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Antibacterial and antiproliferative effects of plant-derived quinoline alkaloids on gut system: A review of literature

BACHELOR'S THESIS

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Declaration

I hereby declare that I have done this thesis entitled Antibacterial and antiproliferative effects of plant-derived quinoline alkaloids: A review of literature 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.

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Wildová Anna

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Abstract

The gastrointestinal system can be affected by a large variety of diseases, whereas bacterial diarrhoea and colorectal cancer are one of the most common serious ones. Plant-derived molecules such as quinoline and isoquinoline alkaloids are known to be a rich source of diverse scaffolds that could serve as the basis for antimicrobial and anticancer drug design and development. Although their antibacterial and antiproliferative effects on gut system are well reported in the literature, these data have not been systematically analysed yet. The main aim of thesis was a collection and analysis of the data on *in vitro* antimicrobial and antiproliferative effects of quinoline and isoquinoline alkaloids on human gut bacteria and cells. Data on the plant sources and biological (antibacterial and antiproliferative) activity of alkaloids on gut were collected from scientific databases and summarized in four review tables. As a result, 406 bioactive alkaloids were identified, which were present in 168 plant species belonging to 29 families. 25 molecules were classified as antibacterial agents, and 87 compounds were significantly cytotoxic. The number of taxa containing quinoline and isoquinolines alkaloids was originated in tropical regions. Among all compounds collected from the literature, avicine, neothalfine, dutadrupine, and 6-methoxydihydrosanguinarine have been found to produce significant antimicrobial and/or antiproliferative effects promising for further research, however, further biological tests will be necessary to confirm their efficacy and safety.

Key words: quinoline, isoquinoline, alkaloids, botany, intestinal infection, intestinal cancer, antibacterial, anticancer

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List of the abbreviations used in the thesis

MIC – minimum inhibitory concentration

SAR – structure-activity relationship

CRC – colorectal cancer

IBS – irritable bowel syndrome

WHO – World Health Organization

IC_{50} – half-maximal inhibitory concentration

ED_{50} – effective dose for 50% of the treated population

1. Gut system

The gut (gastrointestinal tract) is the long tube that runs from the mouth to the back passage (anus), its function is the digestion, which is the complex process of turning the food into nutrients absorbed by the body or into waste passed out as faeces. The gut consists of the mouth, oesophagus, stomach, the small intestine, colon, rectum, and anus [1]. The tract itself is divided into upper and lower gastrointestinal tract. The exact boundary between the upper and the lower tracts is the suspensory muscle of duodenum, which is beginning part of lower gastrointestinal tract and of the small intestine [2]. According to dictionary managed by U.S. National Medicine Library the lower gastrointestinal tract is the segment of GI tract that most of includes the intestines [3]. It is a continuous tube that runs from the stomach to the anus, its main function is to absorb most of nutrients and water, and it is usually divided into three parts: the small intestine, the large intestine, and the rectum [4]. The intestines in humans is subdivided into structural parts: the small intestine (small bowel) is further divided into the duodenum, jejunum, and ileum, while the large intestine (the colon, large bowel) is divided into the cecum, ascending colon, right colic flexure, transverse colon, left colic flexure, descending and sigmoid colon, rectum, and anal canal [2].

Other important function of the gut system is the hosting of the human microbiome. These digestive-tract associated microbes are referred to as the intestinal (gut) microbiome (microbiota, microflora). Their concentration increases continuously along the gastrointestinal tract, with small number in the stomach but with very high amount in the colon. They have a significant impact on digestion and nutrient adsorption, pathogen protection, immune system stimulation, and affects the gut health [5,6].

1.1. Intestinal microbiota

The intestinal microbiota is complex system, in healthy human functions as a symbiont that protects from pathogens and prevents tumorigenesis. In the gastrointestinal tract, there are around 100 trillion microorganisms (mostly bacteria, but also viruses, fungi, and protozoa) [7], they provide nutrient and drug metabolism, prevent colonization by pathogenic microorganisms, and function as an intestinal barrier.

Composition of human gut microflora is formed by over 35 000 bacterial species [8] represented mostly by members of 4 phyla: Bacteroidetes, Firmicutes, Actinobacteria and Proteobacteria which co-occur and maintain a relatively stable ecology in gut [9,10].

1.2. Gut dysbiosis

Disruption in the equilibrium of putative species of protective versus harmful gut bacteria is known as dysbiosis [11]. There are three types of dysbiosis formation: loss of protective bacteria, overgrowth of harmful bacteria, and loss of overall gut microbiome diversity [12]. Balance of the gut microbial community (eubiosis) can be also disturbed by an inflammatory environment in the host, which is triggered due to different ways of attaching and colonizing the gut epithelium based on causative bacteria [13]. Dysbiosis through a variety of pathways (including immunological dysregulation, changed energy management, altered gut hormone regulation, and pro-inflammatory processes) promotes metabolic complications and diet-induced obesity [7]. Furthermore, dysbiosis-associated metabolic, physiologic, and cellular responses in the host can modulate cancer risk [9], whereas inflammations in gastrointestinal tract may be a precursor of cancer formation [14-16]. Dysbiosis can also cause or aggravate development of pathogenesis of colon, gastric, oesophageal, pancreatic, laryngeal, and other carcinomas, which is closely tied to host inflammation [9].

1.3. Gut eubiosis

Eubiosis is status characterized by a gut microbiota with prevalence of probiotic bacterial species, belonging mainly to phylum Firmicutes and Bacteroides, while potentially pathogenic species, such as those from the phyla Enterobacteriaceae, are present in a very low percentage [17]. According to The International Scientific Association for Probiotics and Prebiotics consensus, the definition of probiotic is “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” [18]. Beneficial microorganisms also affect physiology and metabolism of the host, they have a major role in microbiome balance and nutrition, complement gaps in host metabolic pathways, e.g., synthesis of essential vitamins and oligo-elements, energy extraction from indigestible carbohydrates [19]. A few bacterial species of the gut

microbiota have dedicated metabolism and key function in gut homeostasis e.g., *Bifidobacterium* spp. and butyrate-producing colon bacteria [20]. A balanced microflora plays an important role in prevention of resistant microbial strains colonisation in gut, reduces the opportunities for pathogens establishment. By treatment with selectively antimicrobial agents, that do not disturb microflora, the risk of emergence and spread of resistant strains is reduced [21]. In case of tumorigenesis, Enzler *et al.* (2003) assume that the immune system seeks to maintain the balance of the intestinal microflora instead of directly inhibiting cancer in gut [22].

2. Diseases

There is a large variety of diseases affecting the digestive tract, which we can divide into two types: functional (gut looks normal) and structural. Common examples of functional diseases are constipation, irritable bowel syndrome (IBS), nausea, food poisoning, gas, bloating, gastroesophageal reflux disease, and diarrhoea. The examples of structural diseases include strictures, stenosis, haemorrhoids, diverticular disease, colon polyps and cancer, and inflammatory bowel disease [23]. Each year gastrointestinal infections are responsible for significant morbidity and mortality worldwide.

The World Health Organization (WHO) estimates that over four billion episodes of gastrointestinal infections (especially diarrhoeal diseases) annually, with 2.2 million deaths attributed to diseases in 2004, making it the fifth leading cause of death globally at all ages [24]. Diseases of gut system are among the most common problems in tropical countries. They commonly manifest as diarrhoea, abdominal pain, abdominal distention, gastrointestinal bleeding, intestinal obstruction, malabsorption, or malnutrition. Generally, improvement in sanitation and better socioeconomic conditions reduce the burden of diseases [25].

2.1. Infections (diarrhoea)

Disturbance of healthy intestinal microflora caused by pathogens domination may appear as pathogenic infectious diarrhoea. According to WHO in 2017 nearly 1.7 million children had suffered from diarrhoeal disease. As the second leading cause of death in children under 5, diarrhoeal disease was responsible for losses of 525 000 children [26].

Patients are characterized by gut microbial dysbiosis, growth inhibition and decrease in the number of beneficial bacteria are the main ways of pathogens interaction in the gut [27]. Main causative bacteria of infectious diarrhoea are *Bacillus cereus, Campylobacter jejuni, Clostridium perfringens, C. difficile, Enterococcus faecalis, Escherichia coli, Listeria monocytogenes, Salmonella spp., Shigella spp., Vibrio cholerae, V. parahaemolyticus* and *Yersinia enterocolitica* [27,28].

Some pathogens causing inflammatory diarrhoea (*Salmonella spp.* (not *typhi*), *Shigella dysentereae, C. jejuni*, enterohemorrhagic and entero-invasive *E. coli, C. difficile, L. monocytogenes* and *Y. enterocolitica)* increase risk factor of developing inflammations in gut [26,29]. Furthermore, domination of various diarrhoeagenic pathogens can result in the shift of the microbiota composition from a mutualistic to a pro-carcinogenic. This is caused by presence of bacterial drivers, which are defined as intestinal bacteria showing pro-carcinogenic feature and can initiate the process of carcinogenesis. Several drivers involved in colorectal cancer with pro-inflammatory effects are members of Enterobacteriaceae, such as *Shigella* and *Salmonella,* or superoxide-producing *E. faecalis*, genotoxin-producing *E. coli.* As already mentioned, domination of some diarrhoeagenic bacteria in gut may result in persistent inflammation and development of intestinal cancer [19].

2.2. Cancer

Intestinal cancer is one of the most frequent diseases in the number of causes and deaths worldwide, it is the second most common diagnosed cancer in women and third most common in men [30]. In addition, in 2020 rectum and intestinal (also known as a colon, colorectal, and bowel) cancers were the third leading cause of new cases of cancer worldwide with 1.93 million cases, and the second most common cause of death with 935 000 deaths [31]. Interestingly, incidence rates of cases are highest in the western developed world, especially in the newly economically developed countries such as Czechia and Slovakia in Eastern Europe. In contrast, the lowest incidence rates were in database in Asia, Africa, and South America [32]. There are several types of intestinal cancer based on morphology of the tissue samples. The most common type in the gastrointestinal part is adenocarcinoma, which starts in the glandular tissue lining the bowel and forms in the mucus-secreting glands [33].

Colorectal cancer (CRC) is a heterogeneous disease in which cells in the colon or rectum are growing out of control with three distinct, but partially overlapping, molecular phenotypes. The invaluable tools for biomedical research to shape our understanding of the genetic and epigenetic changes that drive the process of malignancy of CRC are the cell lines [34]. They are the populations of cells from a multicellular organism that would normally not proliferate indefinitely but they have escaped normal cellular senescence due to mutation and can continue to divide. The cell lines are frequently used as a simple model for more complex biological systems, such as in the study of mammalian (including human) biochemistry and biology [35]. Improved genetic and epigenetic description of them from the same type of cancer has helped in the selection of suitable *in vitro* models for descriptive and functional research with the aim of choosing the best tool [34].

According to available public databases and The International Cell Line Authentication Committee (ICLAC), twenty-four cell lines cause carcinomas of intestines, which have been observed by short tandem repeat. The cultures of lines causing colorectal adenocarcinoma (COLO 320, DLD-1, HCT-15 , HT-29), colorectal carcinoma (HCT-116) and human colonic adenocarcinoma (Caco-2) are the fastest growing, with a doubling time of 20-24 hours. [34,36]. Other cancer diseases in gut which are indicated by cell cultures are colon adenocarcinoma (HCT-8, SW480), colon adenocarcinoma derived from metastatic site (COLO 201, LOVO, SW620) and papillomavirus-related endocervical adenocarcinoma (BGC-823, SGC-7901) [36].

