annonaceae	**7,90,122**
		Houttuynia cordata	Saururaceae	**7**
		Illigera pentaphylla	Hernandiaceae	**7**
		Isolona congolana, I. maitlandii	Annonaceae	**7**
		Lindera glauca	Lauraceae	**7**
		Liriodendron tulipifera	Magnoliaceae	**7**
		Meiogyne monosperma	Annonaceae	**7**
		Miliusa spp.	Annonaceae	**7**
		Nelumbo nucifera	Nelumbonaceae	**7**
		Oxandra xylopioides	Annonaceae	**7**
		Stephania cephalantha, S. corymbosa	Menispermaceae	**7**
		Telitoxicum peruvianum	Menispermaceae	**7**
		Trivalvaria macrophylla	Annonaceae	**7**
		Unonopsis guatterioides, Unonopsis spectabilis	Annonaceae	**7**
		Uvaria mocoli	Annonaceae	**7**
		Xylopia aethiopica	Annonaceae	**7**
		Ziziphus jujuba	Rhamnaceae	**7**
205	Liriodenine	*Anisocycla* spp.	Menispermaceae	**7**
		Annickia polycarpa	Annonaceae	**7**
		Annona acuminata, A. ambotay, A. cherimola, A. crassiflora, A. dioica, A. emarginata, A. foetida, A. glabra, A. macroprophyllata, A. montana, A. mucosa, A. muricata, A. neosericea, A. papilionella, A.	Annonaceae	**7,54,121,132**

purpurea, A. reticulata, A. salzmannii, A. senegalensis, A. squamosa, A. vepretorum		
Artabotrys hexapetalus, A. zeylanicus	Annonaceae	**7,57**
Asimina triloba	Annonaceae	**7**
Atherosperma moschatum	Atherospermataceae	**7**
Beilschmiedia alloiophylla	Lauraceae	**7**
Broussonetia papyrifera	Moraceae	**7**
Cananga odorata	Annonaceae	**7**
Cardiopetalum calophyllum	Annonaceae	**7**
Chelonanthus albus	Gentianaceae	**7**
Chydenanthus excelsus	Lecythidaceae	**7**
Cleistopholis patens	Annonaceae	**7**
Dasymaschalon longiflorum	Annonaceae	**7**
Desfontainia spinosa	Columelliaceae	**7**
Disepalum anomalum, D. pulchrum	Annonaceae	**7**
Doryphora sassafras	Atherospermataceae	**7**
Eupomatia bennettii, E. laurina	Eupomatiaceae	**7**
Fissistigma glaucescens	Annonaceae	**7**
Friesodielsia velutina	Annonaceae	**7**
Glossocalyx brevipes, G. longicuspis	Siparunaceae	**7**
Goniothalamus amuyon, G. cheliensis, G. scortechinii, G. tapis	Annonaceae	**7**
Greenwayodendron oliveri	Annonaceae	**7**
Guatteria amplifolia, G. blepharophylla, G. citriodora, G. friesiana, G. guianensis, G. hispida, G. megalophylla, G. modesta, G. multivenia, G. oliviformis, G. punctata	Annonaceae	**7,102**
Hexalobus crispiflorus, H. monopetalus	Annonaceae	**7**
Huberantha cerasoides	Annonaceae	**7**
Illigera luzonensis	Hernandiaceae	**7**
Isolona congolana, I. maitlandii	Annonaceae	**7**

Laurelia novae-zelandiae	Atherospermataceae	**7**
Lettowianthus stellatus	Annonaceae	**7**
Licaria triandra	Lauraceae	**7**
Liriodendron tulipifera	Magnoliaceae	**7**
Litsea glaucescens, L. sericea	Lauraceae	**7**
Magnolia baillonii, M. cathcartii, M. champaca, M. coco, M. compressa, M. doltsopa, M. elegans, M. grandiflora, M. kobus, M. lanuginosa, M. liliifera, M. mexicana, M. obovata, M. odora, M. officinalis, M. salicifolia, M. tsiampacca	Magnoliaceae	**7**
Meiogyne monosperma, M. virgata	Annonaceae	**7**
Microcos paniculata, M. paniculata	Malvaceae	**7,102**
Miliusa cuneata, M. horsfieldii, M. velutina	Annonaceae	**7**
Mitrephora glabra, M. maingayi, M. thorelii, M. tomentosa	Annonaceae	**7**
Mollinedia gilgiana, M. schottiana	Monimiaceae	**7**
Monodora junodii, M. tenuifolia	Annonaceae	**7**
Monoon borneense, M. cupulare	Annonaceae	**7**
Nelumbo nucifera	Nelumbonaceae	**7**
Neolitsea acuminatissima, N. sericea	Lauraceae	**7**
Ocotea spp.	Lauraceae	**7**
Oxandra asbeckii, O. xylopioides	Annonaceae	**7**
Pachygone ovata	Menispermaceae	**7**
Phaeanthus ophthalmicus	Annonaceae	**7**
Phoebe formosana	Lauraceae	**7**
Polyalthia insignis, P. macropoda, P. microtus, P. stenopetala	Annonaceae	**7**
Pseuduvaria indochinensis, P. rugosa, P. trimera	Annonaceae	**7**
Rhigiocarya racemifera	Menispermaceae	**7**
Sapranthus palanga	Annonaceae	**7**
Sinomenium acutum	Menispermaceae	**7**

		Siparuna brasiliensis, S. guianensis, S. thecaphora	Siparunaceae	**7**
		Stephania corymbosa, S. rotunda, Stephania venosa	Menispermaceae	**7,69**
		Thalictrum javanicum	Ranunculaceae	**7**
		Trivalvaria costata, T. macrophylla	Annonaceae	**7**
		Unonopsis guatterioides, U. spectabilis	Annonaceae	**7**
		Uvaria argentea, U. mocoli, U. rufa, U. versicolor	Annonaceae	**7**
		Xylopia aethiopica	Annonaceae	**7**
		Zanthoxylum nitidum, Z. scandens, Z. simulans	Rutaceae	**7,102**
206	Isomoschatoline	*Aquilegia oxysepala*	Ranunculaceae	**7**
		Aristolochia littoralis	Aristolochiaceae	**7**
		Cleistopholis patens	Annonaceae	**7**
		Guatteria blepharophylla, G. megalophylla	Annonaceae	**71,122**
		Uvaria mocoli	Annonaceae	**7**
207	Splendidine	*Abuta rufescens*	Menispermaceae	**131**
		Houttuynia cordata	Saururaceae	**7**
		Sinomenium acutum	Menispermaceae	**71**
208	Subsessiline	*Guatteria blepharophylla*	Annonaceae	**122**
		Abuta rufescens	Menispermaceae	**131**
209	3-methoxyoxoputerine N-oxide	*Dasymaschalon rostratum*	Annonaceae	**130**
210	1-Demethyl dicentrinone	*Toddalia asiatica*	Rutaceae	**33**
211	Dicentrinone	*Alstonia angustiloba*	Apocynaceae	**7**
		Annona cherimola, A. cherimola	Annonaceae	**7**
		Artemisia pectinata	Asteraceae	**7**
		Avena fatua	Poaceae	**7**
		Baccharis grandicapitulata	Asteraceae	**7**
		Baptisia australis	Fabaceae	**7**
		Beesia calthifolia	Ranunculaceae	**7**
		Boschniakia rossica	Orobanchaceae	**7**

Botrychium ternatum	Ophioglossaceae	**7**
Bursera kerberi	Burseraceae	**7**
Cardamine amara	Brassicaceae	**7**
Clerodendrum trichotomum	Lamiaceae	**7**
Clinacanthus nutans	Acanthaceae	**7**
Coffea liberica	Rubiaceae	**7**
Crotalaria stolzii	Fabaceae	**7**
Curcuma aeruginosa	Zingiberaceae	**7**
Dasymaschalon blumei, D. dasymaschalum	Annonaceae	**7**
Delphinium giraldii	Ranunculaceae	**7**
Duguetia furfuracea	Annonaceae	**7**
Duguetia surinamensis	Annonaceae	**7**
Eucalyptus albens	Myrtaceae	**7**
Euonymus fortunei	Celastraceae	**7**
Euploca racemosa	Boraginaceae	**7**
Gutierrezia dracunculoides	Asteraceae	**7**
Hedysarum gmelini	Fabaceae	**7**
Helenium integrifolium	Asteraceae	**7**
Helichrysum fulvum	Asteraceae	**7**
Hymenothrix wislizeni	Asteraceae	**7**
Illigera luzonensis, I. pentaphylla	Hernandiaceae	**7**
Juniperus scopulorum	Cupressaceae	**7**
Lasianthaea podocephala	Asteraceae	**7**
Lindera megaphylla	Lauraceae	**7**
Litsea sericea	Lauraceae	**7**
Lupinus cosentinii	Fabaceae	**7**
Magnolia coco	Magnoliaceae	**7**
Melampodium leucanthum	Asteraceae	**7**

Mitrephora maingayi	Annonaceae	**7**
Morella pensylvanica	Myricaceae	**7**
Nassauvia uniflora	Asteraceae	**7**
Ocotea leucoxylon, O. macropoda	Lauraceae	**7**
Ormosia dasycarpa	Fabaceae	**7**
Papaver pseudocanescens	Papaveraceae	**7**
Pellacalyx axillaris	Rhizophoraceae	**7**
Pentzia albida	Asteraceae	**7**
Phillyrea latifolia	Oleaceae	**7**
Phlomis crinita	Lamiaceae	**7**
Piper brachystachyum, P. sylvaticum	Piperaceae	**7**
Psidium acutangulum	Myrtaceae	**7**
Renealmia alpinia	Zingiberaceae	**7**
Rhododendron mucronulatum	Ericaceae	**7**
Sarcophyton flexuosum	Lamiaceae	**7**
Selinum libanotis	Apiaceae	**7**
Senecio congestus	Asteraceae	**7**
Sideritis dasygnaphala	Lamiaceae	**7**
Silene viridiflora	Caryophyllaceae	**7**
Sinomenium acutum	Menispermaceae	**7**
Stellaria media	Caryophyllaceae	**7**
Stephania abyssinica, S. dinklagei, S. mashanica, S. tetrandra, S. zippeliana	Menispermaceae	**7**
Tephroseris kirilowii	Asteraceae	**7**
Toddalia asiatica	Rutaceae	**33**
Valeriana ficariifolia	Caprifoliaceae	**7**
Verbena littoralis	Verbenaceae	**7**
Wikstroemia hainanensis	Thymelaeaceae	**7**

		Xylopia amazonica, X. championi, X. poilanei	Annonaceae	**7**
		Zephyranthes flava	Amaryllidaceae	**7**
AMARYLLIDACEAE ALKALOIDS				
212	9-O-demethylgalanthine	*Zephyranthes robusta*	Amaryllidaceae	**133**
213	Galanthine	*Crinum asiaticum*	Amaryllidaceae	**7**
		Galanthus elwesii	Amaryllidaceae	**7**
		Hippeastrum puniceum	Amaryllidaceae	**7**
		Lycoris incarnata, L. sanguinea	Amaryllidaceae	**7**
		Sternbergia lutea	Amaryllidaceae	**7**
		Zephyranthes carinata, Z. citrina, Z. robusta	Amaryllidaceae	**7,133**
214	Caranine	*Clivia miniata*	Amaryllidaceae	**7**
		Crinum bulbispermum	Amaryllidaceae	**7**
		Drimia altissima	Asparagaceae	**7**
		Scadoxus pseudocaulus	Amaryllidaceae	**134**
215	Amarbellisine	*Amaryllis belladonna*	Amaryllidaceae	**7**
		Scadoxus pseudocaulus	Amaryllidaceae	**134**
216	Lycorine	*Acis autumnalis*	Amaryllidaceae	**7**
		Amaryllis belladonna	Amaryllidaceae	**7**
		Ammocharis coranica, A. longifolia, A. tinneana	Amaryllidaceae	**7**
		Brunsvigia gregaria, B. orientalis, B. radulosa	Amaryllidaceae	**7**
		Chlidanthus fragrans	Amaryllidaceae	**133**
		Clivia miniata	Amaryllidaceae	**7**
		Clivia nobilis	Amaryllidaceae	**7**
		Crinum americanum, C. asiaticum, C. bulbispermum, C. firmifolium, C. glaucum, C. jagus, C. kirkii, C. latifolium, C. lugardiae, C. macowanii, C. moorei, C. stuhlmannii, C. yemense	Amaryllidaceae	**7,135-137**
		Crossyne flava	Amaryllidaceae	**7**
		Drimia altissima	Asparagaceae	**7**

		Eucharis amazonica	Amaryllidaceae	**7**
		Galanthus elwesii, G. nivalis	Amaryllidaceae	**7**
		Hippeastrum puniceum, H. vittatum	Amaryllidaceae	**7**
		Hymenocallis littoralis, H. rotata, H. tubiflora	Amaryllidaceae	**7**
		Lapiedra martinezii	Asparagaceae	**7**
		Leucojum aestivum, L. vernum	Amaryllidaceae	**7**
		Lycoris incarnata, L.s radiata, L. sanguinea	Amaryllidaceae	**7**
		Narcissus jacetanus, N. leonensis, N. papyraceus, N. pseudonarcissus, N. tazetta, N. tortuosus	Amaryllidaceae	**7**
		Pancratium canariense, P. maritimum, P. sickenbergeri, P. trianthum	Amaryllidaceae	**7,138,139**
		Scadoxus pseudocaulus	Amaryllidaceae	**134**
		Sternbergia clusiana, S. lutea	Amaryllidaceae	**7**
		Zephyranthes candida, Z. chlorosolen, Z. citrina, Z. drummondii, Z. robusta, Z. rosea	Amaryllidaceae	**7,133**
217	O-Acetyllycorine	*Ammocharis coranica*	Amaryllidaceae	**7**
		Brunsvigia radulosa	Amaryllidaceae	**7**
		Crinum kirkii, C. latifolium, C. macowanii, C. moorei	Amaryllidaceae	**7,137,140**
		Lycoris traubii	Amaryllidaceae	**7**
218	Acetylcaranine	*Amaryllis belladonna*	Amaryllidaceae	**7**
		Ammocharis coranica	Amaryllidaceae	**7**
		Drimia altissima	Asparagaceae	**7**
		Nerine bowdenii	Amaryllidaceae	**141**
219	Ungeremine	*Crinum americanum, C. asiaticum*	Amaryllidaceae	**7**
		Galanthus nivalis	Amaryllidaceae	**7**
		Hymenocallis littoralis	Amaryllidaceae	**142**
		Pancratium maritimum	Amaryllidaceae	**7**
		Scadoxus pseudocaulus	Amaryllidaceae	**134**
220	Hippadine	*Ammocharis coranica*	Amaryllidaceae	**7**

