

Review

The Biological Activity of Natural Alkaloids against Herbivores, Cancerous Cells and Pathogens

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Abstract: The growing incidence of microorganisms that resist antimicrobials is a constant concern for the scientific community, while the development of new antimicrobials from new chemical entities has become more and more expensive, time-consuming, and exacerbated by emerging drug-resistant strains. In this regard, many scientists are conducting research on plants aiming to discover possible antimicrobial compounds. The secondary metabolites contained in plants are a source of chemical entities having pharmacological activities and intended to be used for the treatment of different diseases. These chemical entities have the potential to be used as an effective antioxidant, antimutagenic, anticarcinogenic and antimicrobial agents. Among these pharmacologically active entities are the alkaloids which are classified into a number of classes, including pyrrolizidines, pyrrolidines, quinolizidines, indoles, tropanes, piperidines, purines, imidazoles, and isoquinolines. Alkaloids that have antioxidant properties are capable of preventing a variety of degenerative diseases through capturing free radicals, or through binding to catalysts involved in different oxidation processes occurring within the human body. Furthermore, these entities are capable of inhibiting the activity of bacteria, fungi, protozoan and etc. The unique properties of these secondary metabolites are the main reason for their utilization by the pharmaceutical companies for the treatment of different diseases. Generally, these alkaloids are extracted from plants, animals and fungi. Penicillin is the most famous natural drug discovery deriving from fungus. Similarly, marines have been used as a source for thousands of bioactive marine natural products. In this review, we cover the medical use of natural alkaloids isolated from a variety of plants and utilized by humans as antibacterial, antiviral, antifungal and anticancer agents. An example for such alkaloids is berberine, an isoquinoline alkaloid, found in roots and stem-bark of *Berberis asculin* P. Renault plant and used to kill a variety of microorganisms.

Keywords: alkaloids; natural sources; anticancer; antibacterial; antiviral; antifungal

Key Contribution: Alkaloids are secondary plant metabolites that have been shown to possess potent pharmacological activities. These activities are mainly beneficial, except for pyrrolizidine alkaloids, which are known to be toxic.

1. Introduction

Ample research has been conducted on natural products in order to obtain new antimicrobial agents to compensate for the increasingly microbial resistance. In fact, the problem with the currently used antiviral drugs is the development of resistance by the microorganism.

Many traditionally used plants for viral infections have been studied. Extracted compounds, including terpenes (e.g., mono-, di- and tri-), flavonoids, phenols and polyphenols have been found to be active against HSV virus [1,2]. Flavonoids extracted from plants are utilized by people for their health benefits, and have been shown to have viral activity against HCMV [3]. Fourteen new alkaloids were isolated from *Cladosporium* species (spp.) PJX-41 fungi and showed inhibitory activity against influenza virus A (H1N1) [4].