3. Treatment

In the original sense, chemotherapy relates to the use of drugs that specifically bind and kill (inhibit) microorganism or tumour cells [37]. The work of Paul Ehrlich (1854–1915) have laid the foundations of modern chemotherapy. His hypothesis about drugs was, that they are substances, which selectively bind only to pathogens and not the host cell and are effective against the pathogens without producing harmful effects on the host. Since the chemotherapy was discovered, scientists have developed many bioactive agents bringing the successful treatment of many diseases, including bacterial infections and cancer [38].

Depending on the cause of the disease, effects and use, chemotherapy can be divided into antimicrobial and anticancer. Antimicrobial chemotherapy is used to cure an infectious disease with different pharmacological properties, such as mechanisms of action or spectra of activity. Original term “antibiotic” describes a natural substance that is released by bacteria or fungi into the environment as a compound protecting and inhibiting other competitive organisms at low concentrations [39]. There are several classes of antimicrobial agents based on sites of action: targeting cell wall (beta-lactam antibiotics, glycopeptides), inhibition of protein biosynthesis (inhibitors of 30S and 50S subunit), inhibition of DNA replication (quinolones) and inhibition of folic acid metabolism (sulphonamides and trimethoprim) [39,40]. Nowadays, term chemotherapy is often understood as a treatment of cancer, which kills fast-growing cells [41,42].

3.1. Anti-diarrhoeal therapy

Symptomatic therapy is used as the one of the main components in the diarrhoea treatment. During diarrhoea there is a big loss of water and electrolytes (sodium, chloride, potassium and bicarbonate), so the therapy should be focused on the oral rehydration, and electrolyte maintenance (WHO 2005). "Antidiarrheal" drugs and anti-emetics have not benefit for ill children below 5 years and can bring dangerous, sometimes fatal effect [43,44]. It should be taken in consideration, that mostly antimicrobial agents cause disturbances in the ecology of intestinal microflora [21]. Diagnostic panel before the initiation of chemotherapy is necessary. The targeted antimicrobial therapy in the cases of salmonellosis, yersiniosis, shigellosis, infections caused by *Campylobacter* and pathogenic *E. coli* is still described [45]. Most common pathogens treated by antibiotics are *Salmonella* spp., *Shigella* spp., *Yersinia* spp., *Campylobacter* spp., Enterotoxic/ enteropathogenic *E. coli* (ETEC, EPEC), *V. cholerae, C. difficile*. In these cases of infections the most used medicaments are quinolone antibiotic ciprofloxacin and macrolide azithromycin [44].

Ciprofloxacin, which is most used antibacterial medicament, is a fluoroquinolone carboxylic acid belonging to class fluoroquinolones. This class according to the side of action is part of inhibitors of DNA replication class: inhibits the bacterial enzyme DNA gyrase, cuts double-stranded DNA to form negative supercoils and then reseals the cut ends. Even though some quinolones show high *in vitro* activity against anaerobic

microorganisms (mainly Enterobacteriaceae) and do not cause significant disturbances to intestinal gut, the increasing evidence of resistance to fluoroquinolones should be taken into consideration [21,44]. Other widely used antibiotic is macrolide azithromycin. Macrolides affect protein synthesis (specifically translocation) by targeting conserved sequences of the peptidyl transferase centre of the 23S r-RNA ribosomal subunit 50S. This leads to uncoupling of incomplete peptide chains in the early stage of protein synthesis [40]. Generally, macrolides are commonly used to treat both Gram-positive and Gram-negative infections, but present low activity against *Enterobacteriaceae*. Azithromycin due to its basic character is used as promising alternative to treat diarrhoea caused specific *Enterobacteriaceae* [46]. Even though using azithromycin as an alternate treatment for diarrhoeagenic *E. coli* is efficient, still the newly emerging mutations in *Enterobacteriaceae* causes the potential utility of these medicines in the future [47].

The discovery of antibiotics had brought the optimism that infections can be treated, controlled, and prevented. However, infections are still leading cause of death worldwide, it is due to the occurrence of new infections, re-emergence of diseases, and development of antimicrobial resistance. With almost every new drug, drug resistance appears, which is considered as a serious problem in treatment in both hospitals and in the community [40]. In general, application of antibiotics provides selection pressure on the microorganisms, that can develop multi-drug resistance [39,48], antibiotics should not be used routinely also [43]. Even though that quinolones are generally suitable for treatment of infections caused by enteropathogenic bacteria, certain problems persist; for example the drug resistance among *Campylobacter* and *Salmonella* species after the therapy with quinolone antibiotics [49]. This negative adverse effects caused by overuse of antibiotics has created a need for the diverse, novel drug development with other mechanisms of bioactivity [50].

3.2. Cancer Treatment

Conventional anticancer treatment (chemotherapy, surgeries, and radiation therapy) is widely used as a key treatment to control cancer. In case of colorectal cancer (CRC), surgeries and chemotherapies have been the first choices for treatment of patients for the long time. Despite the fact that these new treatment options have increased overall survival for advanced disease to three years, those with non-metastasized disease still

have the best chance of survival [30]. Single-agent therapy, which is primarily based on fluoropyrimidine (5-fluorouracil), as well as multiple-agent regimens containing one or more drugs, such as oxaliplatin, irinotecan, and capecitabine, are currently available and used as a targeted treatment of CRC [51]. Advantage of anticancer chemotherapy is the possibility of treatment in various stages [52].

Despite the fact, that these treatments are often used, there are many disadvantages in conventional treatment of cancer. Surgeries and radiation therapy are most successful in early staged cancer and the success rate decreases when the disease is diagnosed later. The difficulty in dosage selection and lack of drug-target specificity in chemotherapy results in cytotoxicity to normal cells [53]. In addition, chemotherapeutic treatments can result in a wide range of side effects. For example, 5-fluorouracil (fluoropyrimidine) as a common described treatment for CRC, is known to cause several side effects such as myelotoxicity, cardiotoxicity and other [54]. In the treatment of CRC, single agent therapy with oxaliplatin were accompanied by toxic effects as peripheral neuropathy and laryngopharyngeal dysesthesia [55]. Major disadvantage of conventional chemotherapy is decrease of effectivity treatment due the growing ability of resistance in cancer cells. Recently, resistant cancer cells via mechanism, for example expression of pumps on cells surface p-glycoprotein and intercellular antioxidant efflux, prevent the chemotherapeutic agents from induce growth-inhibition or cancer-cells apoptosis [56].

4. Plant-derived drugs

It is estimated that nearly 80% of the world's population relies on traditional (mostly herbal) medicine to meet their primary healthcare needs [57]. The natural world is used as the source of medicinal agents, with higher plants being by far the most abundant. They are still important sources of novel compounds that can be used as direct medicinal, chemotherapeutic agents. In the anticancer and antibacterial area, 74 and 70 percent of the total number of small molecules drugs are related to natural compounds [58].

Indeed, plants are equipped with effective defence mechanisms, one of them is production of secondary metabolites. They play a major role in plants adaptation to their environment, they are by-products (secondary product derived from a of non-essential

metabolic pathways), and are responsible for the specific odours, tastes, and colours of plant tissues. Secondary metabolites are also produced to combat pests and pathogens before causing serious damage [59], the major classes like quinones, tannins, coumarins, alkaloids, and essential oils are studied for their antimicrobial, antiviral and anti-inflammatory properties, and they are being widely researched for their effects [60].

It is well-established fact that the foremost requirement of purity in the modern drug development causes low solubility, single drug or molecule is hardly absorbed by biological systems than is a mixture of compounds. [58]. The growing demand to the natural products as a source of new lead pharmacological agents can be contributed to the therapeutic requirement to obtain wide range of effective active compounds of secondary metabolites [50]. Plant-derived compounds that possess therapeutic effects may act by similar or different pathways compare to conventional agents [61], their interesting biological activity have found direct medicinal application as drug scaffolds, they are effective as "leads" or model compounds (templates) for drug synthesis or semi-synthesis [62].

4.1. Antibacterial agents

A large spectrum of plant-derived compounds and their secondary metabolites have antimicrobial activity [63]. According to systematic review written by Chassagne *et al.* antibacterial activity is found in 51 of 79 vascular plant orders throughout the phylogenetic tree, most are reported within eudicots. The most represented plant families are Lamiaceae, Fabaceae and Asteraceae while the most studied species were *Cinnamomum verum*, *Rosmarinus vulgaris* and *Thymus vulgaris* [59]. Exist two reasons, why to be interested in the topic of plant-derived antibacterial agents. Firstly, several phytochemicals will find their way into the arsenal of drugs because they are already being tested in humans. Secondly, the public is becoming aware of problems with the over prescription or misuse of conventional antibiotics [64]. Plant-derived antimicrobial compounds have high therapeutic potential since they have fewer adverse effects than conventional agents and have a low risk of resistance development [63]. Major classes of agents are phenolics, terpenoids, essential oils, alkaloids, lectins and polypeptides, and polyacetylenes [64].

4.2. Antiproliferative agents

Plants continue to have great potential to provide innovative medications and represent a reservoir of natural compounds with chemoprotective potential against cancer [54]. Agents with antiproliferative effects are substances that prevent or retard the spread of cells, especially malignant cell lines into surrounding tissues. The first plant-derived antiproliferatives to enter clinical use were vinca alkaloids, vinblastine and vincristine, isolated from the flowering plant *Catharanthus roseus,* which is endemic to Madagascar [66]. Today's plant-derived anticancer drugs fall into four categories: vinca alkaloids (vinblastine, vincristine and vindesine), epipodophyllotoxins (etoposide and teniposide), taxanes (paclitaxel and docetaxel) and camptothecin derivatives (camptothecin and irinotecan).

5. Quinoline alkaloids

Wilhelm Meissner, a German pharmacist, introduced the term "alkaloid," traditional definitions of these natural compounds focused on their bitter taste, basicity, plant origin, and physiological actions. The presence of at least one nitrogen atom is characteristic for chemical structure of alkaloids [67]. This class of compounds have a wide range of chemical structures, including heterocyclic ring systems, and they are predominantly derived from amino acids. They are found in 20% of plant species, many of the approximately 20 000 known alkaloids have been utilised as pharmaceuticals, stimulants, narcotics and poisons [68]. Naturally occurring quinoline and isoquinoline alkaloids are classes of N-based heterocyclic bioactive products, they are very large group of structurally diverse secondary metabolites. Their core structure consists of quinoline or isoquinoline, which are heterocyclic aromatic organic isomers with the chemical formulas C_9H_7N. They differ in the position of the nitrogen in the ring structure (position 1 for quinoline and 2 for isoquinoline). Most of these compounds possess broad and significant biological activity. They have role as major precursors of antidiarrheal and anticancer agents in drug development [69,70].