		Crinum americanum, C. asiaticum, C. bulbispermum, C. kirkii, C. latifolium, C. macowanii	Amaryllidaceae	**7,143**
		Hippeastrum vittatum	Amaryllidaceae	**7**
		Imperata cylindrica	Poaceae	**7**
		Lycoris sanguinea	Amaryllidaceae	**7**
		Pancratium maritimum	Amaryllidaceae	**138**
		Scadoxus pseudocaulus	Amaryllidaceae	**134**
		Sternbergia lutea	Amaryllidaceae	**7**
221	Crinine	*Ammocharis tinneana*	Amaryllidaceae	**7**
		Brunsvigia gregaria, B. orientalis, B. radulosa	Amaryllidaceae	**7**
		Calostemma purpureum	Amaryllidaceae	**7**
		Crinum americanum, C. asiaticum, C. bulbispermum, C. jagus, C. kirkii, C. latifolium, C. lugardiae, C. macowanii, C. moorei, C. stuhlmannii	Amaryllidaceae	**7,136,137,144**
		Crossyne flava	Amaryllidaceae	**7**
		Galanthus elwesii	Amaryllidaceae	**7**
		Hymenocallis littoralis	Amaryllidaceae	**7**
		Nerine bowdenii	Amaryllidaceae	**141**
		Pancratium maritimum	Amaryllidaceae	**7**
222	Vittatine	*Amaryllis belladonna*	Amaryllidaceae	**7**
		Crinum asiaticum, C. bulbispermum, C. yemense	Amaryllidaceae	**7**
		Eucharis amazonica	Amaryllidaceae	**7**
		Hippeastrum papilio, H. puniceum, H. vittatum	Amaryllidaceae	**7**
		Hymenocallis littoralis, H. rotata	Amaryllidaceae	**7**
		Ismene narcissiflora	Amaryllidaceae	**7**
		Lycoris radiata	Amaryllidaceae	**7**
		Narcissus cantabricus	Amaryllidaceae	**7**
		Nerine bowdenii, N. sarniensis	Amaryllidaceae	**7,141**
		Pancratium canariense, P. illyricum, P. maritimum, P. sickenbergeri	Amaryllidaceae	**7,139**

		Scadoxus pseudocaulus	Amaryllidaceae	**134**
		Sternbergia lutea, S. sicula	Amaryllidaceae	**7**
		Zephyranthes citrina	Amaryllidaceae	**7**
223	Buphanisine	*Nerine bowdenii*	Amaryllidaceae	**141**
224	Buphanidrine	*Ammocharis tinneana*	Amaryllidaceae	**7**
		Boophone disticha	Amaryllidaceae	**7**
		Brunsvigia orientalis	Amaryllidaceae	**7**
		Crinum latifolium, C. macowanii	Amaryllidaceae	**7**
		Nerine bowdenii	Amaryllidaceae	**141**
225	Crinamine	*Ammocharis coranica*	Amaryllidaceae	**7**
		Brunsvigia orientalis, B. radulosa	Amaryllidaceae	**7**
		Crinum asiaticum, C. bulbispermum, C. firmifolium, C. glaucum, C. jagus, C. latifolium, C. macowanii, C. stuhlmannii, C. yemense	Amaryllidaceae	**7,135,137,144**
		Crossyne flava	Amaryllidaceae	**7**
		Dioscorea dregeana	Dioscoreaceae	**7**
		Narcissus cantabricus	Amaryllidaceae	**7**
		Zephyranthes rosea	Amaryllidaceae	**7**
226	Haemanthamine (Natalensine)	*Alangium salviifolium*	Cornaceae	**145**
		Zephyranthes ajax, Z. robusta	Amaryllidaceae	**7**
227	Haemanthidine	*Zephyranthes robusta*	Amaryllidaceae	**133**
228	Hamayne	*Ammocharis coranica*	Amaryllidaceae	**7**
		Brunsvigia radulosa	Amaryllidaceae	**7**
		Crinum asiaticum, C. bulbispermum, C. firmifolium, C. glaucum, C. jagus, C. kirkii, C. latifolium, C. lugardiae, C. macowanii, C. stuhlmannii, C. yemense	Amaryllidaceae	**7,135,136**
		Crossyne flava	Amaryllidaceae	**7**
		Galanthus nivalis	Amaryllidaceae	**7**
		Hippeastrum morelianum	Amaryllidaceae	**7**
		Zephyranthes robusta	Amaryllidaceae	**133**

229	3-O-Acetyl-hamayne	*Crinum asiaticum, C. bulbispermum, C. latifolium, C. macowanii, C. moorei, C. yemense*	Amaryllidaceae	**7,137,144**
		Crossyne flava	Amaryllidaceae	**7**
230	Ambelline	*Amaryllis belladonna*	Amaryllidaceae	**7**
		Ammocharis tinneana	Amaryllidaceae	**7**
		Chlidanthus fragrans	Amaryllidaceae	**133**
		Crinum asiaticum, C. latifolium	Amaryllidaceae	**7**
		Nerine undulata	Amaryllidaceae	**7**
231	Distichamine	*Nerine bowdenii*	Amaryllidaceae	**141**
		Scadoxus pseudocaulus	Amaryllidaceae	**134**
232	Buphanamine	*Boophone disticha*	Amaryllidaceae	**147**
233	1-Epideacetylbowdensine	*Brunsvigia radulosa*	Amaryllidaceae	**7**
		Crinum asiaticum, C. macowanii, C. moorei	Amaryllidaceae	**7,136,144**
234	1-O-Acetylbulbisine	*Crinum asiaticum*	Amaryllidaceae	**7**
235	Crinamidine	*Ammocharis tinneana*	Amaryllidaceae	**7**
		Boophone disticha	Amaryllidaceae	**7**
		Brunsvigia gregaria, B. orientalis	Amaryllidaceae	**7**
		Crinum asiaticum, C. bulbispermum, C. latifolium, C. macowanii, C. moorei	Amaryllidaceae	**7,136,144**
		Nerine bowdenii, N. sarniensis, N. undulata	Amaryllidaceae	**7**
236	Undulatine	*Amaryllis belladonna*	Amaryllidaceae	**7**
		Ammocharis tinneana	Amaryllidaceae	**7**
		Boophone disticha	Amaryllidaceae	**7**
		Brunsvigia gregaria, B. orientalis	Amaryllidaceae	**7**
		Chlidanthus fragrans	Amaryllidaceae	**133**
		Crinum latifolium, C. macowanii, C. moorei	Amaryllidaceae	**7,137**
		Crossyne flava	Amaryllidaceae	**7**
		Galanthus nivalis	Amaryllidaceae	**7**

		Nerine bowdenii, N. undulata	Amaryllidaceae	**7**
		Tecomella undulata	Bignoniaceae	**7**
237	Lycoricidine	*Hymenocallis littoralis*	Amaryllidaceae	**7**
		Lycoris radiata, L. sanguinea, L. squamigera	Amaryllidaceae	**7**
		Portulaca oleracea	Convolvulaceae	**114**
238	Narciclasine	*Hymenocallis littoralis*	Amaryllidaceae	**142**
		Narcissus spp.	Amaryllidaceae	**7**
239	Pancratistatin	*Delphinium denudatum*	Ranunculaceae	**7**
		Hymenocallis littoralis, H. speciosa	Amaryllidaceae	**7,142**
		Pancratium maritimum	Amaryllidaceae	**7**
		Scadoxus pseudocaulus	Amaryllidaceae	**134**
		Zephyranthes carinata	Amaryllidaceae	**7**
240	6,9,11-trihydroxybenzo[1, 3]dioxolo[4,5-c]phenanthridin-5(4H)-one	*Portulaca oleracea*	Convolvulaceae	**114**
241	6,11-dihydroxy-8,9-dimethoxybenzo[1,3]dioxolo[4,5-c]phenanthridin-5(4H)-one	*Portulaca oleracea*	Convolvulaceae	**114**
OTHERS				
242	Norrufescine	*Abuta rufescens*	Menispermaceae	**131**
		Cissampelos pareira	Menispermaceae	**7**
		Pericampylus glaucus	Menispermaceae	**7**
		Telitoxicum peruvianum	Menispermaceae	**7**
243	Imeluteine	*Abuta rufescens*	Menispermaceae	**131**
244	Grandirubrine	*Abuta grandifolia, A. rufescens*	Menispermaceae	**7,131**
		Cissampelos pareira	Menispermaceae	**131**
245	Isoimerubrine	*Abuta rufescens*	Menispermaceae	**131**
		Cissampelos pareira	Menispermaceae	**7**
246	Imerubrine	*Abuta rufescens*	Menispermaceae	**131**
		Pericampylus glaucus	Menispermaceae	**7**

247	Sinomenine	*Dictamnus angustifolius*	Rutaceae	**8**
		Menispermum dauricum	Menispermaceae	**7**
		Sinomenium acutum	Menispermaceae	**148**
		Stephania cephalantha, S. rotunda	Menispermaceae	**7,69**
248	(-)-alpha-Hydrastine	*Corydalis spp.*	Papaveraceae	**149**
		Fumaria officinalis, F. vaillantii	Papaveraceae	**149**
249	beta-Hydrastine	*Berberis aquifolium, B. laurina*	Berberidaceae	**7**
		Coptis teeta	Ranunculaceae	**7**
		Fumaria indica, F. parviflora, F. vaillantii	Papaveraceae	**7,154**
		Hydrastis canadensis	Ranunculaceae	**150**
		Papaver heterophyllum	Papaveraceae	**7**
250	Noscapine	*Corydalis heterocarpa, C. ochotensis, C. ophiocarpa, C. solida*	Papaveraceae	**7**
		Papaver armeniacum, P. orientale, P. pseudo-orientale, P. rhoeas, P. somniferum	Papaveraceae	**7**
251	Capnoidine	*Capnoides sempervirens*	Papaveraceae	**7**
		Corydalis cava, C. dubia, C. solida	Papaveraceae	**7,101**
		Fumaria capreolata, F. parviflora, F. petteri, F. vaillantii	Papaveraceae	**7,151,154,156**
252	Bicuculline	*Adlumia fungosa*	Papaveraceae	**7**
		Capnoides sempervirens	Papaveraceae	**7**
		Corydalis bungeana, C. caseana, C. cava, C. crispa, C. decumbens, C. intermedia, C. nobilis, C. racemosa, C. repens, C. scouleri, C. solida	Papaveraceae	**7**
		Dicentra cucullaria, D. peregrina	Papaveraceae	**7**
		Fumaria asepala, F. barnolae, F. bracteosa, F. capreolata, F. densiflora, F. indica, F. kralikii, F. macrocarpa, F. parviflora, F. vaillantii	Papaveraceae	**149,151-156**
		Pseudofumaria lutea	Papaveraceae	**7**
253	Yohimbine	*Pausinystalia yohimbe*	Rubiaceae	**157**
		Tabernaemontana corymbosa	Apocynaceae	**7**

254	Vincamine	*Vinca minor*	Apocynaceae	**157**
		Tabernaemontana corymbosa	Apocynaceae	**7**
255	Isotubulosine	*Pogonopus tubulosus*	Rubiaceae	**158**
256	Jozimine A2	*Ancistrocladus abbreviatus*	Ancistrocladaceae	**159**
257	Jozilebomine A	*Ancistrocladus ileboensis*	Ancistrocladaceae	**160**
258	Jozilebomine B	*Ancistrocladus ileboensis*	Ancistrocladaceae	**160**

Table 2 Biological effects of (iso)quinolines on intestinal bacteria and/or cells

No.	Compound	Bacteria/Cells	MIC/(IC_{50}/ED_{50}) (μg/ml) ([a]active, [b]inactive,)	References
SIMPLE QUINOLINES				
1	8-Hydroxyquinoline	*Bacillus cereus*	4-512	**2,120,161,162**
		Enterococcus faecalis	4-512	**120,161,163**
		Listeria monocytogenes	1-10	**2,120**
		Staphylococcus aureus	2-25,>62.5	**2,162,163**
		Salmonella Enteridis	32-256	**120,161**
		Salmonella Typhi	>62.5	**162**
		Salmonella Typhimurium	32-512	**2,120,161**
		Escherichia coli	32-256, >62.5	**2,161-163**
		Escherichia coli 0175:H7	256	**120**
		Shigella flexneri	128, >62.5	**120,162**
		Shigella dysenteriae	4	**161**
		Clostridium difficile	128	**120**
		Clostridium perfringens	32-128	**120,164**
		Yersinia enterocolitica	512	**120**
		Klebsiella pneumoniae	64, >62.5	**161,162**
		Plesiomonas shigelloides	4	**161**
		Lacticaseibacillus casei	>512	**120**
		Lacticaseibacillus rhamnosus	>512	**120**
		Lactobacillus reuteri	>512	**120**
		Bifidobacterium breve	>512	**120**
		Bifidobacterium animalis spp. lactis	>512	**120**
		Bifidobacterium adolescentis	512	**120**
		Bifidobacterium bifidum	512	**120**