The Biological Activities of Alkaloids

Alkaloids are grouped into several classes. This classification is based on their heterocyclic ring system and biosynthetic precursor. They include tropanes, pyrrolidines, isoquinoline purines, imidazoles, quinolizidines, indoles, piperidines and pyrrolizidines. There is a great interest in the chemical nature of these alkaloids and their biosynthetic precursors. Alkaloids have been extensively researched because of their biological activity and medicinal uses. Serotonin and other related compounds are belonging to the commonly used indole alkaloids. It is estimated that about 2000 compounds are classified as indole alkaloids. They include vinblastine, strychnine, ajmaline, vincamine, vincristine and ajmalicine, which are among the most researched members, due to their pharmacological activities. For example, vincristine and vinblastine, named spindle poison, are generally utilized as anticancer agents [5]. Convolvulaceae, Erythroxylaceae and Solanaceae families include the pharmacologically active tropane alkaloids which have an 8-azabicyclo octane moiety derived from ornithine [5,6]. Hyoscyamine, cocaine, scopolamine and atropine alkaloids are the most known members of this group and possess a variety of pharmacological effects. Quinoline and isoquinoline known as benzopyridines are heterocyclic entities containing fused benzene, and pyridine rings have many medical uses [6]. Quinine, a quinoline alkaloid isolated from *Cinchona ledgeriana* (Howard) and *Calendula officinalis* L. was proved to be poisonous to *Plasmodium vivax* and organisms with single cell or *Protozoans* that cause malaria. Other members of the quinine alkaloids include cinchonidin, folipdine, camptothecin, chinidin, dihydroquinine, echinopsine and homocamptothecin [5,7]. These chemical entities have demonstrated significant pharmacological effects, such as anticonvulsant, analgesic, antifungal, anthelmintic, anti-inflammatory, antimalarial, anti-bacterial and cardiotonic [7]. Other important alkaloids are those derived from isoquinoline, a quinoline isomer, which are classified into various classes, based on the addition of certain groups: Phthalide isoquinolines, simple isoquinolines and benzyloisoquinolines. Among the well-known alkaloids belong to this category are morphine (analgesic and narcotic drug), codeine (cough suppressant), narcotines, protopines, and thebaine [8]. In addition, this class of alkaloids has demonstrated various pharmacological activities, such as antitumor, antihyperglycemic and antibacterial [6]. Among the most important alkaloids from the purine class (xanthenes) are theophylline, aminophylline and caffeine. This class of alkaloids possesses a variety of pharmacological activities, including anti-inflammatory, antioxidant, antidiabetic, anti-obesity and anti-hyperlipidemic [9]. On the other hand, the alkaloids derived from piperidine are generally obtained from *Piper nigrum* L. and *Conium maculatum* L. plants. It is estimated that 700 members of this class have been researched. These alkaloids possess a saturated heterocyclic ring (piperidine nucleus) and are familiar with their toxicity. They have many pharmacological activities which include anticancer, antibacterial, antidepressant, herbicidal, anti-histaminic, central nervous system stimulant, insecticidal and fungicidal [10,11]. The famous poison of hemlock known as *Conium maculatum* presents in the piperidine alkaloids. Members of the piperidine alkaloids include lobeline, coniine and cynapine. The pyridine alkaloids have a quite similar chemical structure to that of piperidine alkaloids except the unsaturated bonds exist in their heterocyclic nucleus. Anatabin, anatabine, anabasin, epibatidine and nicotine are some members of the pyridine alkaloids [12]. Imidazole alkaloids are compounds containing an imidazole ring in their chemical structure and are derived from L-histidine.

The most known member of this class is pilocarpine which is obtained from *Pilocarpus cearensis* Rizzini and is used as a drug in ophthalmic preparations to treat glaucoma [13]. The pyrrolizidine alkaloids, containing a necine base, are present only in plants, such as Leguminosae, Convolvulaceae, Boraginaceae, Compositae, Poaceae and Orchidaceae. Among the most known members of this class are heliotrine, echinatine, senecionine and clivorine which are biosynthesized by the plants for protection from herbivores. These are hepatotoxic causing several diseases, such as liver cancer. Due to their glycosidase inhibition activity, they are used to treat diabetes and cancer [14]. Pyrrolizidine alkaloids are compounds composed of aza five membered rings that are derived from ornithine and lysine. Hygrine, cuscohygrine and putrescine are some members of this class. Biological studies conducted on this class have revealed significant antifungal, antitubercular and antibacterial activities among a large number of these compounds [15].

Quinolizidine alkaloids contain two fused 6-membered rings that share nitrogen and derived from the genus *Lupinus* and are known as lupine alkaloids. Among the members of this class are lupinine and lupanine cytosine and sparteine. The last two members are the most distributed quinolizidine alkaloids and are characterized by their antimicrobial activities [16].

Bacterial infections are considered as a major health problem worldwide. Moreover, they are increasing, due to multidrug resistance, which subsequently causes mortality and morbidity. Therefore, new antibacterial remedies are needed, and the plants represent a wide source for novel natural compounds [17]. Three alkaloids solanine, solasodine and B-solamarine have been extracted from *Solanum dulcamara* L. (Solanaceae), commonly known as bitter-sweet plant, and have demonstrated significant antibacterial activity against *Staphylococcus aureus* [17]. Bis-indole alkaloids were obtained from marine invertebrates and showed antibacterial activity against *S. aureus*, including MRSA (methicillin resistance *Staphylococcus aureus*) [18]. Berberine and hydrastine alkaloids were extracted from Goldenseal (*Hydrastis canadensis* L., Ranunculaceae) and have demonstrated a potent antibacterial activity mostly against *Streptococcus pyogenes* and *Staphylococcus aureus* [19]. Cocsoline alkaloid was isolated from *Epinetrum villosum* (Exell), it has a wide antibacterial activity; inhibits *Shigella* strains, *Campylobacter jejuni* and *Campylobacter coli* [20].