Isoquinolines are a large class of alkaloids found mostly in higher plants. This group has a wide range of medicinal properties, including antiviral, antifungal, anticancer, antioxidant, antispasmodic, and enzyme inhibitor properties, the major and widely

studied are morphine and codeine [71]. The most known members are opium alkaloids (morphine, noscapine, codeine, thebaine, papaverine) obtained from the mature capsules of *Papaver somniferum*. They are mainly used as analgesic, sedatives or psychotropics, the first information about their production is found on Sumerian clay tablets in about 3000 BC [72], morphine was firstly isolated from the *P. somniferum* in the early 19th century. Isoquinolines have a high probability of success as reflected by several revolutionary compounds in the drug discovery and development process, such as the analgesic morphine, antibacterial berberine, antitussive codeine, antirheumatic sinomenine, and acetylcholinesterase inhibitor galanthamine [70].

Quinoline alkaloids are important heterocyclic aromatic compounds with a broad range of bioactivities. Their antitumor, antimalarial, antibacterial, anti-inflammatory and other activities were documented [69]. The most known are cinchonine, cinchonidine, quinine, and quinidine [71]. Discovery of the quinoline alkaloid quinine in 1820, which was isolated from the bark of the *Cinchona* spp., replaced the crude bark in the treatment of malaria [69], the antimalarial quinoline-containing drugs such as chloroquine, quinine, and mefloquine are essential parts of our malaria chemotherapeutic arsenal [73]. The other very known quinoline alkaloid is camptothecin, which possesses anticancer effect from the Chinese tree *Camptotheca acuminata* was isolated in the early 1960s [69].

Many novel quinoline compounds and pharmacological activities were discovered and investigated by researchers worldwide. Moreover, a number of their synthetic analogues have also been prepared due to their significant bioactivities; e. g. anticancer alkaloids quinine and camptothecin and their analogues chloroquine, topotecan, or anticancer and antibacterial isoquinoline alkaloid sanguinarine with a potential in synthesis of additional derivates with similar bioactivity [74].

Recently, several thousands of publications on activity of quinoline and isoquinoline alkaloids have been updated, more than 800 of these plant-derived compounds have been reported with pharmacological bioactivities to the year 2018 [69,70,75]. However, the data with a special attention on the antimicrobial and anticancer activity hasn’t been summarized and analysed yet. Hence, we suppose that review focused on compounds with antibacterial and antiproliferative effects of quinoline and isoquinoline alkaloids in the gut will bring more comprehensive data as well as possible hints for future drug development.

6. Aims of the Thesis

The main aim of this thesis was to collect and analyse the data on *in vitro* antimicrobial and antiproliferative effects of plant-derived quinoline and isoquinoline alkaloids on human gut bacteria and cells. Identification of main plant taxa containing quinoline and isoquinoline alkaloids with antimicrobial and anticancer properties and characterization of structure-activity relationship of main chemical compounds perspective for future development of pharmaceutical drugs was additional aim of this review.

7. Methodology

Data on biological (antibacterial and antiproliferative) activity of quinoline and isoquinoline alkaloids on gut were collected from scientific databases (Web of Knowledge, PubMed and Google Scholar) using the variation of following keywords: *quinolin*, phyto* or botan* or flora or plant*, *diarrh* or gastroenter* or intestinal infection*, intestin* or gut or colo* or *cancer*, antibacterial or antimicrobial or MIC, antiprolifer* or cytotoxic* or antitumor* or anticancer* or IC50. Plant names were verified using online databases, namely World Flora Online, The Plant List (TPL), Useful Tropical Plants. Information on introduction was retrieved from the scientific databases (Web of Knowledge, PubMed and Google Scholar) or from other scientific literature. The compounds were sorted according to the theory of structure–activity relationship (SAR), which is defined as a relationship between a molecule's chemical structure and its biological activity.

The data with antibacterial and antiproliferative effects concerned only intestinal bacteria/cell line involved in development of infection/cancer. The thresholds for inclusion the compound as an antibacterial or as an antiproliferative agent in Table 3 and 4 were the concentrations marked as 'active' (with the MIC value <100 μg/ml) and as 'moderately cytotoxic' (with the IC_{50}/ED_{50} values <125 μg/ml) for antibacterial and antiproliferative effects, respectively [48,76]. If the pharmacological activity (antibacterial or antiproliferative effect) of the compound was demonstrated in another assay (e.g., disc diffusion method), it was marked as 'active' (A) and the further explanation on the effective dose and its impact on the bacterium/cell line was added in a footnote.

8. Literature Review

8.1. Chemotaxonomical distribution in plants

Using literature analysis, 406 molecules of quinoline and isoquinoline alkaloids with antibacterial or antiproliferative activity in gut were identified. Both groups, quinolines and isoquinolines were represented by 121 and 285 compounds, respectively. All compounds identified belong to 33 different chemical classes, whereas 9 of them are quinolines and 24 are isoquinolines. Among quinoline alkaloids, furoquinolines were the largest chemical class represented by 80 compounds, followed by 11 indoloquinolines and 8 acridones. Most isoquinolines were members of aporphines (79 structures), followed by 39 protoberberines, and 32 bisbenzylisoquinolines. The most abundant and the strongest alkaloids are marked in the results by the numbers **1-11** in bold after the compound names. The chemical structures of these numbered compounds are displayed in Figure 1. The most common compound was berberine (**1**), which was present in 20 plant species. Palmatine (**2**) and skimmianine (**3**) were also abundant compounds present in 19 and 16 plant species, respectively.

As far as distribution of quinoline and isoquinoline alkaloids in individual plant taxa is considered, they were present in 168 plant species belonging to 29 families. The most plants were from the families Rutaceae (32 species), Euphorbiaceae (22 species) and Menispermaceae (17 species). The broadest spectrum of chemical structures (especially quinolines) was found in the genus *Dictamnus*, whereas *D. angustifolius* contained highest number (40) of different alkaloids. Furthermore, many compounds were present in *D. albus* (38), *D. dasycarpus* (38), *D. hispanicus* (29). Following species *Cissampelos pareira* (24), *Stephania glabra* (19), *Berberis petiolaris* (17) and *Melicope semecarpifolia* (16) were the most important plant sources of isoquinoline. The number of taxa containing quinoline and isoquinolines alkaloids was originated in tropical regions. The names of compounds, their chemical classes and plant sources (species and family) are shown in Tables 1 and 2 for isoquinolines and quinolines, respectively.

Table 1. Classification and plant sources of isoquinolines with antibacterial or antiproliferative effects

Class of alkaloids	Compound	Plant (Family)	Reference
Simple isoquinolines	Isoquinoline-1-carbonitrile	*Eleutherine bulbosa* (Iridaceae)	[77]
	Mahimbrine A	*Mahonia imbricata* (Berberidaceae)	[78]
	1,3,6,6-Tetramethyl-5,6,7,8-tetrahydro-isoquinolin-8-one	*Annona vepretorum (Annonaceae)*	[79]
Aporphines	Anonaine	*Annona muricata (Annonaceae)*	[80]
		Annona salzmannii (Annonaceae)	[79,81,82, 83]
		Artabotrys hexapetalus (Annonaceae)	[84]
	Isoboldine	*Annona hypoglauca (Annonaceae)*	[85]
		Berberis petiolaris (Berberidaceae)	[86]
	Actinodaphnine	*A. hypoglauca*	[85]
		Litsea polyantha (Lauraceae)	[87]
	Magnoflorine	*Stephania glabra (Menispermaceae)*	[88]
		Berberis iliensis (Berberidaceae)	[89]
		Coptis japonica (Berberidaceae)	[90]
		B. petiolaris	[86]
		Hernandia nymphaeifolia (Hernandiaceae)	[91]
	Nornuciferine	*Guatteria blepharophylla*	[82]
		A. muricata	[80]
	Magniflorine	*Cissampelos pareira (Ranunculaceae)*	[92]
	Nuciferine	*C. pareira*	[92]
	Bulbocarpine	*C. pareira*	[92]
	Corytuberine	*C. pareira*	[92]
	(+)-Cissaglaberrimine	*Cissampelos glaberrima (Ranunculaceae)*	[92]
	(+)-Trilobinine	*C. glaberrima*	[92]
	Dicentrine	*C. pareira*	[92]
		Talauma arcabucoana (Magnoliaceae)	[93]

		Lindera megaphylla (Lauraceae)	[95]
	Nordicentrine	*T. arcabucoana*	[93]
	Dicentrinone	*T. arcabucoana*	[93]
	(+)-N-(Methoxycarbonyl)-N-nordicentrin	*Litsea cubeba (Lauraceae)*	[94]
	(+)-N-(Methoxycarbonyl)-N-norpredicentrine	*L. cubeba*	[94]
	Dehydrodicentrine	*L. cubeba*	[94]
	Roemerine	*S. glabra*	[88]
	Stephararine	*S. glabra*	[88]
	Tuduranine	*S. glabra*	[88]
	(+)-N-(Methoxycarbonyl)-N-norglaucine	*L. cubeba*	[94]
	Glaucine	*Corydalis turtschaninovii (Fumariaceae)*	[96]
		Codiaeum variegatum (Euphorbiaceae)	[97]
		Croton linearis (Euphorbiaceae)	[98]
		Ocotea macrophylla (Lauraceae)	[99]
		Ocotea quixos (Lauraceae)	[99]
	Arcabucoine	*T. arcabucoana*	[93]
	Menisperine	*B. petiolaris*	[86]
	3-Methoxy-nordomesticine	*O. macrophylla*	[99]
	N-Ethoxycarbonyl-3-methoxy-Nordomesticine	*O. macrophylla*	[99]
	N-Formyl-3-methoxy-nordomesticine	*O. macrophylla*	[99]
	N-Methoxycarbonyl-3-methoxy-nordomesticine	*O. macrophylla*	[99]
	Nantenine	*O. quixos*	[99]
		O. macrophylla	[99]
	Dehydronantenine	*O. quixos*	[99]
		O. macrophylla	[99]
	Dasymaroine A	*Dasymaschalon rostratum* (Annonaceae)	[100]

	Crebanine	*S. glabra*	[101]
	Dehydrocrebanine	*S. glabra*	[101]
	Xylopine	*A. muricata*	[80,97]
	3-Methoxyguadiscidine	*Guatteria citriodora (Annonaceae)*	[102]
	Guattescidine	*G. citriodora*	[102]
	Asimilobine	*A. muricata*	[80,97]
		A. salzmannii	[79,83]
	Demethylsonodione	*H. nymphaeifolia*	[97]
	Corydine	*Chelidonium majus (Papaveraceae)*	[103]
	Isocorydine	*B. petiolaris*	[86]
		O. quixos	[99]
		O. macrophylla	[99]
	Norcorydine	*A. salzmannii*	[79]
	Norisocorydine	*A. hexapetalus*	[84]
	(+)-N-(Methoxycarbonyl)-N-norisocorydione	*L. cubeba*	[94]
	(+)-N-(Methoxycarbonyl)-N-norbulbodione	*L. cubeba*	[94]
	Laurolitsine	*Lindera aggregata (Lauraceae)*	[104]
	Laurelliptinhexadecan-1-one	*Cocculus orbiculatus (Menispermaceae)*	[105]
	Laurelliptinoctadecan-1-one	*C. orbiculatus*	[105]
	(+)-8-Methoxyisolaurenine-N-oxide	*L. cubeba*	[94]
	Laureline	*A. hexapetalus*	[84]
	Atherospermidine	*A. hexapetalus*	[84]
	Artabonatine B	*A. hexapetalus*	[84]
	(+)-N-Hydroxyhernangerine	*H. nymphaeifolia*	[91]
	N-Formyldehydrooviger ine	*H. nymphaeifolia*	[91]
	(+)-Hernovine	*H. nymphaeifolia*	[91]
	(+)-N-Methylhernovine	*H. nymphaeifolia*	[91]
	(+)-Laurotetanine	*H. nymphaeifolia*	[91]