		Bifidobacterium longum ssp. longum	512-1024	**120,164**
		Bifidobacterium animalis subsp. animalis	512	**164**
		Bifidobacterium gallinarum	512	**164**
		Bacteroides fragilis	32	**120**
		Bacillus subtilis	4-31.3	**161,162**
		HT-29	0.94-1.3	**120,165**
		Caco-2	0.3-3.24	**120,163**
		FHs 74 Int	10.7	**120**
2	Lepidine	*Bacillus cereus*	50	**3**
		Listeria monocytogenes	25	**3**
		Staphylococcus aureus	12.5	**3**
		Salmonella Typhimurium	75	**3**
		Shigella sonnei	100	**3**
3	Quinaldic acid	*Escherichia coli*	NA	**5**
		Clostridium difficile	A[a]	**5**
		Clostridium perfringens	A	**5**
		Lacticaseibacillus casei	NA[b]	**5**
		Bifidobacterium bifidum	NA	**5**
		HT-29	72.6-391.932	**166**
		Caco-2	130.64-290.32	**166**
		LS180	72.6-624.188	**166**
4	Quinoline-4-carboxaldehyde	*Escherichia coli*	NA	**6**
		Clostridium perfringens	A	**6**
		Bifidobacterium bifidum	NA	**6**
		Bifidobacterium longum ssp. longum	NA	**6**
FUROQUINOLINES				
5	Dictamnine (syn. Dictamine)	*Enterococcus spp.*	25	**9**

		Staphylococcus aureus	86-100, >1000	**9,15,36**
		Staphylococcus aureus (MRSA)	>1000	**36**
		Salmonella Typhimurium	100, >1000	**9,36**
		Escherichia coli	100, 109, >1000, A, NA	**8,9,12,15,36**
		HT-29	26.7	**13**
		LOVO	27.9, A	**8,15**
6	Robustine	*Enterococcus faecalis*	5.37	**16**
		Staphylococcus aureus	92, >50	**15,16**
		Escherichia coli	110, A	**8,15**
		LOVO	A	**8**
7	Confusameline	*Staphylococcus aureus*	>32	**17**
		Escherichia coli	>32	**17**
		HT-29	0.24	**34**
8	γ-Fagarine	*Enterococcus faecalis*	A	**18**
		Enterococcus spp.	100	**9**
		Staphylococcus aureus	50-500, A	**9,15,18,25,36**
		Staphylococcus aureus (MRSA)	500	**36**
		Salmonella Typhimurium	100, >1000, A	**9,18,36**
		Escherichia coli	100-128, >1000	**8,9,15,25,36**
		HT-29	24.35	**13**
		LOVO	29.4, A	**8,15**
9	Evolitrin	*Staphylococcus aureus*	>32	**17**
		Escherichia coli	>32	**17**
10	Pteleine	*Staphylococcus aureus*	>32	**17**
		Escherichia coli	>32	**17**
11	Melineurine	*Staphylococcus aureus*	>32	**17**
		Escherichia coli	>32	**17**

12	Leptanoine D	*Staphylococcus aureus*	>32	**17**
		Escherichia coli	>32	**17**
13	Confusadine	HT-29	4.3	**34**
14	Haplopine	HT-29	3.3	**34**
15	Skimmianine	*Enterococcus faecalis*	A	**18**
		Staphylococcus aureus	100-103, >1000, A, NA	**15,18,25,36,33**
		Staphylococcus aureus (MRSA)	>1000	**36**
		Salmonella Typhimurium	>1000, A	**18,36**
		Escherichia coli	144, >100, >1000, A, NA	**8,15,25,33,36**
		Klebsiella pneumoniae	NA	**33**
		Shigella dysenteriae	NA	**33**
		HT-29	0.12-0.38	**21,34**
		LOVO	33.1, A	**8,15**
		HCT15	36.6	**33**
16	7-O-Isopentenyl-γ-fagarine	*Enterococcus faecalis*	A	**18**
		Staphylococcus aureus	A	**18**
		Salmonella Typhimurium	A	**18**
17	Evoxine	*Enterococcus faecalis*	A	**18**
		Staphylococcus aureus	1000	**36**
		Staphylococcus aureus (MRSA)	>1000	**36**
		Salmonella Typhimurium	>1000, A	**18,36**
		Escherichia coli	>1000, NA	**12,36**
18	Anhydroevoxine	*Enterococcus faecalis*	A	**18**
		Staphylococcus aureus	A	**18**
		Salmonella Typhimurium	A	**18**
		Escherichia coli	NA	**12**

19	Lecomtequinoline A	*Escherichia coli*	18.7	**12**
20	Lecomtequinoline B	*Escherichia coli*	16.2	**12**
21	Lecomtequinoline C	*Escherichia coli*	15.7	**12**
22	Kokusaginine	*Enterococcus faecalis*	A	**18**
		Enterococcus spp.	25	**9**
		Staphylococcus aureus	39.06-100, >32, A	**9,17,18,23**
		Salmonella Typhi	9.76	**23**
		Salmonella Typhimurium	100, A	**9,18**
		Escherichia coli	4.88-512, >32	**9,17,23,26**
		Klebsiella aerogenes	128-512	**26**
		HT-29	1.4	**34**
23	Nkolbisine (montrifoline)	*Staphylococcus aureus*	>78.12	**23**
		Salmonella Typhi	9.76	**23**
		Escherichia coli	NA	**23**
		HCT116	A	**72**
24	Acronycidine	*Escherichia coli*	>20000	**28**
25	Platydesmine	*Staphylococcus aureus*	>1000	**36**
		Staphylococcus aureus (MRSA)	>1000	**36**
		Salmonella Typhimurium	>1000	**36**
		Escherichia coli	>1000	**36**
		HT-29	>50	**11**
26	N-methylplatydesminium	*Staphylococcus aureus*	>32	**17**
		Escherichia coli	>32	**17**
27	(+-)-8-Methoxyplatydesmine	HT-29	>50	**34**
28	(S)-(-)-7,8-Dimethoxyplatydesmine	HT-29	1.9	**34**
29	(+)-7,8-Dimethoxymyrtopsine	HT-29	41.6	**11**
30	Melicarpinone	HT-29	30.5	**34**
31	5-Hydroxy-4,8-dimethoxy furoquinoline	*Staphylococcus aureus*	134	**15**

		Escherichia coli	187	**15**
		LOVO	32.8	**15**
32	Megistoquinone I	*Escherichia coli*	4750	**28**
33	Maculine	*Enterococcus spp.*	100	**9**
		Staphylococcus aureus	100, >78.12	**9,23**
		Salmonella Typhi	9.76	**23**
		Salmonella Typhimurium	100	**9**
		Escherichia coli	100, >78.12	**9,23**
34	Flindersiamine	*Enterococcus spp.*	50	**9**
		Staphylococcus aureus	100	**9**
		Salmonella Typhimurium	100	**9**
		Escherichia coli	100	**9**
35	7-(3-Anilino-2-hydroxyprenyloxy)-8-methoxydictamine	*Escherichia coli*	15.3	**32**
36	5-Methoxydictamnine	*Escherichia coli*	NA	**33**
		Klebsiella pneumoniae	NA	**33**
		Shigella dysenteriae	NA	**33**
		Staphylococcus aureus	NA	**33**
37	Dimethyl rhoifolinate	HT-29	3.4-3.6	**34**
38	Dutadrupine	HT-29	0.13	**34**
39	Semecarpine	HT-29	29.3	**34**
40	Choisyine	*Staphylococcus aureus*	>1000	**36**
		Staphylococcus aureus (MRSA)	>1000	**36**
		Salmonella Typhimurium	>1000	**36**
		Escherichia coli	>1000	**36**
41	Melicarpine	HT-29	2.5	**34**
42	Megistoquinone II	*Escherichia coli*	1020	**28**
43	Zanthonitidine A	*Enterococcus faecalis*	12.54-21.97	**16**
		Staphylococcus aureus	21.97-25.1	**16**

44	Isodictamnine	*Staphylococcus aureus*	44	**15**
		Escherichia coli	76	**15**
		LOVO	18.6	**15**
45	Acrophylline	*Staphylococcus aureus*	>32	**17**
		Escherichia coli	>32	**17**
46	(S)-(+)-Isoplatydesmine	HT-29	1.5	**34**
47	Balfouridine	*Staphylococcus aureus*	>1000	**36**
		Staphylococcus aureus (MRSA)	>1000	**36**
		Salmonella Typhimurium	>1000	**36**
		Escherichia coli	>1000	**36**
48	Lemobiline	*Staphylococcus aureus*	>1000	**36**
		Staphylococcus aureus (MRSA)	>1000	**36**
		Salmonella Typhimurium	>1000	**36**
		Escherichia coli	>1000	**36**
QUINOLONES				
49	4-methoxy-N-methyl-2- quinolone	*Enterococcus faecalis*	18.91	**16**
		Enterococcus spp.	100	**9**
		Escherichia coli	100	**9**
		Salmonella Typhimurium	100	**9**
		Staphylococcus aureus	>50	**16**
		Staphylococcus aureus	100	**9**
50	Edulitine	*Staphylococcus aureus*	>1000	**36**
		Staphylococcus aureus (MRSA)	>1000	**36**
		Salmonella Typhimurium	>1000	**36**
		Escherichia coli	>1000	**36**
51	Lunacridine	*Staphylococcus aureus*	1000	**36**
		Staphylococcus aureus (MRSA)	>1000	**36**
		Salmonella Typhimurium	>1000	**36**

52	2′-O-trifluoroacetyl lunacridine	*Escherichia coli*	>1000	**36**
		Staphylococcus aureus	256	**38**
		Escherichia coli	>256	**38**
53	Glycocitridine	HT-29	0.52	**34**
54	Melisemine	HT-29	4	**34**
55	Edulinine	HT-29	25.5	**34**
56	Flindersine	*Enterococcus faecalis*	31.25	**39**
		Staphylococcus aureus	62.5	**39**
		Staphylococcus aureus (MRSA)	>250	**39**
		Escherichia coli	>250	**39**
57	Veprisine	*Staphylococcus aureus*	125	**36**
		Staphylococcus aureus (MRSA)	>1000	**36**
		Salmonella Typhimurium	>1000	**36**
		Escherichia coli	>1000	**36**
58	Zanthodioline	*Enterococcus faecalis*	37.83	**16**
		Staphylococcus aureus	>50	**16**
59	Melicodenine C	DLD-1	8.67-21.68	**40**
60	Melicodenine F	DLD-1	8.11-20.27	**40**
61	Melicodenine G	DLD-1	4.3	**40**
62	Vepridimerine A	*Staphylococcus aureus*	>1000	**36**
		Staphylococcus aureus (MRSA)	>1000	**36**
		Salmonella Typhimurium	>1000	**36**
		Escherichia coli	>1000	**36**
63	Melicodenine H	DLD-1	9.15-22.88	**40**
64	Evocarpine	*Campylobacter jejuni*	A	**42**
65	Graveoline (graveolinine)	*Enterococcus faecalis*	500	**22**
		Staphylococcus aureus	1000	**22**
		Escherichia coli	1000	**22**

66	Ribalinine	*Staphylococcus aureus*	>1000	**36**
		Staphylococcus aureus (MRSA)	>1000	**36**
		Salmonella Typhimurium	>1000	**36**
		Escherichia coli	>1000	**36**
67	Rutaecarpine	*Campylobacter jejuni*	A	**42**
		HT-29	31.63	**13**
68	1-Hydroxyrutaecarpine	HT-29	7.39	**13**
69	Evodiamine	*Campylobacter jejuni*	A	**42**
INDOLOQUINOLINES				
70	Quindoline	*Enterococcus faecalis*	>100	**44**
		Escherichia coli	>100	**44**
		Shigella dysenteriae	>100	**44**
		Staphylococcus aureus	>100	**44**
		Vibrio cholerae	>100	**44**
71	Cryptolepine	*Bacillus cereus*	20–40, <7.8	**47,167**
		Bacillus subtilis	10–20	**167**
		Campylobacter coli	25	**168**
		Campylobacter jejuni	12.5	**168**
		Enterococcus faecalis	12.5	**44**
		Escherichia coli	5–80	**44,47,167,169**
		Salmonella Typhimurium	62.5	**47**
		Shigella dysenteriae	6.25	**44**
		Staphylococcus aureus	5-12.5, <7.8, A	**44,47,170**
		Vibrio cholerae	50, <1.5	**44,168**
		HCT116	A	**171**
72	Hydroxycryptolepine	*Enterococcus faecalis*	>100	**44**
		Escherichia coli	>100	**44**
		Shigella dysenteriae	>100	**44**

		Staphylococcus aureus	>100	**44**
		Vibrio cholerae	>100	**44**
73	Neocryptolepine	*Bacillus cereus*	62	**47**
		Escherichia coli	125	**47**
		Salmonella Typhimurium	125	**47**
		Staphylococcus aureus	31	**47**
74	Biscryptolepine	*Bacillus cereus*	500	**47**
		Salmonella Typhimurium	>500	**47**
		Staphylococcus aureus	62	**47**
75	Cryptoquindoline	*Enterococcus faecalis*	50	**44**
		Escherichia coli	>100	**44**
		Shigella dysenteriae	>100	**44**
		Staphylococcus aureus	100	**44**
		Vibrio cholerae	25	**44**
76	Camptothecin	*Escherichia coli*	16.67	**49**
		Staphylococcus aureus	4.16	**49**
		HT-29	0.000263	**172**
		SW620	0.13936	**173**
		Caco-2	3.7	**174**
		HCT116	0.0118456	**175**
		HCT15	2.47	**176**
		SW480	0.101036	**177**
		LS174T	0.003484	**178**
77	Thomsonine B	*Escherichia coli*	3330	**49**
		Staphylococcus aureus	13330	**49**
SIMPLE ISOQUINOLINES				
78	Thalifoline	HT-29	1.745	**51**
79	Northalifoline	HT-29	>50	**51**

SIMPLE BENZYLISOQUINOLINES

80	Coclaurine	HT-29	>50	**53**
		HCT116	8.233	**179**
81	Reticuline	*Enterococcus faecalis*	250	**54**
		Staphylococcus aureus	500, >500	**52,54**
		Escherichia coli	NA	**54**
		HT-29	>50	**51**
82	Laudanosine	*Escherichia coli*	>64	**60**
83	Papaverine	HCT15	>3.39	**61**
84	Oblongine	HT-29	>50	**53**
85	Hexapetaline A	SW480	4.76	**57**
86	Hexapetaline B	SW480	7.47	**57**
87	Cularine	*Escherichia coli*	>64	**60**
88	Thalicfoetine	*Staphylococcus aureus*	100	**62**
		Salmonella Typhi	>100	**62**
		Escherichia coli	6.25	**62**
		Bacillus subtilis	3.2	**62**

BISBENZYLISOQUINOLINES

89	Costaricine	HCT116	29.9	**63**
90	Neferine	HT-29	1	**64**
91	O-Methylneferine	HT-29	0.44	**64**
92	Isoliensinine	HCT15	7.63	**65**
93	Cycleanine	*Salmonella* Typhi	A	**66**
		Bacillus subtilis	A	**66**
		HCT116	330.15	**68**
94	N-Desmethylcycleanine	*Salmonella* Typhi	A	**66**
95	Isochondodendrine	HCT116	17.5	**68**
96	Cycleanine N-oxide	HCT116	41.8	**68**

97	Tetrandrine	HT-29	5.17-14	**53,180,181**
		Caco-2	12.454, A	**74,182**
		HCT15	A	**71**
		HCT116	7.47-10, A	**74,181,182**
		SW480	A	**182**
98	Isotetrandrine	HCT116	A	**72**
99	Berbamine	HT-29	3.71	**73**
100	Fangchinoline	Caco-2	A	**74**
		HCT15	A	**71**
		HCT116	A	**74**
101	Obaberine	HT-29	5.01	**53**
102	Homoaromoline	HT-29	4.8	**53**
103	Thalrugosaminine	*Enterococcus faecalis*	128	**75**
		Staphylococcus aureus	65	**75**
		Escherichia coli	128	**75**
104	Cocsoline	*Enterococcus faecalis*	500	**68**
		Salmonella Typhi	A	**66**
		Salmonella Typhimurium	15.62	**68**
		Escherichia coli	31.25	**68**
		Shigella sonnei	31.25	**68**
		Shigella flexneri	62.5	**68**
		Shigella boydii	62.5	**68**
		Shigella dysenteriae	125	**68**
		Vibrio parahaemolytics	125	**68**
		Vibrio cholerae	250	**68**
		Campylobacter jejuni	15.62	**68**
		Campylobacter coli	31.25	**68**
		HCT116	2.8	**68**

105	Thalmidine (O-Methylthalicberine)	*Enterococcus faecalis*	128	**75**
		Staphylococcus aureus	128	**75**
		Escherichia coli	128	**75**
106	5′-Hydroxythalidasine	*Enterococcus faecalis*	128	**75**
		Staphylococcus aureus	64	**75**
		Escherichia coli	128	**75**
107	Thalrugosidine	HT-29	2.3	**76**
108	Northalrugosidine	HT-29	5.12	**76**
109	Thalidasine	HT-29	3.5	**76**
110	Bersavine	HT-29	5.65	**73**
111	Cepharanthine	SW480	2.85	**77**
112	(+)-2-Norcepharanthine	SW480	2.19	**77**
113	Fangchinoline	Caco-2	A	**74**
		HCT15	A	**71**
		HCT116	A	**74**
114	Tiliarine	*Staphylococcus aureus*	A	**78**
		Escherichia coli 0175:H7	A	**78**
		Vibrio cholerae	NA	**78**
		Bacillus subtilis	A	**78**
115	2′-nortiliacorinine	*Staphylococcus aureus*	A	**78**
		Escherichia coli 0175:H7	A	**78**
		Vibrio cholerae	NA	**78**
		Bacillus subtilis	A	**78**
116	Neothalfine	HCT116	0.0047	**79**
		SW620	0.0038	**79**
		T84 (lung met.)	0.0053	**79**
PROTOBERBERINES				
117	Columbamine	*Escherichia coli*	A	**80**

118	Jatrorrhizine	*Staphylococcus aureus*	300, >1000	**84,183**
		Salmonella Typhi	200	**84**
		Escherichia coli	600, >1000, A	**80,84,183**
		Shigella dysenteriae	>1000	**84**
		Clostridium perfringens	250	**183**
		Klebsiella pneumoniae	>1000	**183**
		Enterobacter cloacae	1000	**183**
		Lactobacillus fermentum	500-1000	**183**
		Bifidobacterium bifidum	31.25–62.5	**183**
		Bacteroides fragilis	>1000	**183**
		Bacillus subtilis	100	**84**
119	Palmatine	*Bacillus cereus*	400	**88**
		Enterococcus faecalis	>1000	**183**
		Staphylococcus aureus	200-393.66, >1000, A	**70,88,183-185**
		Salmonella Typhi	200	**88**
		Escherichia coli	393.66-800, >1000, A	**85,88,89,183,185,186**
		Shigella dysenteriae	>1000	**88**
		Clostridium perfringens	15.75-125, A	**87,183**
		Helicobacter pylori	3.12-186.77	**88,185**
		Klebsiella aerogenes	128	**85**
		Klebsiella pneumoniae	128, >1000	**85,183**
		Enterobacter cloacae	>1000	**183**
		Lacticaseibacillus casei	NA	**187**
		Lactobacillus fermentum	500–1000	**183**
		Bifidobacterium adolescentis	NA	**183**
		Bifidobacterium bifidum	31.25–62.5	**183**
		Bifidobacterium longum ssp. longum	NA	**183**

120 Berberine

Bacteroides fragilis	>1000	**183**
Bacillus subtilis	100	**88**
HT-29	17.30, A	**88,185**
HCT15	>30	**86**
SW480	A	**88**
Bacillus cereus	>512	**120**
Enterococcus faecalis	>1000	**120,183,188**
Listeria monocytogenes	>512	**120**
Staphylococcus aureus	500–1000	**183,188**
Staphylococcus aureus (MRSA)	>64	**188**
Salmonella Enteridis	>512	**120**
Salmonella Typhimurium	512	**120**
Escherichia coli	>1000, A	**80,120**
Escherichia coli 0175:H7	>512	**120**
Shigella flexneri	>512	**120**
Clostridium difficile	17.56, >512	**87,120**
Clostridium perfringens	62.5–256, A	**120,183,187**
Yersinia enterocolitica	>512	**120**
Vibrio parahaemolytics	512	**120**
Helicobacter pylori	A	**189**
Klebsiella pneumoniae	>1000	**183**
Enterobacter cloacae	>1000	**183**
Lacticaseibacillus casei	64, A	**120,187**
Lacticaseibacillus rhamnosus	64	**120**
Lactobacillus reuteri	>512	**120**
Lactobacillus fermentum	250	**183**
Bifidobacterium breve	64	**120**
Bifidobacterium animalis spp. lactis	32	**120**

		Bifidobacterium adolescentis	128, NA	**120,187**
		Bifidobacterium bifidum	31.25–64, NA	**120,183,187**
		Bifidobacterium longum ssp. longum	32, NA	**120,187**
		Bacteroides fragilis	500, >512	**120,183**
		HT-29	2.1-5, A	**120,186,190**
		Caco-2	19.4	**120**
		HCT15	27.2	**86**
		HCT116	0.8-30.2, A	**97,191,192**
		SW620	A	**191**
		SW480	A	**191**
		SGC-7901	5.046	**193**
		IMCE	A	**191**
		SW613	A	**191**
		FHs 74 Int	1	**120**
		NCM460	>67.28	**192**
121	Dehydrocheilanthifoline	*Escherichia coli*	A	**80**
122	Coptisine	*Enterococcus faecalis*	>1000	**183**
		Staphylococcus aureus	>1000	**183**
		Escherichia coli	1000	**183**
		Clostridium perfringens	62.5	**183**
		Klebsiella pneumoniae	>1000	**183**
		Enterobacter cloacae	>1000	**183**
		Lactobacillus fermentum	250	**183**
		Bifidobacterium bifidum	31.25–62.5	**183**
		Bacteroides fragilis	500	**183**
		IEC-6	>3.2	**194**
123	Scoulerine	*Salmonella* Typhi	>250	**101**
		Escherichia coli	>250	**101**

124	Cyclanoline (syn. cissamine)	HT-29	>50	**53**
125	Isocoreximine	HT-29	A	**102**
126	11-Hydroxy-10-methoxy-(2,3)-methylenedioxytetrahydroprotoberberine	*Escherichia coli*	NA	**33**
		Klebsiella pneumoniae	NA	**33**
		Shigella dysenteriae	NA	**33**
		Staphylococcus aureus	NA	**33**
		HCT15	29.8	**33**
127	(2,3,10,11)-Dimethylenedioxytetrahydroprotoberberine	*Escherichia coli*	NA	**33**
		Klebsiella pneumoniae	NA	**33**
		Shigella dysenteriae	NA	**33**
		Staphylococcus aureus	NA	**33**
		HCT15	27.5	**33**
128	Pendulamine A	*Staphylococcus aureus*	A	**103**
		Salmonella Typhimurium	A	**103**
129	Pendulamine B	*Staphylococcus aureus*	A	**103**
		Salmonella Typhimurium	A	**103**
130	8-Oxoberberine (oxyberberine)	*Escherichia coli*	A	**80**
131	8-Oxo-epiberberine	HCT15	34.05	**86**
132	8-Oxocoptisine	HCT15	>30, A	**71,86**
133	Allocryptopine	*Staphylococcus aureus*	250	**104**
		Escherichia coli	125	**104**
134	Protopine (macleyine)	*Enterococcus faecium*	640	**106**
		Staphylococcus aureus	80-250	**104,106**
		Staphylococcus aureus (MRSA)	>250	**101**
		Escherichia coli	125, >250, >640	**101,104,106**
135	Cheilanthifoline	*Staphylococcus aureus* (MRSA)	>250	**101**
		Escherichia coli	>250	**101**
136	Baicalensine A	Caco-2	6.91	**107**

BENZOPHENANTHRIDINES

137	8-Methoxynorchelerythrine	*Escherichia coli*	450	**33**
		Klebsiella pneumoniae	340	**33**
		Shigella dysenteriae	360	**33**
		Staphylococcus aureus	420	**33**
		HCT15	8.9	**33**
138	11-Demethylrhoifoline B	*Escherichia coli*	400	**33**
		Klebsiella pneumoniae	370	**33**
		Shigella dysenteriae	400	**33**
		Staphylococcus aureus	510	**33**
		HCT15	8.5	**33**
139	8-Acetylnorchelerythrine	*Escherichia coli*	110	**33**
		Klebsiella pneumoniae	120	**33**
		Shigella dysenteriae	120	**33**
		Staphylococcus aureus	80	**33**
		HCT15	2	**33**
140	8,9,10,12-tetramethoxynorchelerythrine	*Escherichia coli*	570	**33**
		Klebsiella pneumoniae	460	**33**
		Shigella dysenteriae	420	**33**
		Staphylococcus aureus	390	**33**
		HCT15	4.1	**33**
141	2,3,13-Trimethoxy-[1,3]benzodioxolo[5,6-c]phenanthridine	*Escherichia coli*	320	**33**
		Klebsiella pneumoniae	430	**33**
		Shigella dysenteriae	400	**33**
		Staphylococcus aureus	510	**33**
		HCT15	10.3	**33**
142	Pancorine	*Escherichia coli*	410	**33**
		Klebsiella pneumoniae	390	**33**

		Shigella dysenteriae		310	**33**
		Staphylococcus aureus		440	**33**
		HCT15		8.2	**33**
143	Decarine (syn. Zanthoxyline, Rutaceline)		HCT116	A at 16	**118**
144	Nitidine	*Staphylococcus aureus*		25	**25**
		Escherichia coli		>100	**25**
145	Avicine	*Staphylococcus aureus*		1.5	**25**
		Escherichia coli		1.5	**25**
146	Chelerythrine	*Enterococcus faecalis*		4-32	**188,195**
		Staphylococcus aureus		1.5-31.3, A	**25,95,104,188,195**
		Staphylococcus aureus (MRSA)		4	**188**
		Salmonella Typhi		A	**95**
		Salmonella Typhimurium		>256	**195**
		Escherichia coli		16-125, A	**95,104,195,196**
		Escherichia coli 0175:H7		32	**195**
		Shigella sonnei		A	**95**
		Shigella flexneri		A	**95**
		Shigella boydii		A	**95**
		Klebsiella pneumoniae		>256	**195**
		HCT116		2.5, A	**112,197**
		SW480		2.5	**197**
147	8-Methoxynitidine	*Escherichia coli*		370	**33**
		Klebsiella pneumoniae		490	**33**
		Shigella dysenteriae		430	**33**
		Staphylococcus aureus		470	**33**
			HCT15	6.3	**33**
148	8-Methoxychelerythrine	*Escherichia coli*		350	**33**
		Klebsiella pneumoniae		520	**33**

		Shigella dysenteriae	400	**33**
		Staphylococcus aureus	410	**33**
		HCT15	7.6	**33**
149	Fagaridine	HCT15	0.41	**198**
		HCT116	4.83-6.21	**113**
150	Oxynorchelerythrine	HCT116	6.46	**114**
151	Oxynitidine	*Escherichia coli*	1180	**33**
		Klebsiella pneumoniae	1240	**33**
		Shigella dysenteriae	1090	**33**
		Staphylococcus aureus	880	**33**
		HCT15	14.2	**33**
152	Oxysanguinarine	*Enterococcus faecium*	640	**106**
		Staphylococcus aureus	640	**106**
		Escherichia coli	320-1200	**33,106**
		Klebsiella pneumoniae	1320	**33**
		Shigella dysenteriae	1120	**33**
		HCT15	14.5	**33**
153	6-Oxocorynoline	HCT15	32.76	**115**
154	Dihydrochelerythrine	*Enterococcus faecium*	>640	**106**
		Staphylococcus aureus	18.7-320	**106,199**
		Staphylococcus aureus (MRSA)	46.9	**95**
		Escherichia coli	25-640, >300, NA	**25,104,106,199**
		Enterococcus faecalis	18.7	**199**
		HCT8	0.48	**116**
155	12-Methoxydihydrochelerythrine (6-methoxydihydrochelerythrine)	*Enterococcus faecium*	20	**106**
		Staphylococcus aureus	10	**106**
		Escherichia coli	40	**106**
156	8-Hydroxydihydrochelerythrine	*Staphylococcus aureus* (MRSA)	0.98	**95**