	Thalifoline	*H. nymphaeifolia*	[91]
	Pronuciferine	*S. glabra*	[91]
	Northalifoline	*H. nymphaeifolia*	[91]
Oxoaporphines	O-Methylmoschatoline	*G. citriodora*	[102]
	3-Methoxyoxoputerine	*G. citriodora*	[102]
	Oxoputerine	*G. citriodora*	[102]
	3-Methoxyoxoputerine-N-oxide	*D. rostratum*	[100]
	Isomoschatoline	*Guatteria blepharophylla (Annonaceae)*	[82]
	Lysicamine	*G. citriodora*	[102]
		G. blepharophylla	[82]
		A. vepretorum	[79]
		Abuta rufescens (Menispermaceae)	[106]
	Liriodenine	*G. blepharophylla*	[97]
		G. citriodora	[97]
		Microcos paniculata (Annonaceae)	[97]
		Zanthoxylum nitidum (Annonaceae)	[97]
		Stephania rotunda (Menispermaceae)	[107]
		A. muricata	[80]
		A. vepretorum	[80]
		A. salzmannii	[79,83]
		A. hexapetalus	[84]
	Subsessiline	*G. blepharophylla*	[82]
		A. rufescens	[106]
	Splendidine	*A. rufescens*	[106]
	Bianfugenine (syn. Dauriporphine)	*Sinomenium acutum (Menispermaceae)*	[108]
	Oxonantenine	*A. vepretorum*	[79]
	Lanuginosine	*A. vepretorum*	[79]
Pyridoisoquinolines	Cephealine	*Alangium salviifolium (Alangiaceae)*	[109]
	Isocephaeline	*A. salviiifolium*	[109]
	8-Hydroxyl-cephealine	*A. salviiifolium*	[109]
	Tubulosine	*A. salviiifolium*	[109]
	Δ1′,2′-Deoxytubulosine	*A. salviiifolium*	[109]

	Deoxytubulosine	*A. salviiifolium*	[109]
	Isotubulosine	*Pogonopus tubulosus* (Rubiaceae)	[110]
	Protoemetinol	*A. salviiifolium*	[109]
	10-Demethylprotoemetinol	*A. salviiifolium*	[109]
	Alangimarckine	*A. salviiifolium*	[109]
	Ankorine	*A. salviiifolium*	[109]
Benzylisoquinolines	Oblongine	*B. petiolaris*	[86]
		C. pareira	[111]
	Papaverine	*Papaver somniferum (Papaveraceae)*	[112,113]
	β-Hydrastine	*Hydrastis canadensis (Ranunculaceae)*	[114]
	Reticuline	*A. muricata*	[80,97]
		B. petiolaris	[86]
		Berberis aristata (Berberidaceae)	[115]
		A. salzmannii	[83]
		A. hexapetalus	[84]
		Argemone mexicana (Papaveraceae)	[116]
		Argemone ochroleuca (Papaveraceae)	[117]
		H. nymphaeifolia	[91]
		C. linearis	[98]
	Argenaxine	*A. mexicana*	[116]
	Higenamine	*A. mexicana*	[116]
	Pancorine	*A. mexicana*	[116]
	Cherylline	*Crinum macowanii (Amaryllidaceae)*	[118]
	Galanthamine	*C. macowanii*	[84]
	Taicalensine B	*Thalictrum baicalense* (Ranunculaceae)	[84]
	Hexapetaline A	*A. hexapetalus*	[119]
	Hexapetaline B	*A. hexapetalus*	[119]
Crinines	Crinine	*C. macowanii*	[119]
		Nerine bowdenii (Amaryllidaceae)	[120]
	Crinamine	*C. macowanii*	[119]
	Crinamidine	*C. macowanii*	[119]
	O-Acetyl-hamayne	*C. macowanii*	[119]
	1-Epideacetylbowdensine	*C. macowanii*	[119]

	Haemanthamine	*A. salviiifolium*	[109]
	Buphanidrine	*Scadoxus pseudocaulus (Amaryllidaceae)*	[121]
		N. bowdenii	[120]
	Vittatine	*S. pseudocaulus*	[121]
		N. bowdenii	[120]
	Distichamine	*S. pseudocaulus*	[121]
		N. bowdenii	[120]
	Buphanisine	*S. pseudocaulus*	[121]
		N. bowdenii	[120]
Lycorines	O-Acetyllycorine	*C. macowanii*	[119]
	Lycorine	*S. pseudocaulus*	[121]
	Hippadine	*C. macowanii*	[119]
		S. pseudocaulus	[121]
	Amarbellisine	*S. pseudocaulus*	[121]
	Caranine	*S. pseudocaulus*	[121]
	Acetylcaranine	*N. bowdenii*	[120]
Phenanthridines	trans-Dihydrolycoricidine	*S. pseudocaulus*	[121]
	Oxynorchelerythrine	*Portulaca oleracea (Convolvulaceae)*	[122]
	Lycoricidine	*P. oleracea*	[122]
	6,9,11-Trihydroxybenzo[1,3]dioxolo[4,5-c]phenanthridin-5(4H)-one	*P. oleracea*	[122]
	6,11-Dihydroxy-8,9-dimethoxybenzo[1,3]dioxolo[4,5-c]phenanthridin-5(4H)-one	*P. oleracea*	[122]
	Narciclasine	*Hymenocallis littoralis (Amaryllidaceae)*	[123]
	Ungeremine	*H: littoralis*	[123]
		S. pseudocaulus	[121]
	Pancratistatin	*H: littoralis*	[123]
		S. pseudocaulus	[121]
	Cheilanthifoline	*Corydalis dubia (Fumariaceae)*	[124]
	Scoulerine	*C. dubia*	[124]
		A. ochroleuca	[117]
	Dehydrocheilanthifoline	*Berberis brevissima (Berberidaceae)*	[126]

		Berberis parkeriana (Berberidaceae)	[126]
	Laudanosine	*C. linearis*	[98]
	Laudanidine	*C. linearis*	[98]
Protoberberines	Berberine	*H. canadensis*	[114,127, 128]
		Coptis chinensis (Ranunculaceae)	[128,129]
		Xanthorhiza simplicissima (Ranunculaceae)	[127]
		C. japonica	[128,130, 131]
		Phellondendron chinense (Ranunculaceae)	[128]
		Phellodendron amurense (Rutaceae)	[128]
		C. turtschaninovii	[96]
		C. pareira	[92]
		B. iliensis	[89]
		Berberis aquifolium (Berberidaceae)	[89]
		B. aristata	[89,92,115]
		Berberis vulgaris (Berberidaceae)	[132]
		B. brevissima	[126]
		B. parkeriana	[126]
		Berberis buxifolia (Berberidaceae)	[133]
		C. majus	[103]
		A. ochroleuca	[117]
		C. chinensis	[135]
		Coptis deltoidea (Ranunculaceae)	[135]
		Coptis teeta (Ranunculaceae)	[135]
	Baicalensine A	*T. baicalense*	[118]
	Corypalmine	*A. muricata*	[80]
	Pendulamine A	*Polyathia longifolia var. pendula (Annonaceae)*	[136]
	Pendulamine B	*P. longifolia var. pendula*	[136]
	8-Oxoberberine	*B. petiolaris*	[86]
		B. brevissima	[126]
		B. parkeriana	[126]
		C. japonica	[131]
	Epiberberine	*C. chinensis*	[135]
		C. deltoidea	[135]

		C. teeta	[135]
	8-Oxo-epiberberine	*C. japonica*	[135]
	Demethyleneberberine	*B. petiolaris*	[86]
	N-Methyltetrahydroberberine	*B. petiolaris*	[86]
	Tetrahydroberberine	*B. petiolaris*	[86]
	Palmatine	*C. chinensis*	[129,135, 137,138]
		C. deltoidea	[135]
		C. teeta	[135]
		C. japonica	[130,131]
		Fibraurea recisa (Menispermaceae)	[138]
		Tinospora cordifolia (Menispermaceae)	[137]
		Tinospora sagittata (Menispermaceae)	[137]
		Enantia chlorantha (Annonaceae)	[138]
		P. amurense	[137,138]
		C. turtschaninovii	[96]
		Corydalis yanhusuo (Fumariaceae)	[137]
		G. citriodora	[102]
		B. iliensis	[89]
		B. aristata	[115]
		S. glabra	[88]
		S. rotunda	[107]
		Stephania yunnanensis (Menispermaceae)	[137]
		Mahonia bealei (Berberidaceae)	[140]
		Albizia adianthifolia (Fabaceae)	[141]
	8-Oxopalmatine	*B. petiolaris*	[86]
	Alangiifoliumine A	*A. salviiifolium*	[109]
	Tetrahydrothalifendine	*B. petiolaris*	[86]
	Thalifendine	*B. petiolaris*	[86]
	8-Oxothalifendine	*B. petiolaris*	[86]
	Columbamine	*S. glabra*	[88]
		C. japonica	[90]
		C. chinensis	[135]
		C. deltoidea	[135]

		C. teeta	[135]
		B. petiolaris	[86]
		B. brevissima	[126]
		B. parkeriana	[126]
	Stepharanine	*S. glabra*	[88]
	Dehydrocorydalmine	*S. glabra*	[88]
	Palmatrubine	*S. glabra*	[88]
	11-Hydroxypalmatine	*S. glabra*	[88]
	Jatrorrhizine	*S. glabra*	[88]
		C. japonica	[90]
		C. chinensis	[129,135, 139]
		C. deltoidea	[135]
		C. teeta	[135]
		C. turtschaninovii	[96]
		B. iliensis	[89]
		B. aristata	[115]
		B. brevissima	[126]
		B. parkeriana	[126]
		Tinospora capillipes (Menispermaceae)	[142]
	Coptisine	*C. turtschaninovii*	[96]
		C. japonica	[90,130]
		C. chinensis	[129,135, 139]
		C. deltoidea	[135]
		C. teeta	[135]
		A. ochroleuca	[117]
		C. majus	[143]
	Pseudocoptisine	*C. turtschaninovii*	[96]
		C. japonica	[96]
	8-Oxocoptisine	*C. japonica*	[108,131]
	Pseudodehydrocorydaline	*C. turtschaninovii*	[96]
	Dehydrocorybulbine	*C. turtschaninovii*	[96]
	Corydaline	*C. turtschaninovii*	[96]
	Cyclanoline)	*C. pareira*	[92,111]
	Stylopine	*C. majus*	[103]
	6-([1,3]-Dioxolo[4,5-g]isoquinoline-5 -carbonyl)-2,3-dimethoxy-benzoic acid methyl ester	*C. japonica*	[131]

protopine-type	Allocryptopine	*C. majus*	[86,103, 117]
		B. petiolaris	[86]
		A. ochroleuca	[117]
	Allocryptopine	*Macleaya cordata (Papaveraceae)*	[144]
	Protopine	*C. dubia*	[124]
		Hylomecon japonica (Papaveraceae)	[145]
		C. majus	[146]
		M. cordata	[144,147]
Tetrahydroberberines	Isocoreximine	*G. blepharophylla*	[98]
		C. flavens	[82,97]
		C. salutaris	[125]
	Corydalmine	*S. glabra*	[125]
	Hemiargyrine	*Croton hemiargyreus (Euphorbiaceae)*	[88]
	Stepholidine	*S. glabra*	[88]
	Capaurine	*S. glabra*	[125]
	Corynoxidine	*S. glabra*	[88]
Cularines	Cularine	*C. linearis*	[88]
Spirobenzylisoquinoline	Thalicfoetine	*Thalictrum foetidum* (Ranunculaceae)	[148]
Benzophenanthridines	Sanguinarine	*C. majus*	[103,134, 146]
		Sanguinaria canadensis (Papaveraceae)	[149]
		Eschscholzia californica (Papaveraceae)	[150]
		H. japonica	[145]
		Macleaya microcarpa (Papaveraceae)	[151]
		Bocconia latisepala (Papaveraceae)	[151]
		Bocconia cordata (Papaveraceae)	[151]
		Bocconia frutescens (Papaveraceae)	[151]
		M. cordata	[151]
		A. ochroleuca	[144]
	Dihydrosanguinarine	*A. ochroleuca*	[144]
		H. japonica	[145]
		B. cordata	[151]
		B. frutescens	[151]
		M. cordata	[151]