157	6-Methoxyldihydrochelerythrine (Angoline)	*Bacillus subtilis*	8.27	**117**
		Staphylococcus aureus	25-33	**111,117**
		Enterococcus faecalis	25	**111**
158	6-Butoxydihydrochelerythrine	HCT8	0.69, A	**111,116**
		BGC-823	A	**111**
159	6-Acetonyldihydrochelerythrine	HCT116	A at 2	**118**
160	Zanthocapensine	HCT116	A at 25	**118**
161	(2′,6′-epoxy-1′,2′α,3′β,4′α,5′α - pentahydroxy)hexane-(1′ → 6)-dihydrochelerythrine	HCT8	1.001642	**116**
162	Bis[6-(5,6-dihydrochelerythrinyl)]ether	HCT8	1.140384	**116**
163	Sanguinarine	*Bacillus cereus*	128	**120**
		Enterococcus faecalis	8-32	**120,188**
		Listeria monocytogenes	16	**120**
		Staphylococcus aureus	1.56-31.3, A	**95,104,188,200**
		Staphylococcus aureus (MRSA)	2	**188**
		Salmonella Enteridis	256	**120**
		Salmonella Typhi	A	**95**
		Salmonella Typhimurium	512	**120**
		Escherichia coli	31.3-256, A	**95,104,120,196**
		Escherichia coli 0175:H7	128	**120**
		Shigella sonnei	A	**95**
		Shigella flexneri	64, A	**95,120**
		Shigella boydii	A	**95**
		Clostridium difficile	64	**120**
		Clostridium perfringens	128	**120**
		Yersinia enterocolitica	256	**120**
		Vibrio parahaemolytics	32	**120**
		Lacticaseibacillus casei	32	**120**

		Lacticaseibacillus rhamnosus	64	**120**
		Lactobacillus reuteri	32	**120**
		Bifidobacterium breve	32	**120**
		Bifidobacterium animalis spp. lactis	32	**120**
		Bifidobacterium adolescentis	16	**120**
		Bifidobacterium bifidum	32	**120**
		Bifidobacterium longum ssp. longum	64	**120**
		Bacteroides fragilis	>512	**120**
		HT-29	0.9	**120**
		Caco-2	0.8	**120**
		HCT116	0.66	**197**
		DLD-1	0.49-0.51	**112,197**
		SW480	0.59	**197**
		FHs 74 Int	1	**120**
164	Dihydrosanguinarine	*Enterococcus faecium*	80	**106**
		Staphylococcus aureus	9.3-20, NA	**104,106,199**
		Staphylococcus aureus (MRSA)	23.4	**95**
		Escherichia coli	320, NA	**104,106,111**
		Enterococcus faecalis	9.3	**199**
		HCT8	0.43	**116**
165	8-Hydroxydihydrosanguinarine	*Staphylococcus aureus* (MRSA)	0.49	**95**
166	10-Methoxydihydrosanguinarine	*Enterococcus faecium*	>160	**106**
		Staphylococcus aureus	>160	**106**
		Escherichia coli	>160	**106**
167	6-Methoxydihydrosanguinarine	*Enterococcus faecium*	5	**106**
		Staphylococcus aureus	2.5	**106**
		Escherichia coli	20	**106**
		HCT8	0.18, A	**111,116**

		BGC-823	0.21, A	**111,116**
168	Corynoline	HCT15	2.26	**115**
169	Chelidonine	*Escherichia coli*	A	**196**
170	Corynoloxine	HCT15	16.12	**115**
171	Maclekarpine C	HCT8	A	**111**
		BGC-823	A	**111**
172	(5′R)-3′-Methyl-2′(5′H)-furanone-(5′ → 6)-(6R)-dihydrosanguinarine	HCT8	0.84	**116**
173	Isointegriamide	*Escherichia coli*	1200	**33**
		Klebsiella pneumoniae	1110	**33**
		Shigella dysenteriae	1128	**33**
		Staphylococcus aureus	1230	**33**
		HCT15	9.6	**33**
174	Arnottianamide	*Escherichia coli*	1210	**33**
		Klebsiella pneumoniae	1190	**33**
		Shigella dysenteriae	1131	**33**
		Staphylococcus aureus	1210	**33**
		HCT15	11.1	**33**
APORPHINES				
175	Nornuciferine	HT-29	A	**122**
176	Asimilobine	*Enterococcus faecalis*	100	**54**
		Staphylococcus aureus	>500	**54**
		Escherichia coli	NA	**54**
177	Anonaine	*Bacillus cereus*	A	**201**
		Enterococcus faecalis	NA	**54**
		Staphylococcus aureus	>500, A	**54,201**
		Escherichia coli	A, NA	**54,201**
178	Roemerine	*Salmonella* Typhimurium	A	**202**
		Escherichia coli	A	**202**

179	Xylopine	HCT116	A	**52**
180	Dehydrocrebanine	SGC-7901	A	**124**
181	Crebanine	SGC-7901	A	**124**
182	Actinodaphnine (column fractions)	*Enterococcus faecalis*	40	**123**
		Staphylococcus aureus	70	**123**
		Escherichia coli	90	**123**
		KM-12	A	**123**
183	Laurolitsine	HCT116	8.5	**63**
184	(+)-Laurotetanine	HT-29	1.822	**51**
185	Isoboldine (column fractions)	*Enterococcus faecalis*	40	**123**
		Staphylococcus aureus	70	**123**
		Escherichia coli	>100	**123**
		KM-12	A	**123**
186	Laurelliptinhexadecan-1-one	*Staphylococcus aureus*	>256	**126**
		Escherichia coli	>256	**126**
187	Laurelliptinoctadecan-1-one	*Staphylococcus aureus*	>256	**126**
		Escherichia coli	>256	**126**
188	d-Dicentrine	SW620	4.6	**127**
		COLO 201	2.6	**127**
189	Glaucine	*Escherichia coli*	>64	**60**
		HCT116	100	**102**
		HCT15	6.62	**102**
190	(+)-N-(methoxycarbonyl)-N-norpredicentrine	BGC-823	A	**129**
		SGC-7901	A	**129**
191	(+)-N-(methoxycarbonyl)- N-norglaucine	BGC-823	A	**129**
		SGC-7901	A	**129**
192	(+)-N-(methoxycarbonyl)-N-nordicentrin	BGC-823	A	**129**
		SGC-7901	A	**129**

193	(+)-Hernovine	HT-29	5.993	**51**
194	(+)-N-Methylhernovine	HT-29	>50	**51**
195	(+)-N-Hydroxyhernangerine	HT-29	1.616	**51**
196	Corydine	*Escherichia coli*	>64	**60**
197	Magnoflorine	HT-29	13.5	**51**
198	(+)-8-methoxyisolaurenine-N-oxide	BGC-823	A	**129**
		SGC-7901	A	**129**
199	(+)-N-(methoxycarbonyl)-N-norisocorydione	BGC-823	A	**129**
		SGC-7901	A	**129**
200	(+)-N-(methoxycarbonyl)-N-norbulbodione	BGC-823	A	**129**
		SGC-7901	A	**129**
201	3-Methoxy-nordomesticine	*Enterococcus faecalis*	A	**128**
202	Dasymaroine	*Bacillus cereus*	NA	**130**
		Staphylococcus aureus	1.045975	**130**
		Escherichia coli	0.502068	**130**
203	N-Formyldehydroovigerine	HT-29	0.512	**51**
204	Lysicamine	HT-29	A	**122**
		HCT116	4.6	**131**
205	Liriodenine	*Enterococcus faecalis*	NA	**54**
		Staphylococcus aureus	3.13, >500	**54,203**
		Staphylococcus aureus (MRSA)	3.13	**203**
		Escherichia coli	NA	**54**
		HT-29	NA	**122**
		SGC-7901	A	**69**
206	Isomoschatoline	HT-29	A	**122**
207	Splendidine	HCT116	2.8	**131**
208	Subsessiline	HT-29	NA	**122**
		HCT116	5.7	**131**

209	3-methoxyoxoputerine N-oxide	*Bacillus cereus*	NA	**130**
		Escherichia coli	A	**130**
210	1-Demethyl dicentrinone	*Escherichia coli*	NA	**33**
		Klebsiella pneumoniae	NA	**33**
		Shigella dysenteriae	NA	**33**
		Staphylococcus aureus	NA	**33**
		HCT15	18.1	**33**
211	Dicentrinone	*Escherichia coli*	NA	**33**
		Klebsiella pneumoniae	NA	**33**
		Shigella dysenteriae	NA	**33**
		Staphylococcus aureus	NA	**33**
		HCT15	17.8	**33**
AMARYLLIDACEAE ALKALOIDS				
212	9-O-demethylgalanthine	HT-29	7.72	**133**
		Caco-2	11.7	**133**
		FHs 74 Int	23	**133**
213	Galanthine	HT-29	16	**133**
		Caco-2	18	**133**
		FHs 74 Int	>31.74	**133**
214	Caranine	*Escherichia coli*	2048	**134**
		HT-29	12.6	**141**
		Caco-2	17.4	**141**
		FHs 74 Int	>27	**141**
215	Amarbellisine	*Escherichia coli*	A	**134**
216	Lycorine	*Escherichia coli*	A	**134**
		HT-29	0.34	**133**
		Caco-2	0.28	**133**
		FHs 74 Int	6.51	**133**

217	O-Acetyllycorine	*Staphylococcus aureus*	>250	**144**
		Escherichia coli	>250	**144**
218	Acetylcaranine	HT-29	6	**141**
		Caco-2	9.24	**141**
		FHs 74 Int	20.7	**141**
219	Ungeremine	*Staphylococcus aureus*	25–50, 265	**134**
		Escherichia coli	25–50	**134**
		KM20L2	A	**142**
220	Hippadine	*Staphylococcus aureus*	200-250	**144**
		Salmonella Typhi	200-250	**144**
		Escherichia coli	200-250, A	**134,144**
221	Crinine	*Staphylococcus aureus*	>250	**144**
		Escherichia coli	>250	**144**
		HT-29	13.8	**141**
		Caco-2	17.5	**141**
		FHs 74 Int	>27	**141**
222	Vittatine	*Escherichia coli*	A	**134**
223	Buphanisine	*Staphylococcus aureus*	1024	**134**
		Escherichia coli	1024	**134**
		HT-29	1.51	**141**
		Caco-2	2.45	**141**
		FHs 74 Int	6.5	**141**
224	Buphanidrine	*Staphylococcus aureus*	63	**134**
		Escherichia coli	63	**134**
225	Crinamine	*Staphylococcus aureus*	A	**144**
		Escherichia coli	>250	**144**
226	Haemanthamine	HT-29	0.1777906	**133**
		Caco-2	0.298327	**133**

		SW480	1.32589	**146**
		FHs 74 Int	5.87613	**133**
227	Haemanthidine	HT-29	0.539478	**133**
		Caco-2	1.047222	**133**
		FHs 74 Int	3.681144	**133**
228	Hamayne	HT-29	3.5511516	**133**
		Caco-2	4.950351	**133**
		FHs 74 Int	15.3165	**133**
229	3-O-Acetyl-hamayne	*Staphylococcus aureus*	>250	**144**
		Escherichia coli	>250	**144**
230	Ambelline	HT-29	16.629652	**133**
		Caco-2	24.55343	**133**
		FHs 74 Int	29.76635	**133**
231	Distichamine	*Staphylococcus aureus*	63	**134**
		Escherichia coli	63	**134**
232	Buphanamine	HT-29	14.3407706	**133**
		Caco-2	16.12772	**133**
		FHs 74 Int	>30.134	**133**
233	1-Epideacetylbowdensine	*Staphylococcus aureus*	>250	**144**
		Escherichia coli	>250	**144**
234	1-O-Acetylbulbisine	HT-29	17.325516	**133**
		Caco-2	12.06715	**133**
		FHs 74 Int	22.16105	**133**
235	Crinamidine	*Staphylococcus aureus*	>250	**144**
		Escherichia coli	>250	**144**
236	Undulatine	HT-29	17.693446	**133**
		Caco-2	17.13669	**133**
		FHs 74 Int	23.3405	**133**

237	Lycoricidine	HCT116	16.12	**114**
238	Narciclasine	KM20L2	A	**142**
239	Pancratistatin	KM20L2	A	**142**
240	6,9,11-trihydroxybenzo[1, 3]dioxolo[4,5-c]phenanthridin-5(4H)-one	HCT116	16.29	**114**
241	6,11-dihydroxy-8,9-dimethoxybenzo[1,3]dioxolo[4,5-c]phenanthridin-5(4H)-one	HCT116	8.64	**114**
OTHERS				
242	Norrufescine	HCT116	7.7	**131**
243	Imeluteine	HCT116	7	**131**
244	Grandirubrine	HCT116	1	**131**
245	Isoimerubrine	HCT116	3.3	**131**
246	Imerubrine	HCT116	2	**131**
247	Sinomenine	Caco-2	A	**148**
		SGC-7901	A	**69**
		SW1116	A	**148**
248	(-)-alpha-Hydrastine	*Staphylococcus aureus*	A	**149**
		Escherichia coli	A	**149**
249	beta-Hydrastine	*Helicobacter pylori*	100	**150**
250	Noscapine	Caco-2	>4	**204**
251	Capnoidine	*Staphylococcus aureus*	>250	**101**
		Escherichia coli	>250	**101**
252	Bicuculline	*Staphylococcus aureus*	A	**149**
		Escherichia coli	A	**149**
253	Yohimbine	*Enterococcus faecalis*	2	**157**
		Staphylococcus aureus	2	**157**
		Staphylococcus aureus (MRSA)	64	**157**
		Escherichia coli	4-250	**157,205**

254	Vincamine	*Enterococcus faecalis*	2	**157**
		Staphylococcus aureus	2	**157**
		Staphylococcus aureus (MRSA)	64	**157**
		Escherichia coli	8	**157**
255	Isotubulosine	HT-29	9.8	**158**
256	Jozimine A2	HT-29	9	**159**
257	Jozilebomine A	PANC-1	1.6	**160**
258	Jozilebomine B	PANC-1	0.63	**160**

Table 3 Ethnobotanical Use of Plants Containing (Iso)quinolines

Family/Genus	Species	Occurrence	Uses	Reference
RUTACEAE				
Zanthoxylum	*Z. acanthopodium*	Southeast Asia	diarrhoea, stomach-ache	**206**
	Z. alatum	South Asia	cancer, cholera, diarrhoea, dyspepsia, microbial infections, stomach-ache	**207-209**
	Z. americanum	North America	dysentery, dyspepsia	**207**
	Z. armatum	South Asia	cancer, cholera, dyspepsia, gas problems, indigestion, stomach disorders	**210,211**
	Z. avicennae	Southeast Asia	colitis	**212**
	Z. bungeanum	East Asia	abdominal pain, diarrhoea, dysentery, food additive, stomach-ache	**207,213**
	Z. clava-herculis	North America	dysentery, dyspepsia	**207**
	Z. gilletii	Central Africa	cancer, stomach-ache	**214**
	Z. leprieurii	Central Africa	abdominal pain, asthma	**215,216**
	Z. myriacanthum	East Asia	colitis, enteritis	**217**
	Z. nitidum	East Asia, South East Asia	cholera, diarrhoea, gastric ulcer, stomach-ache	**218-220**
	Z. oxyphyllum	South Asia	stomach-ache, ulcers	**221**
	Z. piperitum	East Asia	abdominal pain, cancer, diarrhoea, intestinal worms	**222-224**
	Z. planispinum	East Asia	gastritis	**207**
	Z. rhetsa	South, East, and South East Asia	asthma, cholera, diarrhoea, dysentery, dyspepsia, stomach infection	**14**
	Z. schinifolium	East Asia	diarrhoea, stomach-ache	**225,226**
	Z. simulans	East Asia	abdominal pain, diarrhoea, dyspepsia	**207**
	Z. tessmannii	Central Africa	cancer	**113**
	Z. zanthoxyloides	West Africa	diarrhoea, dysentery, stomach-ache	**227,228**
	Zanthoxylum spp.	South America	diarrhoea, enteritis, ulcers	**229**
Melicope	*M. madagascariensis*	Indian Ocean	stomach-ache	**21**
	M. pteleifolia	Southeast Asia	stomach-ache	**230**
	M. triphylla	East and Southeast Asia, Malesia, Pacific	diarrhoea, intestinal worms, stomach-ache	**231**

Haplophyllum	*H. dauricum*	Northern Asia	antitumor	**232**
	H. perforatum	Central Asia	tesicular cancer	**233**
	H. tuberculatum	Tropical Africa, West Asia	asthma, dyspepsia, gastric disorders	**231,234**
Ruta	*R. graveolens*	Europe, East Africa, South Asia	indigestion, intestinal worms, ulcers	**235,236**
	R. angustifolia	Europe, Southeast Asia	intestinal worms	**237**
	R. chalepensis	East Africa, Central America	diarrhoea, dysentery, stomach-ache	**238-240**
Acronychia	*A. pedunculata*	South, East and Southeast Asia	stomach-ache	**231**
PAPAVERACEAE				
Corydalis	*C. aurea*	North America	diarrhoea, stomach-ache	**207**
	C. crispa	South Asia	bile disorders, liver infections	**241**
	C. dubia	South Asia	liver infections, pancreas infections	**241**
	C. govaniana	East Asia	abdominal pain	**207**
	C. heterocarpa	East Asia	dysentery	**242**
	C. incisa	East Asia	rectal collapse	**207**
	C. saxicola	East Asia	bleeding hemorrhoids, diarrhoea, dysentery, hepatitis, stomach-ache	**243,244**
	C. ternata	East Asia	abdominal pain	**207**
	C. turtschaninovii	East Asia	allergy	**245**
	C. yanhusuo	East Asia	abdominal pain, anticancer, ulcers	**207**
Fumaria	*F. bastardi*	North Africa	hepatobiliary and digestive disorders	**246**
	F. capreolata	North Africa	diarrhoea, hepatobiliary and digestive disorders	**246,247**
	F. indica	South Asia	abdominal pain, anthelmintic, antidyspeptic, diarrhoea	**248**
	F. officinalis	Europe	hepatobiliary and digestive disorders	**249**
	F. parviflora	West and South Asia	abdominal pain, asthma, diarrhoea, indigestion	**250-252**
	Fumaria spp.	Central Asia, Europe, North Africa	hepatobiliary and digestive disorders	**253**
Papaver	*P. rhoeas*	Europe, South America, South Asia	diarrhoea, indigestion, nervous digestive disorders	**207,254**

	P. somniferum	Europe, South America, South Asia	diarrhoea, dysentery, intestinal pain	**207,255-257**
Bocconia	*B. arborea*	Central and Southern America	antitumor	**111**
	B. frutescens	Central and Southern America	diarrhoea	**258**
OTHER PLANT GENERA				
Berberis	*B. amurensis*	East Asia	cancer, dysentery, enteritis	**259,260**
	B. aristata	East Asia	cancer, diarrhoea	**261,262**
	B. bealei	East Asia	diarrhoea, dysentery	**186,263**
	B. canadensis	North America	diarrhoea	**207**
	B. chitria	East Asia	peptic ulcers	**207**
	B. heteropoda	East Asia	dysentery, gastroenteritis	**264**
	B. hispanica	North Africa	colon cancer, stomach infection	**265**
	B. lycium	East Asia	diarrhoea, intestinal colic	**207,266**
	B. vulgaris	Europe	diarrhoea, peptic ulcers, stomach cancer	**207,267**
	B. wallichiana	South East Asia	diarrhoea, dysentery, dyspepsia	**207**
Thalictrum	*T. collinum*	Europe	stomach-ache	**207**
	T. foliolosum	East Asia	dyspepsia, gastrointestinal disease, haemorrhoids, indigestion, intestinal obstruction, peptic ulcers, stomach-ache	**207,268**
	T. fortunei	East Asia	dysentery, antitumor and immunoregulatory	**269,270**
	T. minus	East and West Asia	dysentery, stomach-ache	**207,271**
Stephania	*S. glabra*	Southeast and East Asia	asthma, cancer, dysentery, intestinal complaints	**70**
	S. japonica	Eastern and southern Asia, Australia, and Pacific	diarrhoea, dyspepsia, gastritis	**272**
	S. rotunda	Southeast Asia	asthma, diarrhoea	**69**
	S. tetrandra	Southeast and East Asia	asthma, cancer, dysentery	**182,273**
OTHERS				
Annona	*A. cherimola*	South America	cancer, diarrhoea, dysentery	**274,275**
	A. crassiflora	South America	diarrhoea	**276**
	A. dioica	South America	diarrhoea	**277**

	A. muricata	West Africa, South America, South and Sotheast Asia	diarrhoea; gastric, liver, and colon cancer	**278,279**
	A. senegalensis	West and Central Africa	diarrhoea, stomach-ache	**280**
	A. squamosa	West Africa, South America, South and Sotheast Asia	cancer, dysentery	**281,282**
Sida	*S. cordata*	South Asia	cholera, dysentery	**283**
	S. cordifolia	South Asia	diarrhoea, dysentery, dyspepsia	**284**
	S. rhombifolia	South Asia	abdominal pain, asthma, cholera, dysentery	**207,285**
	S. spinosa	South Asia	asthma, diarrhoea	**286**
Centaurea	*C. benedicta*	Europe	stomach infection	**287**
	C. cyanus	Europe	indigestion	**207**
	C. jacea	Europe	indigestion, stomach-ache	**207**
Ophiorrhiza	*O. leptantha*	Pacific	diarrhoea	**231**
	O. mungos	South Asia	cancer, stomach-ache	**231**
	O. rugosa	South and Southeast Asia	dysentery	**288**
Rinorea	*R. oblongifolia*	Africa	stomach-ache	**289**
	R. subintegrifolia	Africa	stomach-ache	**290**
Tabernaemontana	*T. coronaria*	South, East and Southeast Asia	ulcers	**291**
	T. corymbosa	South Asia	abdominal tumours	**292**
	T. divaricata	South, East and Southeast Asia	asthma, abdominal tumours, diarrhoea	**293**
	T. elegans	East Africa	cancer	**294**
	T. heyneana	South Asia	cancer	**295**
	T. pachysiphon	Tropical Africa	stomach-ache	**231**
	T. pandacaqui	South, East and Southeast Asia, Malesia, Pacific	diarrhoea, stomach-ache	**231**
	T. persicariifolia	Indian Ocean	dysentery, intestinal worms	**231**
	T. rostrata	South, East and Southeast Asia	asthma, dysentery	**231**
	T. stapfiana	East Africa	stomach-ache	**231**

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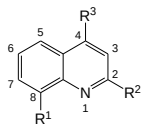

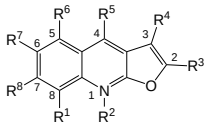

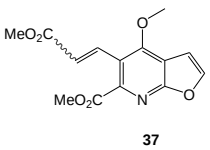

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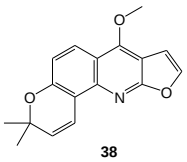

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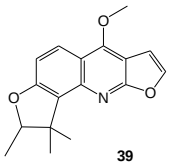

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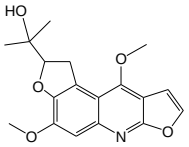

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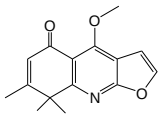
	R^1	R^2	R^3
1	OH	H	H
2	H	H	CH_3
3	H	COOH	H
4	H	H	CHO

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
5	H	-	H	H	CH_3O	H	H	H
6	OH	-	H	H	CH_3O	H	H	H
7	H	-	H	H	CH_3O	H	H	OH
8	CH_3O	-	H	H	CH_3O	H	H	H
9	H	-	H	H	CH_3O	H	H	CH_3O
10	H	-	H	H	CH_3O	H	CH_3O	H
11	H	-	H	H	CH_3O	H	H	3-methylbut-2-enyloxy
12	H	-	H	H	CH_3O	H	H	(E)-3-methyl-4-hydroxy-but-1-enoxy
13	H	-	H	H	CH_3O	H	H	3-methylbut-3-ene-1-oxyl-2-ol
14	CH_3O	-	H	H	CH_3O	H	H	OH
15	CH_3O	-	H	H	CH_3O	H	H	CH_3O
16	CH_3O	-	H	H	CH_3O	H	H	3-methylbut-2-en-1-oxy
17	CH_3O	-	H	H	CH_3O	H	H	3-methylbutane-2,3-diol-1-oxy
18	CH_3O	-	H	H	CH_3O	H	H	(3,3-Dimethyloxiran-2-yl)methoxy
19	3-methylbut-2-en-1-oxy	-	H	H	CH_3O	H	H	3-methylbut-2-en-1-oxy
20	3-methylbut-2-en-1-oxy	-	H	H	CH_3O	H	H	(3,3-Dimethyloxiran-2-yl)methoxy
21	OH	-	H	H	CH_3O	H	H	(3,3-Dimethyloxiran-2-yl)methoxy
22	H	-	H	H	CH_3O	H	CH_3O	CH_3O
23	H	-	H	H	CH_3O	H	3-methylbutane-2,3-diol-1-oxy	CH_3O
24	CH_3O	-	H	H	CH_3O	CH_3O	H	CH_3O
25	H	-	propan-2,2-olyl	H	CH_3O	H	H	H
26	H	CH_3	propan-2,2-olyl	H	CH_3O	H	H	H
27	CH_3O	-	propan-2,2-olyl	H	CH_3O	H	H	H
28	CH_3O	-	propan-2,2-olyl	H	CH_3O	H	H	CH_3O
29	CH_3O	-	propan-2,2-olyl	OH	CH_3O	H	H	CH_3O
30	H	-	H	H	CH_3O	H	H	CH_2
31	CH_3O	H	H	H	CH_3O	H	H	CHO
32	CHO	-	H	H	CH_3O	CHO	H	CH_3O
33	H	-	H	H	CH_3O	H		$-CH_2O_2-$
34	CH_3O	-	H	H	CH_3O	H		$-CH_2O_2-$
35	H	-	H	H	CH_3O	H	H	4-methyl-4-(phenylamino)pentane-2-ol-1-oxy
36	H	-	H	H	CH_3O	CH_3O	H	H



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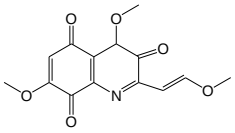

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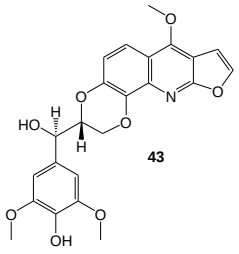

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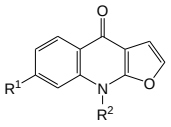
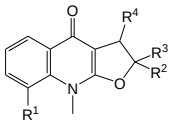
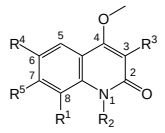


	R^1	R^2
44	H	CH_3
45	CH_3O	2-methylbut-2-ene-4-yl

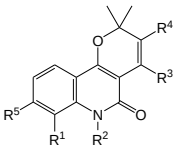


	R^1	R^2	R^3	R^4
46	H	propan-2,2-olyl	H	H
47	CH_3O	propan-2,2-olyl	CH_3	H
48	H	CH_3	CH_3	CH_3