		M. microcarpa	[151]
	Oxysanguinarine	*H. japonica*	[145]
	N-Demethyloxysanguinarine	*A. mexicana*	[116]
	6-Acetonyldihydrosanguinarine	*M. cordata*	[120]
	6-Methoxyldihydrosanguinarine	*M. cordata*	[120]
	Chelerythrine	*C. majus*	[103]
		E. californica	[150]
		S. canadensis	[154]
		M. microcarpa	[151]
		A. mexicana	[116]
		A. ochroleuca	[117]
		M. cordata	[117]
		H. japonica	[145]
		Zanthoxylum rhoifolium (Rutaceae)	[155]
		Zanthoxylum leprieurii (Rutaceae)	[156]
	6-Butoxydihydrocheleerythrine	*M. microcarpa*	[151]
	6-Acetonyl-5,6-dihydrochelerythrine	*Z. leprieurii*	[156]
	6-Methoxydihydrocheleerythrine	*H. japonica*	[145]
	Macarpine	*E. californica*	[150]
	Angoline	*A. mexicana*	[116]
	Decarine	*Z. rhoifolium*	[155]
	Nitidine	*Z. rhoifolium*	[155]
		Toddalia asiatica (Rutaceae)	[193]
	Avicine	*Z. rhoifolium*	[155]
	6-Acetonyldihydrocheleerythrine	*M. cordata*	[147]
	6-Methoxyldihydrocheleerythrine	*M. cordata*	[147]

	6-Methoxydihydrosanguinarine	*H. japonica*	[145]
	10-Methoxydihydrosanguinarine	*M. microcarpa*	[151]
	Dihydrochelerythrine	*C. majus*	[103]
		Z. rhoifolium	[155]
		H. japonica	[145]
		M. microcarpa	[151]
		Bocconia arborea (Papaveraceae)	[151]
		Bocconia integrifolia (Papaveraceae)	[151]
		B. arborea	[151]
		Bocconia Pearcei (Papaveraceae)	[151]
		M. cordata	[151]
	12-Methoxydihydrochelerythrine	*M. microcarpa*	[151]
		B. integrifolia	[151]
	8-Hydroxydihydrosanguinarine	*C. majus*	[103]
	8-Hydroxydihydrochelerythrine	*C. majus*	[103]
	Dihydrosanguinarine	*C. majus*	[103]
	Chelidonine	*C. majus*	[134]
	Maclekarpine C	*M. microcarpa*	[151]
	Corynoline	*Corydalis incisa (Papaveraceae)*	[157]
	Corynoloxine	*C. incisa*	[157]
	6-Oxocorynoline	*C. incisa*	[157]
Tetrahydroisoquinolines	Tetrahydropalmatine	*S. glabra*	[84]
	Gindaricine	*S. glabra*	[84]
		A. hexapetalus	[88]
	Tetrahydrocoptisine	*C. turtschaninovii*	[96]
	1,2,3,4-Tetrahydroisoquinoline,	*Celosia trigyna (Amaranthaceae)*	[158]
	1-[Phenyl (hydroxymethyl)]-6,7-dim ethoxy-2-methyl	*C. trigyna*	[158]

	Coclaurine	*C. pareira*	[111]
		A. muricata	[97]
Erythrinas	Erythraline	*Erythrina abyssinica (Fabaceae)*	[52]
	Erysodine	*E. abyssinica*	[52]
	Erysotrine	*E. abyssinica*	[52]
	B-Oxoerythraline	*E. abyssinica*	[52]
	11-Methoxyerysodine	*E. abyssinica*	[52]
Bisbenzylisoquinolines	Warifteine	*Cissampelos ovalifolia* (Menispermaceae)	[92]
	Methylwarifteine	*C. ovalifolia*	[92]
	Hayatin	*C. pareira*	[92]
	Hayatinine	*C. pareira*	[92]
	Hayatidine	*C. pareira*	[92]
	Pelosine	*C. pareira*	[92]
	cCssampareine	*C. pareira*	[92]
	Curine	*C. pareira*	[111]
	Cycleanine	*Cissampelos capensis* (Menispermaceae)	[92,107, 160,161]
		Epinetrum villosum (Menispermaceae)	[160]
		Albertisia villosa (Menispermaceae)	[161]
		S. rotunda	[107]
	Cocsoline	*E. villosum*	[160]
		A. villosa	[161]
	Cycleanine N-oxide	*E. villosum*	[52,160]
	Isochondodendrine	E. villosum	[160]
		C. pareira	[92]
	N-Desmethylcycleanine	*S. glabra*	[88]
		A. villosa	[161]
	Isotetrandrine	*Xylopia aethiopica* (Annonaceae)	[162]
	5′-Hydroxythalidasine	*Thalictrum minus (Ranunculaceae)*	[163]
	Thalrugosaminine	*T. minus*	[163]
	Thalmidine (O-Methylthalicberine)	*T. minus*	[163]
	Karakoramine	*B. petiolaris*	[86]
	Berbamine	*B. aristata*	[115]
		B. vulgaris	[164]
	Tetrandrine	*Stephania tetrandra (Menispermaceae)*	[108,165, 166,167, 168]
		C. pareira	[111,169]

	Gangchinoline	*S. tetrandra*	[108,]
		S. epigaea	[170]
	Costaricine	*L. aggregata*	[104]
	Bersavine	*B. vulgaris*	[164]
	Neferine	*Nelumbo nucifera (Nelumbonaceae)*	[171]
	O-Methylneferine	*N. nucifera*	[171]
	Northalrugosidine	*Thalictrum alpinum* (Ranunculaceae)	[172]
	Thalrugosidine	*Thalictrum rugosum* (Ranunculaceae)	[172]
	Thalidasine	*Thalictrum dasycarpum* (Ranunculaceae)	[172]
	Cepharanthine	*Stephania epigaea (Menispermaceae)*	[170]
	(+)-2-Norcepharanthine	*S. epigaea*	[170]
	Homaromoline	*S. epigaea*	[170]
	3′,4′-Dihydrostephasubine	*S. epigaea*	[170]
	Obaberine	*C. pareira*	[170]
	Obamegine	*C. pareira*	[170]
	Homoaromoline	*C. pareira*	[170]
	(-)-Nor-N′-chondrocurine	*C. pareira*	[170]
	Tiliacorine	*Tiliacora racemosa (Menispermaceae)*	[173,174]
	Tiliacorinine	*T. racemosa*	[173,174]
	Tiliamosine	*T. racemosa*	[173,174]
	Tiliaresine	*T. racemosa*	[173,174]
	Tiliaimine	*T. racemosa*	[173,174]
	Tiliarine	*T. racemosa*	[173,174]
	N-Methyltiliamosine	*T. racemosa*	[173,174]
	Tiliacosine	*T. racemosa*	[173,174]
	Tiliasine	*T. racemosa*	[173,174]
	2′-Nortiliacorinine	*T. racemosa*	[173]
	N-Methyltiliarine	*T. racemosa*	[173]
	Nordinklacorine	*T. racemosa*	[173]
	Neothalfine	*Thalictrum delavayi* (Ranunculaceae)	[175]
Morphinans	Salutaridine	*C. hemiargyreus*	[125]
		C. flavens	[125]
		C. salutaris	[125]
	Salutarine	*C. flavens*	[125]
		C. salutaris	[125]

	Sebiferine	*C. flavens*	[125]
		C. salutaris	[125]
	Flavinantine	*C. flavens*	[125]
		C. salutaris	[125]
	Norsinoacutine	*C. flavens*	[125]
		C. salutaris	[125]
	Sinomenine	*Dictamnus angustifolius* (Euphorbiaceae)	[176]
		S. rotunda	[177]
		S. acutum	[107]
	Codeine	*P. somniferum*	[113]
	Morphine	*P. somniferum*	[113]
	Thebaine	*P. somniferum*	[113]
Azafluoranthenes	Imeluteine	*A. rufescens*	[106]
	Norrufescine	*A. rufescens*	[106]
	Norimeluteine	*C. pareira*	[92]
	Norruffscine	*C. pareira*	[92]
Tropoloisoquinolines	Pareirubrine A	*C. pareira*	[92]
	Pareirubrine B	*C. pareira*	[92]
	Grandirubrine	*C. pareira*	[92]
		A. rufescens	[124]
	Pareitropone	*C. pareira*	[92]
	Imerubrine	*A. rufescens*	[106]
	Isoimerubrine	*A. rufescens*	[106]
Phthalideisoquinolines	Capnoidine	*C. dubia*	[124]
	Noscapine	*P. somniferum*	[113]
Naphthylisoquinolines	Jozimine A2	*Ancistrocladus abbreviatus* (Ancistrocladaceae)	[178]
	Jozilebomine A	*Ancistrocladus ileboensis* (Ancistrocladaceae)	[179]
	Jozilebomine B	*A. ileboensis*	[179]
Indole alkaloids	Yohimbine	*Pausinystalia yohimbe* (Rubiaceae)	[180]
	Vincamine	*Vinca minor* (Apocynaceae)	[180]
	Dubiamine	*C. dubia*	[124]