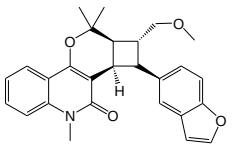
Figure 1 The chemical structures of simple quinolines (1-4) and furoquinolines (5-48)



	R^1	R^2	R^3	R^4	R^5
49	H	CH_3	H	H	H
50	CH_3O	H	H	H	H
51	CH_3O	CH_3	3-methylbutyl-2-ol	H	H
52	CH_3O	CH_3	3-methyl-(4,4,4-trifluoro-butan-2-yl 2,2,2-trifluoroacetate)-yl	H	H
53	CH_3O	H	CH_2O	H	CH_3O
54	H	H	CHO	CH_3O	CH_3O
55	H	CH_3	2-methylbut-4yl-2,3-diol	H	H



	R^1	R^2	R^3	R^4	R^5
56	H	H	H	H	H
57	CH_3O	CH_3	H	H	CH_3O
58	CH_3O	CH_3	OH	OH	H



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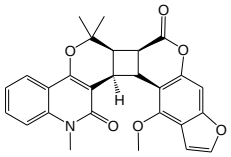

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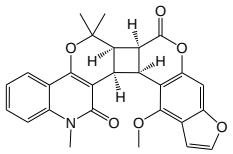

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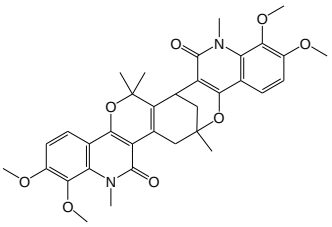

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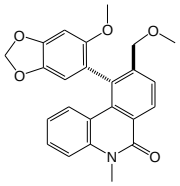

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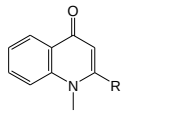
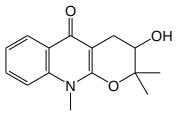


	R
64	(Z)-tridec-13-yl-5-ene
65	benzo[d][1,3]dioxol-5yl



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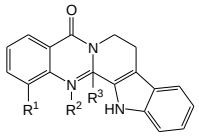
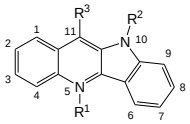
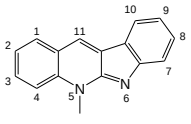


	R^1	R^2	R^3
67	H	-	-
68	OH	-	-
69	H	CH_3	H



	R^1	R^2	R^3
70	-	H	H
71	CH_3	-	H
72	CH_3	-	OH



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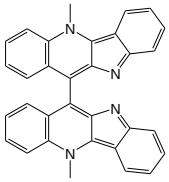
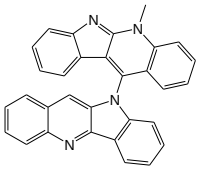
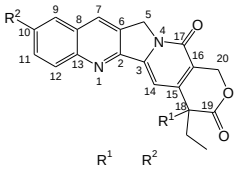


74



75



	R^1	R^2
76	OH	H
77	CH_3O	OH

Figure 2 The chemical structures of quinolones (49-69) and indoloquinolines (70-77)

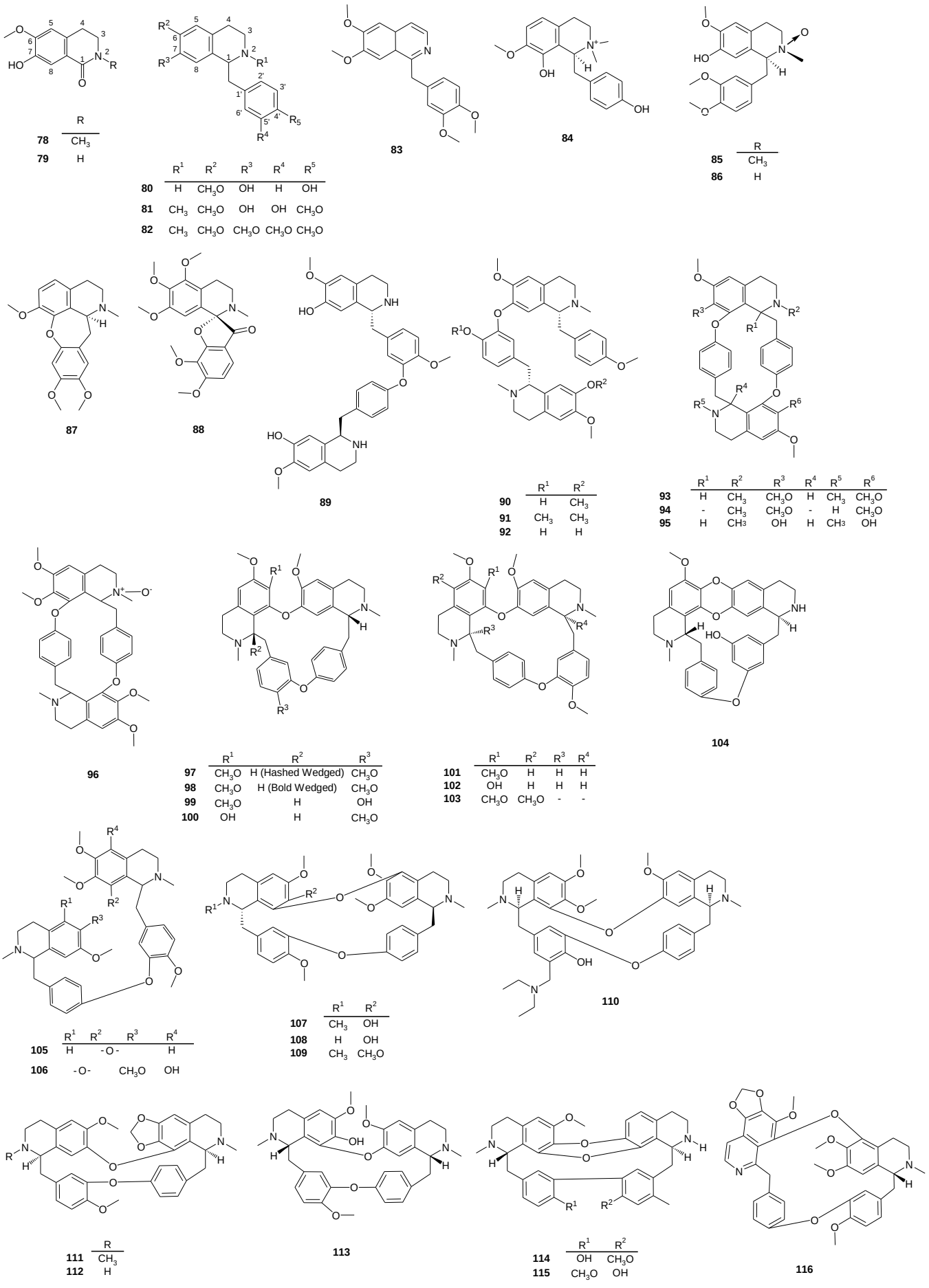
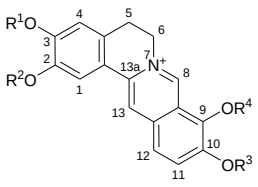
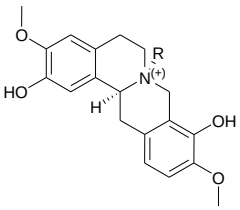
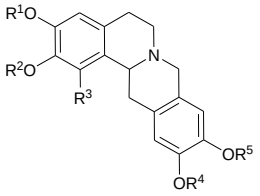
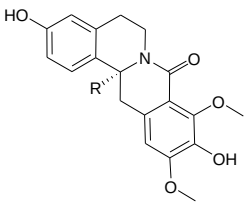


Figure 3 The chemical structures simple isoquinolines (78 and 79) and (bis)benzylisoquinolines (80-116)







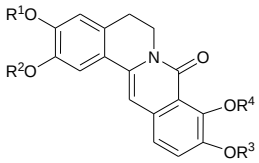


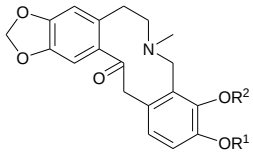
	R^1	R^2	R^3	R^4
117	CH_3	H	CH_3	CH_3
118	H	CH_3	CH_3	CH_3
119	CH_3	CH_3	CH_3	CH_3
120	$-CH_2-$		CH_3	CH_3
121	H	CH_3	$-CH_2-$	
122	$-CH_2-$		$-CH_2-$	

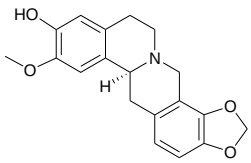
	R
123	-
124	CH_3

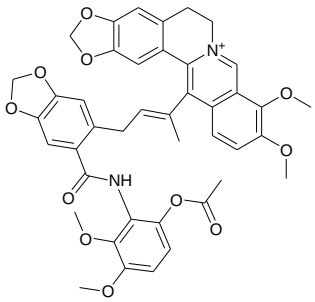
	R^1	R^2	R^3	R^4	R^5
125	H	CH_3	H	H	CH_3
126	$-CH_2-$		CH_3O	$-CH_2-$	
127	$-CH_2-$		H	$-CH_2-$	

	R
128	H
129	-







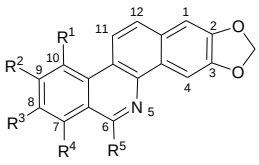


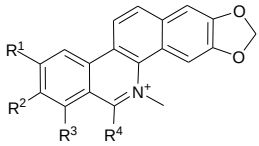
	R^1	R^2	R^3	R^4
130	$-CH_2-$		CH_3	CH_3
131	CH_3	CH_3	$-CH_2-$	
132	$-CH_2-$		$-CH_2-$	

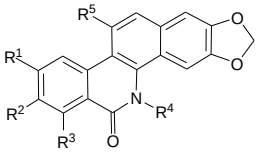
	R^1	R^2
133	CH_3	CH_3
134	$-CH_2-$	

135

136



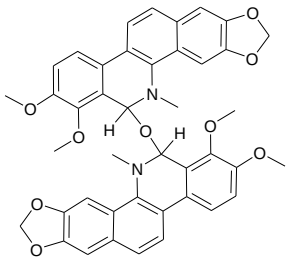


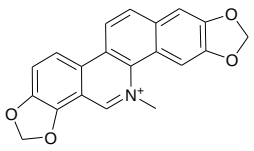


	R^1	R^2	R^3	R^4	R^5
137	H	H	CH_3O	CH_3O	CH_3O
138	H	OH	CH_3O	H	CH_3O
139	H	H	CH_3O	CH_3O	acetyl
140	CH_3O	H	CH_3O	CH_3O	CH_3O
141	H	CH_3O	CH_3O	H	CH_3O
142	H	H	$-CH_2O_2-$		CH_3O

	R^1	R^2	R^3	R^4
143	H	OH	CH_3O	H
144	CH_3O	CH_3O	H	H
145	$-CH_2O_2-$		H	H
146	H	CH_3O	CH_3O	H
147	CH_3O	CH_3O	H	CH_3O
148	H	CH_3O	CH_3O	CH_3O
149	H	CH_3O	OH	H

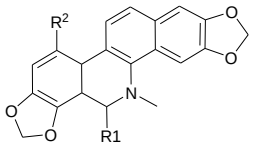
	R^1	R^2	R^3	R^4	R^5
150	H	CH_3O	CH_3O	H	H
151	CH_3O	CH_3O	H	CH_3	H
152	H	$-CH_2O_2-$		CH_3	H
153	H	$-CH_2O_2-$		CH_3	OH



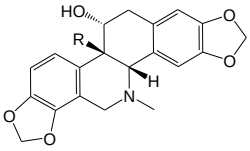


162

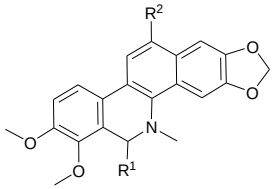
163

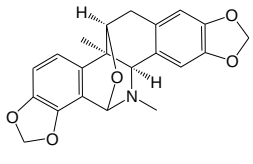


	R^1	R^2	R^3
164	H	H	H
165	OH	H	H
166	H	H	CH_3O
167	CH_3O	H	H

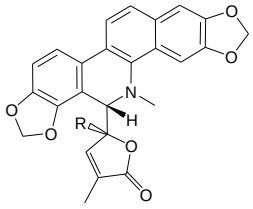


	R
168	CH_3
169	H

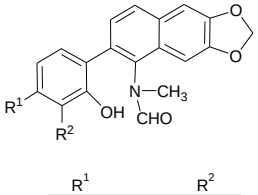




170



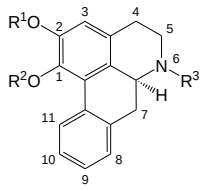
	R
171	H (Hashed Wedged)
172	H (Bold Wedged)



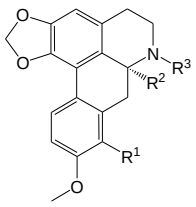
	R^1	R^2
154	H	H
155	H	CH_3O
156	OH	H
157	CH_3O	H
158	OC_4H_9	H
159	propanyl-2-one	H
160	5-methoxy-4-hydroxyphenylethenyl	H
161	(2′,6′-epoxy-1′,2′α,3′β,4′α,5′α -pentahydroxy)hexane-(1′ → 6)-	H

	R^1	R^2
173	$-CH_2O_2-$	
174	CH_3O	CH_3O

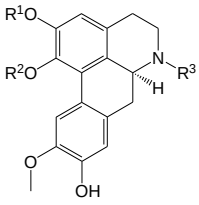
Figure 4 The chemical structures of protoberberines (117-136) and benzophenanthridines (137-174)



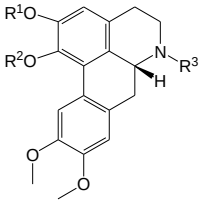
	R^1	R^2	R^3
175	CH_3O	CH_3O	H
176	H	CH_3O	H
177	-CH_2-		H
178	-CH_2-		CH_3