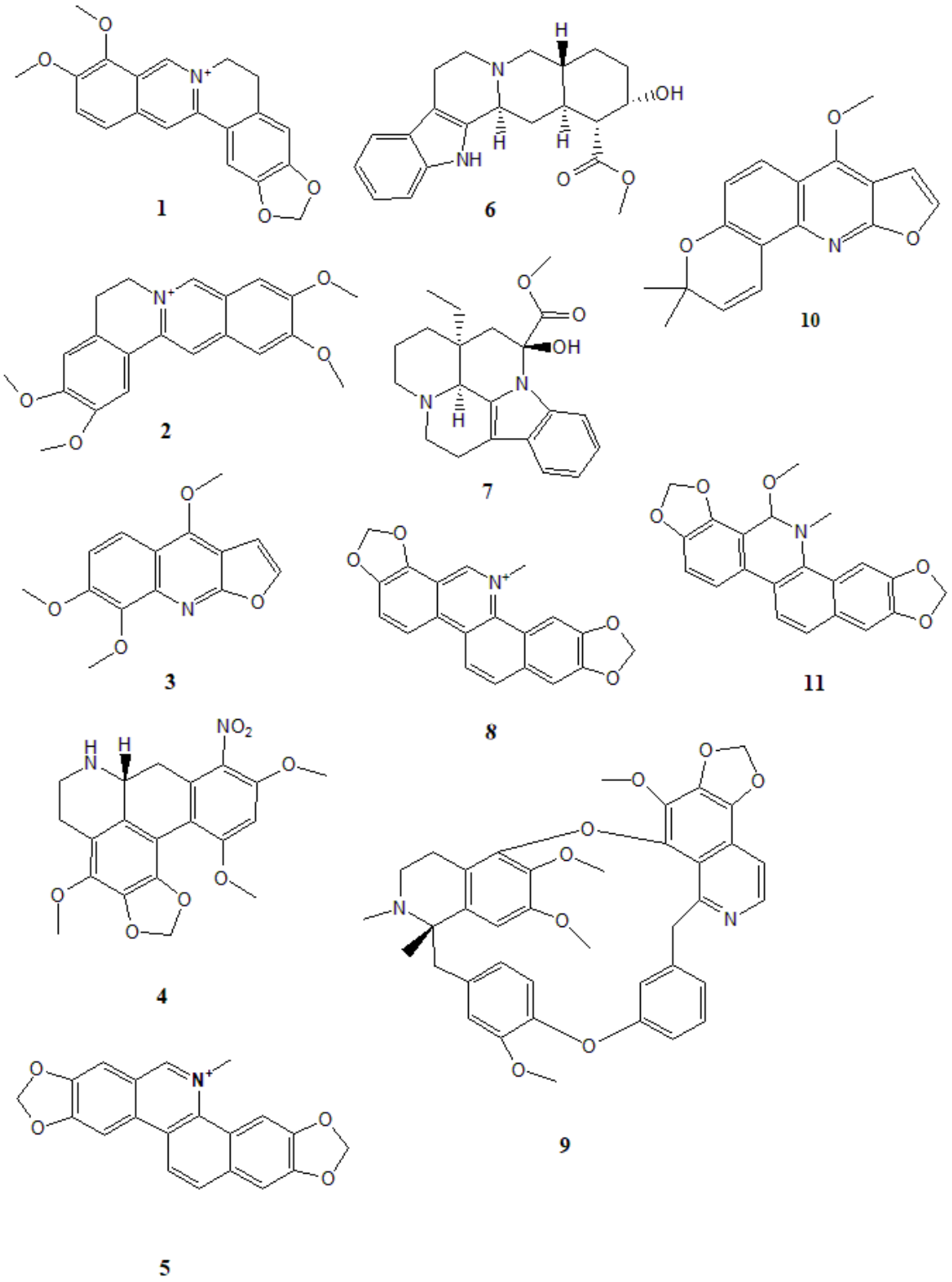

Figure 1. Chemical structures of compounds 1-11.

Table 2. Distribution of quinoline alkaloids with antibacterial or antiproliferative effects in plant taxa.

Class of alkaloids	Compound	Plant (Family)	Reference
Furoquinolines	γ-Fagarine	*Dictamnus angustifolius* (Rutaceae)	[125,176]
		Dictamnus dasycarpus (Rutaceae)	[125,176]
		Dictamnus hispanicus (Rutaceae)	[125,176]
		Helietta apiculata (Rutaceae)	[181]
		Zanthoxylum pistaciiflorum (Rutaceae)	[182]
		Peltostigma guatemalense (Rutaceae)	[183]
	O-Ethylnor-γ-fagarine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
		Zanthoxylum rhoifolium (Rutaceae)	[155]
	7-O-Isopentenyl-γ-fagarine	*P. guatemalense*	[183]
	Skimmianine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
		Melicope madagascariensis (Rutaceae)	[185]
		Melicope semecarpifolia (Rutaceae)	[186]
		Z. rhoifolium	[155]
		Teclea afzelii (Rutaceae)	[187]
		Ruta angustifolia (Rutaceae)	[188]
		Glycosmis pentaphylla (Rutaceae)	[189]
		Zanthoxylum leprieurii (Rutaceae)	[156]
		Melicope pteleifolia (Rutaceae)	[190]
		H. apiculata	[181]
		Z. pistaciiflorum	[182]
		P. guatemalense	[183]
		Tabernaemontana coronaria (Apocynaceae)	[189]
		D. angustifolius	[125,176]

	N-Methylpreskimmianine	*D. albus*	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
	O-Eethylnorskimmianine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
	O-Ethylnordictamnine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
	5-Methoxydictamnine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
	Dictamnine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
		*Vepris lecomteana (*Rutaceae*)*	[191]
		G. Pentaphylla	[189]
		M. pteleifolia	[190]
		H. apiculata	[181]
		M. semecarpifolia	[184]
		Z. pistaciiflorum	[182]
		T. coronaria	[189]
	7-Hydroxydictamnine	*Pitaviaster haplophyllus (*Rutaceae*)*	[192]
		M. pteleifolia	[190]
	Kokusaginine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
		T. afzelii	[187]
		P. haplophyllus	[192]
		M. pteleifolia	[190]
		Esenbeckia almawillia (Rutaceae)	[187]
		Esenbeckia grandifolia (Rutaceae)	[187]
		H. apiculata	[181]
		M. semecarpifolia	[184]
		P. guatemalense	[183]
		*Vepris suaveolens (*Rutaceae*)*	[194]

	Evolitrin	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
		M. pteleifolia	[190]
		P. haplophyllus	[192]
	Maculosidin	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
		H. apiculata	[181]
	Confusameline	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
		M. semecarpifolia	[184,186]
	Haplopine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
		M. semecarpifolia	[184]
	5-Hydroxy-4,8-dimethoxy-furoquinoline	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
		M. semecarpifolia	[184]
	Haploperine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
		M. semecarpifolia	[184]
	Platydesmine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
		M. semecarpifolia	[184]
	(R)-7,8-Dimethoxymyrtopsine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
		M. semecarpifolia	[184]
	Myrtopsine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]

		D. hispanicus	[125,176]
	(-)-1’,2-Anhydro-7,8-dimethoxyplatydesmine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
	(3R)-3,4-Dihydro-5,8,9-trimethoxy-2,2-dimethyl-2H-pyrano[2,3-b]quinolin-3-ol	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
	3-Chloro-8,9-dimethoxygeibalansine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
	5,9-Dimethoxy-2,2-dimethyl-2H-pyrano[2,3-b]quinoline	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
	Deacetyldubinine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
	(S)-7,8-Dimethoxymyrtopsine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
	7,8-Dimethoxyplatydesmine	*D. angustifolius*	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		D. hispanicus	[125,176]
	Melineurine	*P. haplophyllus*	[192]
		M. pteleifolia	[190]
	Pteleine	*P. haplophyllus*	[192]
		M. pteleifolia	[190]
	Leptanoine A	*M. pteleifolia*	[190]
	Leptanoine B	*M. pteleifolia*	[190]
	Leptanoine C	*M. pteleifolia*	[190]
	Leptanoine D	*P. haplophyllus*	[192]
	N-Methylplatydesminium	*P. haplophyllus*	[192]
	Acrophylline	*P. haplophyllus*	[192]
	Melicarpine	*M. semecarpifolia*	[186]
	Semecarpine	*M. semecarpifolia*	[186]

	(+-)-8-Methoxyplatydesmine	*M. semecarpifolia*	[186]
	Dutadrupine	*M. semecarpifolia*	[186]
	Confusadine	*M. semecarpifolia*	[186]
	Melicarpinone	*M. semecarpifolia*	[186]
	Isodictamnine	*Dictamnus caucasicus (Rutaceae)*	[176,195]
		D. angustifolius	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
	Dictangustine A	*D. caucasicus*	[176,195]
		D. angustifolius	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
	8-Hydroxy-9-methyl-furo[2,3-b]quinolin-4(9H)-one	*D. caucasicus*	[176,195]
		D. angustifolius	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
	Isopteleine	*D. caucasicus*	[176,195]
		D. angustifolius	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
	Iso-γ-fagarine	*D. caucasicus*	[176,195]
		D. angustifolius	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
	Isomaculosidine	*D. caucasicus*	[176,195]
		D. angustifolius	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
	Dasycarine	*D. caucasicus*	[176,195]
		D. angustifolius	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
	Preskimmianine	*D. caucasicus*	[176,195]
		D. angustifolius	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
	7-(3-anilino-2-Hydroxyprenyloxy)-8-methoxydictamine	*V. lecomteana*	[196]
	Zanthodioline	*Zanthoxylum nitidum (Rutaceae)*	[197]

	Zanthonitidine A	*Z. nitidum*	[197]
	Robustine	*D. caucasicus*	[176,195]
		D. angustifolius	[125,176]
		D. albus	[125,176]
		D. dasycarpus	[125,176]
		Z. nitidum	[197]
	Maculine	*E. almawillia*	[187]
		E. grandifolia	[187]
		H. apiculata	[181]
	Montrifoline	*Teclea nobilis (Rutaceae)*	[187]
	Tecleaverdoornine	*T. afzelii*	[187]
	Tecleaverdine	*T. afzelii*	[187]
	Tecleine	*T. afzelii*	[187]
	Tecleamine	*T. afzelii*	[187]
	Tecleanatalensine A	*T. afzelii*	[187]
	Tecleanatalensine B	*T. afzelii*	[187]
	Flindersiamine	*T. afzelii*	[187]
		H. apiculata	[181]
	4-Methoxy-N-methyl-2-quinolone	*Z. nitidum*	[197]
	Lecomtequinoline A	*V. lecomteana*	[191]
	Lecomtequinoline B	*V. lecomteana*	[191]
	Lecomtequinoline C	*V. lecomteana*	[191]
	Evoxine	*V. lecomteana*	[191]
		P. guatemalense	[183]
	Anhydroevoxine	*V. lecomteana*	[191]
		P. guatemalense	[183]
	Megistoquinone I	*Sarcomelicope megistophylla* (Rutaceae)	[198]
	Megistoquinone II	*S. megistophylla*	[198]
	Acronycidine	*S. megistophylla*	[198]
	(S)-(-)-7,8-Dimethoxyplatydesmine	*M. semecarpifolia*	[186]
	(S)-(+)-Isoplatydesmine	*M. semecarpifolia*	[186]
	Dimethylrhoifolinate	*M. semecarpifolia*	[186]
	Melisemine	*M. semecarpifolia*	[186]
	Glycocitridine	*M. semecarpifolia*	[186]