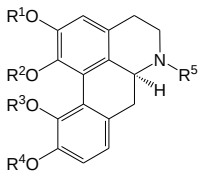
	R^1	R^2	R^3
179	H	H	H
180	CH_3O	-	CH_3
181	CH_3O	H	CH_3



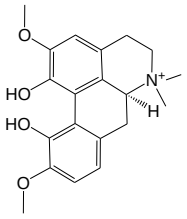
	R^1	R^2	R^3
182	-CH_2-		H
183	H	CH_3	H
184	CH_3	CH_3	H
185	CH_3	H	CH_3
186	CH_3	H	hexadecanyl-1-one
187	CH_3	H	octadecanyl-1-one



	R^1	R^2	R^3
188	-CH_2-		CH_3
189	CH_3	CH_3	CH_3
190	H	CH_3	methoxycarbonyl
191	CH_3	CH_3	methoxycarbonyl
192	-CH_2-		methoxycarbonyl



	R^1	R^2	R^3	R^4	R^5
193	H	CH_3	CH_3	H	H
194	H	CH_3	CH_3	H	CH_3
195	-CH_2-		CH_3	H	OH
196	CH_3	H	CH_3	CH_3	CH_3



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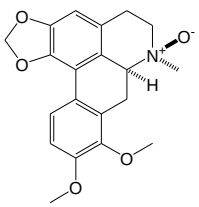
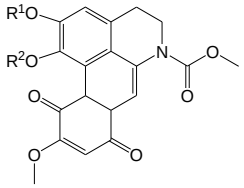
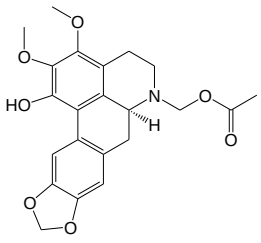


198



	R^1	R^2
199	CH_3	CH_3
200	-CH_2-	



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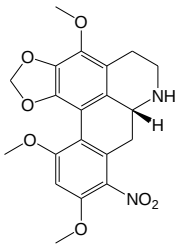

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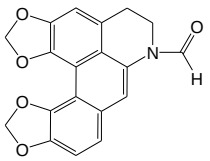
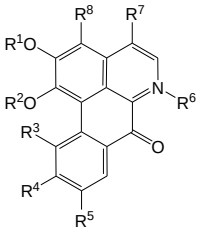
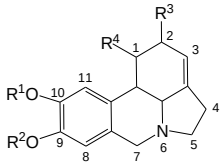


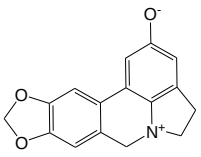
203



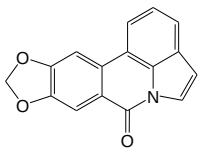
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
204	CH_3	CH_3	H	H	H	-	H	H
205	-CH_2-		H	H	H	-	H	H
206	CH_3	CH_3	H	H	H	-	H	OH
207	CH_3	CH_3	H	H	H	-	CH_3O	H
208	CH_3	CH_3	H	H	OH	-	H	CH_3O
209	-CH_2-		CH_3O	H	H	O^-	H	CH_3O
210	CH_3	H	H	CH_3O	H	-	H	H
211	-CH_2-		H	OH	H	-	H	H



	R^1	R^2	R^3	R^4
212	H	CH_3	CH_3O	OH
213	CH_3	CH_3	CH_3O	OH
214	-CH_2-		H	OH
215	-CH_2-		CH_3O	OH
216	-CH_2-		OH	OH
217	-CH_2-		OH	Acetoxyl
218	-CH_2-		H	Acetoxyl



219



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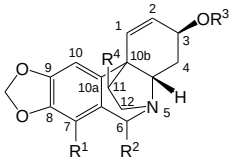
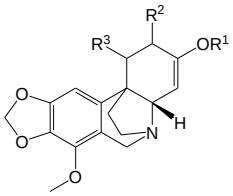
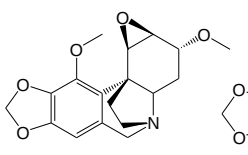


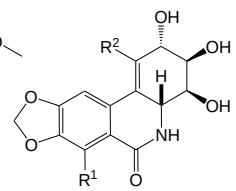
	R^1	R^2	R^3	R^4
221	H	H	H	H
222	H	H	H	H
223	H	H	CH_3	H
224	CH_3O	H	CH_3	OH
225	H	H	CH_3	OH
226	H	H	CH_3	OH
227	H	OH	CH_3	OH
228	H	H	H	OH
229	H	H	Acetoxyl	OH
230	CH_3O	H	CH_3	OH



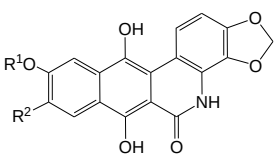
	R^1	R^2	R^3
231	CH_3	H	O
232	H	H	OH
233	H	OH	OH
234	H	OH	Acetoxyl
235	OH	-O-	



236



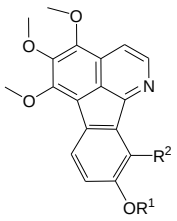
	R^1	R^2
237	H	H
238	OH	H
239	OH	OH



	R^1	R^2
240	H	H
241	CH_3	CH_3O

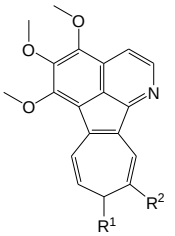
Figure 5 The chemical structures of aporphines (175-211) and Amaryllidaceae isoquinolines (212-241)

AZAFLUORANTHENES



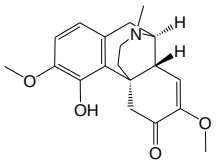
	R^1	R^2
242	H	H
243	CH_3	CH_3O

TROPOLOISOQUINOLINES



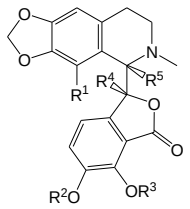
	R^1	R^2
244	O	OH
245	O	CH_3O
246	CH_3O	O

MORPHINANS



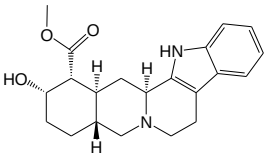
247

PHTHALIDE ISOQUINOLINES

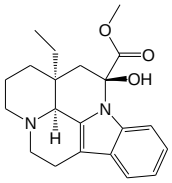


	R^1	R^2	R^3	R^4	R^5
248	H	CH_3	CH_3	H (Hashed Wedged)	H (Hashed Wedged)
249	H	CH_3	CH_3	H (Bold Wedged)	H (Hashed Wedged)
250	CH_3O	CH_3	CH_3	H (Bold Wedged)	H (Hashed Wedged)
251	H	-CH_2-		H (Bold Wedged)	H (Hashed Wedged)
252	H	-CH_2-		H (Hashed Wedged)	H (Bold Wedged)

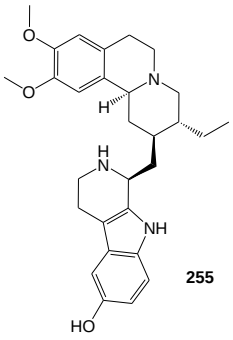
INDOLOISOQUINOLINE



253

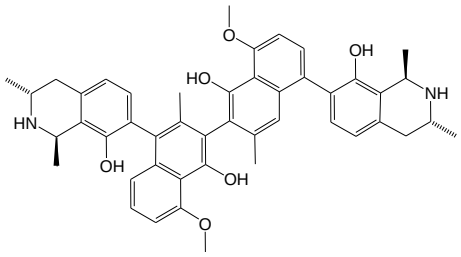


254



255

NAPHTHYLISOQUINOLINES



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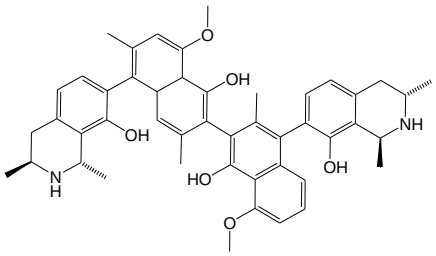
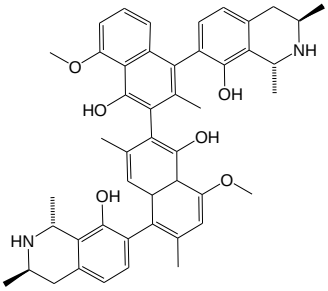


257



258

Figure 6 The chemical structures of other isoquinolines (242-258)

Appendix 2: *Curriculum vitae*

PERSONALIA

Name	**Ing. Tomáš Kudera**
Address	Chotěšovská 675/9, Praha 18
	Czechia
Mobile phone number	+420 721 489 623
E-mail	kuderat@ftz.czu.cz
Date of birth	7 August 1992
Nationality	Czech

EDUCATION

2017 – present	**Doctoral Study**
	Czech University of Life Sciences Prague
	Faculty of Tropical AgriSciences
	Study Programme: Tropical Agrobiology and Bioresource Management
	Thesis: Effect of plant-derived extracts and compounds on human intestinal bacteria and cells *in vitro*
2015 – 2017	**Master's degree**
	Czech University of Life Sciences Prague
	Faculty of Tropical AgriSciences
	Study Programme: Tropical Crop Management and Ecology
	Thesis: *In vitro* growth-inhibitory effect of *Calophyllum inophyllum* leaf ethanol extract against diarrhoea-causing bacteria
2011 – 2015	**Bachelor's degree**
	Czech University of Life Sciences Prague
	Faculty of Tropical AgriSciences
	Study Programme: Zemědělství tropů a subtropů
	Thesis: Plant extracts and their constituents as alternatives to antibiotic treatment of diarrhea in tropical regions

ABROAD EXPERIENCES

04/2017 & 04-06/2018	**Student mobility in Philippines**
	Visayas State University, Baybay
	- plant sample collection
03-04/2019	**Student mobility in Cambodia**
	Royal University of Agriculture, Phnom Penh
	- plant sample collection

PROJECT PARTICIPATION

2020	Evaluation of biological effects and chemical analysis of compounds from tropical plants (IGA 20205001)
2019	Biological activity and chemical composition of compounds obtained from medicinal and edible tropical plants (IGA 20195003)
2018	Chemical composition and biological activity of medicinal and edible tropical plants (IGA 20185019)
2017	Advanced methods for *in vitro* evaluation of antimicrobial activity of plant compounds, extracts and essential oils (CIGA 20175001)
2017	Biologically active compounds in medicinal and edible tropical plants (IGA 20175020)

LANGUAGE SKILLS

Czech:	Mother tongue
English:	Proficient user

Appendix 3: List of author's publications

Publications in scientific journals:

Osei-Owusu, H., **Kudera, T.**, Strakova, M., Rondevaldova, J., Skrivanova E., Novy, P., Kokoska, L., 2022, *In Vitro* Selective Combinatory Effect of Ciprofloxacin with Nitroxoline, Sanguinarine, and Zinc Pyrithione against Diarrhea-Causing and Gut Beneficial Bacteria, Microbiology Spectrum, 10(5), e01063-22. **IF 3.7/Q2**

Promgool, T., Kanokmedhakul, K., Leewijit, T., Song, J., Soytong, K., Yahuafai, J., **Kudera, T.**, Kokoska, L., Kanokmedhakul, S., 2022, Cytotoxic and Antibacterial Depsidones from the Endophytic Fungus *Chaetomium brasiliense* Isolated from Thai rice, Natural Product Research, 36(18), 4605-4613. **IF 2.2/Q3-4**

Kudera T., Fiserova B., Korytakova M., Doskocil I., Salmonova H., Tulin E.E., Nguon S., Bande M.M., Kokoska L. *In Vitro* Selective Antibacterial and Antiproliferative Effects of Ethanol Extracts from Cambodian and Philippine Plants Used in Folk Medicine for Diarrhea Treatment, Frontiers in Pharmacology, 2021, 12:746808. **IF 5.6/Q1**

Frankova, A., Vistejnova, L., Merinas-Amo, T., Leheckova, Z., Doskocil, I., Wong Soon, J., **Kudera, T.**, Laupua, F., Alonso-Moraga, A., Kokoska, L., 2021, *In Vitro* Antibacterial Activity of Extracts from Samoan Medicinal Plants and their Effect on Proliferation and Migration of Human Fibroblasts, Journal of Ethnopharmacology, 264, 113220. **IF 5.4/Q1**

Verner, V., Novy, P., Tauchen, J., Huml, L., Soon, J. W., **Kudera, T.**, Laupua, F., Kokoska, L., 2020, Diversity, Economic Value and Regional Distribution of Plant Food Products at Local Tropical Markets: A Samoa Case Study, Sustainability, 12(23), 10014. **IF 3.9/Q2-3**

Kudera, T., Doskocil, I., Salmonova, H., Petrtyl, M., Skrivanova, E., & Kokoska, L., 2020, *In Vitro* Selective Growth-Inhibitory Activities of Phytochemicals, Synthetic Phytochemical Analogs, and Antibiotics against Diarrheagenic/Probiotic Bacteria and Cancer/Normal Intestinal Cells, Pharmaceuticals, 13(9), 233. **IF 4.6/Q2**

Houdkova, M., Doskocil, I., Urbanova, K., Tulin, E. K. C. B., Rondevaldova, J., Tulin, A. B., **Kudera, T.**, Tulin, E. E., Zeleny, V., Kokoska, L., 2018, Evaluation of Antipneumonic Effect of Philippine Essential Oils Using Broth Microdilution Volatilization Method and their Lung Fibroblasts Toxicity, Natural Product Communications, 13(8), 1934578X1801300. **IF 1.8/Q4**

Kudera, T., Rondevaldova, J., Kant, R., Umar, M., Skrivanova, E., Kokoska, L., 2017, *In Vitro* Growth-Inhibitory Activity of *Calophyllum inophyllum* Ethanol Leaf Extract against Diarrhoea-Causing Bacteria, Tropical Journal of Pharmaceutical Research, 16(9), 2207. **IF 0.6/Q4**