	Edulinine	*M. semecarpifolia*	[186]
	2(1H)-Quinolinone	*D. albus*	[176]
		D. dasycarpus	[176]
	2(1H)-Quinolinone-β-D-Glu	*D. albus*	[176]
		D. dasycarpus	[176]
	3-[1β-Hydroxy-2-(β-D-glucopyranosyloxy)-ethyl]-4-methoxy-2(1H)-quinolinone	*D. albus*	[176]
		D. dasycarpus	[176]
Hydroxyquinolines	8-Hydroxyquinoline	*Microstachys corniculata (Euphorbiaceae)*	[149,199, 200]
		Centaurea diffusa (Asteraceae)	[201]
	Ribalinidine	*D. hispanicus*	[176]
		D. angustifolius	[176]
	7-O-Methylribalinidine	*D. hispanicus*	[176]
		D. angustifolius	[176]
Pyranoquinolines	Flindersine	*D. hispanicus*	[176]
		D. angustifolius	[176]
	Tabouensinium	*P. haplophyllus*	[192]
	Veprisine	*P. haplophyllus*	[192]
	N-Methylflindersine	*Toddalia asiatica* (Rutaceae)	[202]
Dubamines	Dubamine	*D. angustifolius*	[176]
	Graveoline	*R. angustifolia*	[188]
	Graveolinine	*R. angustifolia*	[188]
Azaanthraquinones	Cleistopholine	*Annona muricata* (Annonaceae)	[97]
		Annona salzmannii (Annonaceae)	[83]
	Dielsiquinone	*Goniothalamus tamirensis* (Annonaceae)	[83]
Acridones	Rutacridon	*D. angustifolius*	[176]
		D. albus	[176]
		D. dasycarpus	[176]
		D. hispanicus	[176]
	1,3-Dimethoxy-10-methylacridone	*Oricia suaveolens (Rutaceae)*	[162]
	Evoxanthine	*O. suaveolens*	[162]
	1-Hydroxy-3-methoxy-10-methylacridone	*O. suaveolens*	[162]
	Montrifoline	*O. suaveolens*	[162]
	Norevoxanthine	*O. suaveolens*	[162]

	Arborinine	*Uapaca togoensis* (Euphorbiaceae)	[162]
		R. angustifolia	[188]
		P. haplophyllus	[192]
		T. coronaria	[189]
		G. Pentaphylla	[189]
		Z. leprieurii	[156]
	Fabiocinine	*Z. leprieurii*	[156]
Indoloquinolines	Isocryptolepine	*Cryptolepis sanguinolenta (Apocynaceae)*	[204]
	Cryptolepine	*C. sanguinolenta*	[204,205, 206,207, 208,209]
		Sida cordifolia (Malvaceae)	[210]
		Sida acuta (Malvaceae)	[211]
	Quindoline	*C. sanguinolenta*	[134]
		S. acuta	[211]
	Hydroxycryptolepine	*C. sanguinolenta*	[204]
	Cryptoquindoline	*C. sanguinolenta*	[204]
	Rutaecarpine	*Z. pistaciiflorum*	[182]
		Tetradium ruticarpum (Rutaceae)	[212]
	1-Hydroxyrutaecarpine	*Z. pistaciiflorum*	[182]
	Camptothecin	*Mostuea thomsonii* (Rutaceae)	[213]
		Camptotheca acuminata (Cornaceae)	[214]
		Nothapodytes foetida (Icacinaceae)	[214]
		Merrilliodendron megacarpum (Icacinaceae)	[214]
		Ervatamia heyneana (Apocynaceae)	[214]
		Ophiorrhiza mungos (Rubiaceae)	[214]
		Ophiorrhiza rugosa (Rubiaceae)	[214]
	Thomsonine A	*M. thomsonii*	[213]
	Thomsonine B	*M. thomsonii*	[213]
	Evodiamine	*T. ruticarpum*	[212]
Simple quinolines	Quinoline-4-carboxaldehyde	*Ruta chalepensis* (Rutaceae)	[215]
	Quinoline	*Stephania rotunda* (Menispermaceae)	[107]

	4-Methoxy-1-methyl-quinolin-2-one	*P. guatemalense*	[183]
	Quinaldic acid	*Ephedra pachyclada* (Ephedraceae)	[216]
	6-Methylthiol(1)benzothienoquinoline	*Ficus carica* (Moraceae)	[217]
	4-Methylquinoline	*Citrullus colocynthis* (Cucurbitaceae)	[218]
Bisquinolinones	Melicodenine	*Melicope denhamii* (Rutaceae)	[219]
	Evocarpine	*T. ruticarpum*	[212]
	2′-O-Trifluoroacetyllunacridine	*Lunasia amara* (Rutaceae)	[220]
	N-Methyl-4-methoxy-quinolinone	*H. apiculata*	[181]

8.2. Antibacterial compounds

Alkaloids with significant antibacterial effects are shown in Table 3. Totally, 25 alkaloids were included in Table 3, of which 14 were isoquinolines and 11 quinolines. The most chemical structures with antibacterial effects belonged to the classes benzophenanthridines (10 compounds), furoquinolines (5 compounds) and indoloquinolines (3 compounds). The strongest in vitro growth-inhibitory effect showed dasymaroine A (**4**) and avicine (**5**) against *E. coli* with MICs= 0.5 μg/ml and 1 μg/ml, respectively. Following compounds yohimbine (**6**) and vincamine (**7**) had strong activity against *E. faecalis* with MICs equal to 2 μg/ml. According to the number of inhibited bacteria, sanguinarine (**8**) had the broadest spectrum of action (against 14 pathogens). From a botanical point of view, 66 plant species contained at least one active alkaloid with antibacterial effects and with value of MIC lower than 100 μg/ml. The highest number of contained alkaloids had *Hylomecon japonica* (6), *Chelidonium majus* (6), and *Macleaya macrocarpa* (5) all from the family Papaveraceae. Additionally, the most susceptible bacterial pathogens were *Escherichia coli*, *Enterococcus faecalis*, *Shigella dysenteriae* and *E. faecom*, where the growth inhibition was already evident with the value of MIC lower than 5 μg/ml.

Table 3. Alkaloids with antibacterial effects *in vitro* against intestinal bacteria

Compound	Bacterium	MIC[a] (μg/ml)	Reference
12-Methoxydihydrochelerythrine	*Streptococcus faecalis*	25	[151]
4-Methylquinoline	*Salmonella typhimurium*	75	[218]
	Shigella sonnei	100	[218]
	Listeria monocytogenes	25	[218]
6-Methoxydihydrochelerythrine	*Escherichia coli*	40	[145]
	Enterococcus faecom	20	[145]
6-Methoxydihydrosanguinarine	*E. coli*	20	[145]
	E. faecom	5	[145]
8-Hydroxyquinoline	*Enterococcus faecalis*	1-4	[149]
	L. monocytogenes	≥25	[149]
	Salmonella enteridis	32-256	[149]
	S. typhimurium	32-512	[149,200]
	E. coli	32-256	[149]
	E. coli 0175:H7	256	[149]
	Shigella flexneri	128	[149]
	Shigella dysenteriae	4	[149]
	Clostridium difficile	128	[149]
	Clostridium perfringens	32-128	[183]
	Yersinia enterocolitica	512	[183]
Anhydroevoxine	*E. facealis*	A[b]	[183]
	S. typhimurium	A[b]	[183]
Avicine	*E. coli*	1.5	[160]
Camptothecine	*E. coli*	16.67	[161]
Cocsoline	*E. faecalis*	500	[160]
	S. typhimurium	15.62	[160]
	E. coli	31.25	[160]
	S. sonnei	31.25	[160]
	S. flexneri	62.5	[160]
	Shigella boydii	62.5	[160]
	S. dysenteriae	125	[160]
	Vibrio parahaemolytics	125	[160]
	Vibrio cholerae	250	[160]
	Campylobacter jejuni	15.62	[204]
	Campylobacter coli	31.25	[204]
Cryptolepine	*E. faecalis*	12.5	[204,206, 207]
	S. typhimurium	62.5	[204]
	E. coli	5-80	[204]
	S. dysenteriae	6.25	[204]
	V. cholerae	1.5-50	[204]
	C. jejunu	12.5	[100]

	C. coli	25	[145]
Dasymaroine A	*E. coli*	0.5	[103]
Dihydrochelerythrine	*E. coli*	9.3-640	[145]
	S. faecalis	9.3-300	[103]
Dihydrosanguinarine	*E. faecom*	80	[144,145, 151,155]
	E. coli	9.3-320	[221]
	S. faecalis	9.3–300	[221]
Chelerythrine	*E. faecalis*	4-32	[103]
	E. coli	1.5-125	[103]
	E. coli 0175:H7	32	[103]
Kokusaginine	*E. faecalis*	A[b]	[183]
	S. typhi	9.76	[181,183]
	S. typhimurium	100, A[b]	[181,183]
	E. coli	4.88-512	[187,192, 222]
Maculine	*S. typhi*	9.76	[187]
	S. typhimurium	100	[181]
	E. coli	78.12-100	[181, 187]
Nkolbisine	*S. typhi*	9.76	[187]
Palmatine	*S. typhi*	200	[137]
	E. coli	128-1000	[137,138, 223]
	C. perfingens	15.75-125	[96]
	Helicobacter pylori	3.12-186.8	[137,223]
Quinaldic acid	*C. difficile*	A[c]	[216]
	C. perfingens	A[c]	[216]
Robustine	*E. faecalis*	5.37	[197]
Sanguinarine	*E. faecalis*	8-32	[149, 221]
	L. monocytogenes	16	[149]
	S. enteridis	256	[149]
	S. typhimurium	512	[149]
	E. coli	31.3-256, A[b]	[103,143, 144,149]
	E. coli 0175:H7	128	[149]
	S. sonnei	64	[156]
	S. flexneri	64	[155]
	S. boydii	64	[149]
	C. difficile	64	[149]
	C. perfingens	128	[149]
	Y. enterocolitica	256	[149]
	V. parahaemolytics	32	[149]
Thalicfoetine	*E. coli*	6.25	[148]

Thomsonine A	*E. coli*	15.55	[213]
Vincamine	*E. faecalis*	2	[180]
	E. coli	8	[180]
Yohimbine	*E. faecalis*	2	[180]
	E. coli	4-250	[180,224]

Footnote:

a = minimum inhibitory concentration (MIC) - lowest concentration of a chemical preventing visible growth of a bacterium

b = ranked as active in radial diffusion method (Leher, Rosenmam,Harnig, Jackson, & Eisenhauer, 1991)

c = inhibition zone diameter 10-15 mm at dose 0.1 mg/disc assayed by disc diffusion test

8.3. Antiproliferative compounds

In Table 4 are summarized alkaloids with most promising antiproliferative activity against intestinal cancer cell lines. Totally, 87 alkaloids have showed moderately cytotoxic activity against at least one human intestinal cell line, of which 21 were quinolines and 62 isoquinolines. Most compounds (19 alkaloids) belonged to the class of furoquinolines. Furthermore, many chemicals belonged to the classes of bisbenzylisoquinolines (18) and benzophenanthridines (10). The strongest effect showed neothalfine (**9**) with the IC_{50} values of 0.0047 and 0.0038 μg/ml against HCT116 and SW620, respectively. Significant effect had also dutadrupine (**10**) against HT-29 with the ED_{50} equalled to 0.13 μg/ml and 6-methoxydihydrosanguinarine (**11**) with the IC_{50} values of 0.18 and 0.23 μg/ml against HCT-8 and BGC-823 respectively. Berberine (**1**) and sanguinarine (**8**) had the broadest range of action, each of them was at least moderately cytotoxic against 5 cell lines. Antiproliferative alkaloids have been reported to be present in 99 plants species. *Melicope semecarpifolia* contained the highest number of compounds (16) followed by *Cissampelos pareira* (9) and by *Abuta rufescens* (8). The strongest antiproliferative activity was shown against these cell lines: HCT116, SW620, HCT-8, BGC-823, Caco 2 and HT-29, where the values of the IC_{50} or ED_{50} were lower than 0.5 μg/ml.

Table 4. Alkaloids with strongest antiproliferative *in vitro* activity against intestinal cancer cell lines

Compound	Cell line	IC_{50}[a](μg/ml)	ED_{50}[b](μg/ml)	Reference
(+)-2-Norcepharanthine	SW480	2.19		[170]
(+)-7,8-Dimethoxymyrtopsine	HT-29		41.6	[184]
(2′,6′-Epoxy-1′,2′α,3′β,4′α,5′α -pentahydroxy)hexane-(1′ → 6)-dihydrochelerythrine	HCT-8	1		[225]
(5′R)-3′-Methyl-2′(5′H)-furanone-(5′ → 6)-(6R)-dihydrosanguinarine	HCT-8	0.84		[225]
(S)-(-)-7,8-Dimethoxyplatydesmine	HT-29		1.9	[186]
(S)-(+)-Isoplatydesmine	HT-29		1.5	[186]
1-Hydroxyrutaecarpine	HT-29		7.39	[182]
5-Hydroxy-4,8-dimethoxy furoquinoline	LOVO	32.8		[195]
6,11-Dihydroxy-8,9-dimethoxybenzo[1,3]dioxolo[4,5-c]phenanthridin-5(4H)-one	HCT116	8.64		[122]
6,9,11-Trihydroxybenzo[1, 3]dioxolo[4,5-c]phenanthridin-5(4H)-one	HCT116	16.29		[122]
6-Butoxydihydrochelerythrine	HCT-8	0.69		[225]
6-Methoxydihydrochelerythrine	HCT-8	0.41		[225]
6-Methoxydihydrosanguinarine	HCT-8	0.18		[151,225]
	BGC-823	0.23		[225]
6-Oxocorynoline	HCT-15		32.76	[157]
8-Hydroxyquinoline	HT-29	1.3		[149]
	Caco 2	0.3		[149]
8-Oxo-epiberberine	HCT-15		34.05	[131]
Acetylcaranine	HT-29	6		[120]
	Caco 2	9.24		[120]
Baicalensine A	Caco 2	6.91		[118]
Berbamine	HT-29	3.71		[164]
Berberine	HT-29	2.1-25		[149,228]
	Caco 2	19.4		[149]
	HCT-15		27.2	[131]
	HCT116	0.8-1.7		[131]
	SGC-7901		5	[226]
Bersavine	HT-29	5.65		[164]

Bis[6-(5,6-dihydrochelerythrinyl)]ether	HCT-8	1.14		[225]
Buphanisine	HT-29	1.51		[120]
	Caco 2	2.45		[120]
Caranine	HT-29	12.6		[120]
	Caco 2	17.4		[120]
Cepharanthine	SW480	2.85		[170]
Chelerythrine	HCT116	2.5		[227]
	SW480	2.5		[227]
Cocsoline	HCT116	2.8		[52,160]
Confusadine	HT-29		4.3	[186]
Confusameline	HT-29		0.24	[186]
Corynoline	HCT-15		2.26	[157]
Corynoloxine	HCT-15		16.12	[157]
Costaricine	HCT116	29.9		[104]
Crinine	HT-29	13.8		[120]
	Caco 2	17.5		[120]
Curine	HT-29	4.83		[111]
Cycleanine N-oxide	HCT116	41.8		[52,160]
Dicentrine	SW620	4.6		[95]
	COLO 201	2.6		[95]
Dictamnine	HT-29		26.07	[182]
	LOVO	27.9		[195]
Dihydrochelerythrine	HCT-8	0.48		[225]
Dihydrosanguinarine	HCT-8	0.43		[225]
Dutadrupine	HT-29		0.13	[186]
Edulinine	HT-29		25.5	[186]
Glaucine	HCT116	A[c]		[97]
	HCT-15	6.62		[97]
Glycocitridine	HT-29		0.52	[186]
Grandirubrine	HCT116	1		[106]
Hernovine	HT-29		5.993	[91]
Hexapetaline A	SW480	4.76		[84]
Hexapetaline B	SW480	7.47		[84]
Homoaromoline	HT-29	4.8		[111]
Imeluteine	HCT116	7		[106]
Imerubrine	HCT116	2		[106]
Isodictamnine	LOVO	18.6		[195]
Isochondodendrine	HCT116	17.5		[52,160]
Isoimerubrine	HCT116	3.3		[106]
Jozimine A2	HT-29	9		[178]
Kokusaginine	HT-29		1.4	[186]
Laurolitsine	HCT116	8.5		[104]

Laurotetanine	HT-29		1.822	[91]
Lycoricidine	HCT116	16.12		[122]
Lysicamine	HCT116	4.6		[106]
Magnoflorine	HT-29		13.5	[91]
Melicarpine	HT-29		2.5	[186]
Melicarpinone	HT-29		30.5	[186]
Melisemine	HT-29		4	[186]
Neferine	HT-29	1		[171]
Neothalfine	HCT116	0.0047		[176]
	SW620	0.0038		[176]
N-Formyldehydroovigerine	HT-29		0.512	[91]
N-Hydroxyhernangerine	HT-29		1.616	[91]
Norrufescine	HCT116	7.7		[106]
Northalrugosidine	HT-29	5.12		[172]
Obaberine	HT-29	5.01		[111]
Obamegine	HT-29	11.6		[111]
O-Methylneferine	HT-29	0.44		[171]
Oxyberberine	HCT-15		1.47	[131]
Oxynorchelerythrine	HCT116	6.46		[122]
Palmatine	HT-29	17.30		[223]
	SW480	A[d]		[137]
Pteleine	HT-29		15.2	[184]
Rutaecarpine	HT-29		31.63	[182]
Sanguinarine	HT-29	0.9		[149]
	Caco 2	0.8		[149]
	HCT116	0.66		[227]
	DLD-1	0.49-0.51		[227]
	SW480	0.59		[227]
Semecarpine	HT-29		29.3	[186]
Skimmianine	HT-29		0.12-0.38	[182,185,184]
	LOVO	33.1		[195]
Splendidine	HCT116	2.8		[106]
Subsessiline	HCT116	5.7		[84]
Tetrandrine	HT-29	5.17-14		[111,167,168]
	Caco 2	12.45		[165]
	HCT116	7.47-10		[165,168,169]
Thalidasine	HT-29	3.5		[172]
Thalifoline	HT-29		1.745	[91]
Thalrugosidine	HT-29	2.3		[172]
γ-Fagarine	HT-29		24.35	[182]
	LOVO	29.4		[195]

Footnote:

a= The half maximal inhibitory concentration (IC_{50}) is a measure of concentration of an inhibitor that is required for apoptosis of 50% of cancer cells.

b= ED_{50} is effective dose of medication that effects in 50% of patients taking it.

c= 66.8% inhibition of cell viability at concentration of 100 µg/ml

d= reduced the expression of inflammatory factor, granulocyte-colony and granulocyte macrophage colony stimulating factor at dose 10 mg/kg/day

9. Discussion

It has been observed that strongest antibacterial effect was shown for dasymaroine A, avicine, vincamine and yohimbine. Interestingly, the compounds with the most potent inhibitory concentration dasymaroine A and avicine haven't been studied more detailly yet. Dasymaroine A has been mentioned as a bioactive aporphine alkaloid contained in a folk medicinal plant *Dasymaschalon rostratum*. However, its antibacterial activity against intestinal pathogenic bacteria was evaluated only against *E. coli* [229]. The antibacterial effects and SAR of avicine have been more explored, still the antibacterial effects have been tested only against *E. coli* [155]. Vincamine and yohimbine are more known as commercially available natural compounds used in dietary supplements than as antibacterial agents. Their activity was evaluated using the strains of *E. coli* and *E. faecalis* [180]. In contrast, antimicrobial activity of sanguinarine is well described in the literature [155,221,225]. This compound produced broadest spectrum of antibacterial action and showed activity against 14 bacterial pathogens. According to Tavares et al. (2014), the structure of benzophenanthridines (e. g.: sanguinarine, avicine) is responsible for its antimicrobial activity. They are isomers differing only in a position of dioxole group. It can therefore be supposed that the previously unknown avicine may exhibit a similar spectrum of action to sanguinarine, which can be tested in future *in vitro* assays against gut bacteria.

According to results, the strongest antiproliferative effect had neothalfine, dutadrupine and 6-methoxydihydrosanguinarine. Neothalfine, which is not so known bisbenzylisoquinoline alkaloid was tested against metastatic colorectal cancer (HCT116, SW620) and was firstly mentioned as novel alkaloid isolated from *Thalictrum atriplex* in 2006 [175, 230]. To our best knowledge, with exception its antiproliferative effect there are no other reports on biological activity of neothalfine. Dutadrupine had stronger cytotoxic activities than other furoquinolines. Its antiproliferative action was shown against colorectal adenocarcinoma (HT-29) [186]. It has previously been observed by Chen et al. 2003 that furoquinolines (dutadrupine) showed more potent cytotoxic activity than the dihydrofuroquinoline alkaloids. The third strongest antiproliferative activity had 6-methoxydihydrosanguinarine against BGC-823 and HCT-8. This compound is known to be present in *Hylomecon* spp. Yin et al. (2005) investigated the mechanisms of its ability to induce cell death [231], but no other experiment for cytotoxic activity against

other intestinal cell lines has been performed yet. Sanguinarine and berberine have the broadest spectrum of action against cell lines. However, these alkaloids have intensively been studied in the past. For example, berberine was discovered in 1830 and 1426 papers have been published from 1985 to 2018 [232].

Possible area of future research could be related *in vitro* tests with alkaloids which have not been tested so far and which have shown to be active in previous experiments. Tables 3 and 4 may provide some examples of such compounds with quinoline or isoquinoline structure. Another perspective direction of research could be experiments focused on a more detailed mechanism of the antibacterial or antiproliferative action of not well-known alkaloids with potent results (e.g., neothalfine). A third possible future theme for further experiments could be a comparison study of the pharmaceutical activity of well-known compounds to their structurally similar analogues (e.g., sanguinarine and avicine, 6-methoxydihydrosanguinarine).

10. Conclusions

In this study, the data on quinoline and isoquinolines alkaloids with the significant *in vitro* antibacterial or antiproliferative effects on human gut bacteria and cells were collected and analysed. As a result, 406 alkaloids were identified, which were present in 168 plant species belonging to 29 families. The number of taxa containing quinoline and isoquinolines alkaloids was originated in tropical regions. Furthermore, 25 molecules were classified as active against bacteria causing gastrointestinal diseases and 87 compounds were reported to produce cytotoxic effects. Less researched compounds with the potent bioactivity, namely avicine, neothalfine, dutadrupine, and 6-methoxydihydrosanguinarine, have also been identified. All these compounds could have a potential for future development of anti-infective and anticarcinogenic drugs, however, further biological tests will be necessary to confirm their efficacy and safety.

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Appendices

List of the Appendices:

Photos of potential plants with the highest content of active alkaloids:

Figure 2. *Dictamnus angustifolius*, plant with the broadest spectrum of quinolines [233]

Figure 3. *Cissampelos pareira*, plant with the broadest spectrum of isoquinolines [234]

Figure 4. *Hylomecon japonica*, plant with the highest content of antibacterial agents [235]

Figure 5. *Melicope semecarpifolia*, plant with the highest content of antiproliferative agents [236]