Antifungal agents to treat fungal infections have serious side effects and developed fungal resistance, hence, there is a pressing need to look for new and novel antifungal agents. Alkaloids extracted from the leaves of *Ruta graveolens* L. were shown to possess fungitoxic activity [21]. Tomadini Glycoalkaloids have been extracted from tomato and proved to have antifungal activity [22]. Quinoline alkaloids and flavonoids extracted from *Waltheria Indica* L. Roots were approved to have antifungal activity against *Candida albicans* [23].

Cancer is second in the list of diseases causing death worldwide. Phytochemicals represent a source for anticancer agents, due to their low toxicity and high effectiveness. Hersutin alkaloid is a major alkaloid found in *Uncaria* genus; hersutin was found to cause apoptosis in HER2-positive and the p53-mutated breast cancer cells [24]. Oxymatrine, a natural alkaloid extracted from *Sophora chrysophylla* (Salisb.) roots, was found to have anticancer activity in human cervical cancer Hela cells, due to its cytotoxic effects and apoptosis [25].

Herein, we report a comprehensive review on the medical use of some natural alkaloids, such as antibacterial, antiviral, antifungal and anticancer agents.

2. Natural Alkaloid Used to Control Agricultural Pests (Herbivores)

Glycoalkaloids extracted from Potato leaves were demonstrated to exert negative effects on the hatching success of *Spodoptera exigua* eggs, and on the heart contractile activity of three beetle species *Zophobas atratus*, *Tenebrio molitor*, and *Leptinotarsa decemlineata* [26].

Similar effects were shown on *Zophobas atratus* F. and *Tenebrio molitor* L. by commercial glycoalkaloids (solamargine, solasonine, α -chaconine, α -solanine, α -tomatine) and by aqueous extracts from *Solanum tuberosum* L., *Lycopersicon esculentum* Mill., and *Solanum nigrum* L. [27]. Furthermore, Potato leaf extracts and commercial α -solanine were proved to influence the life history parameters and

antioxidative enzyme activities in the midgut and fat body of *Galleria mellonella* L. [28]. Additionally, *Solanum tuberosum* L, *Lycopersicon esculentum* Mill., and *Solanum nigrum* L. Leaf extracts and single pure glycoalkaloids have been demonstrated to affect the development and reproduction of *Drosophila melanogaster* [29,30].

3. Natural Alkaloid Used as Anticancer Agents

Alkaloids are the most biologically active compounds found in natural herbs and the source of some important drugs currently marketed. These include some anticancer agents, such as camptothecin (CPT) and vinblastine. The cytotoxicity and mechanisms of action for the following derived alkaloids, berberine, evodiamine, matrine, piperine, piplartine, sanguinarine, tetrandrine, aporphine, harmine, harmaline, harmalacine and vasicinone, (1–12, respectively, in Figure 1), is our main focus in this section, since they are believed to have fewer side effects and lower resistance compared to other chemotherapeutic agents.

Berberine (1 in Figure 1) is an isoquinoline derivative extract from *Coptis chinensis* Franch, Berberidaceae. This secondary metabolite possesses a variety of pharmacological effects, which include antibacterial, antidiabetes, anti-inflammatory and antiulcer ones. In addition, Also, it had been found to be beneficial for the cardiovascular system [19,20,22,23]. It has been demonstrated that *Coptis chinensis* Franch, the plant in which berberine present, has an inhibitory effect on proliferation of breast and liver cancer cells. The anticarcinogenic activity of berberine was studied in FaDu cells, which are human pharyngeal squamous carcinoma cells; berberine was found to have a cytotoxic effect and has decreased the viability of these cells in a concentration-dependent manner [31]. In vitro and in vivo experiments on berberine have demonstrated anticancer activity by causing cell cycle arrest at the G1 or G2/M phases and tumor cell apoptosis [24,32]. In addition, berberine was found to cause endoplasmic reticulum stress and autophagy, which had resulted in inhibition of tumor cell metastasis and invasion [2,33–36].

Besides its apoptotic effects, berberine was found to reduce angiogenesis by reducing VEGF expression. Also, it resulted in decreased cancer cell migration [31]. The anticancer activity of berberine was studied in the human promonocytic U937 and murine melanoma B16 cell line; cytotoxic activity was found to be concentration-dependent. Intraperitoneal administration of berberine in mice had caused a reduction of 5 to 10 kg of tumor weight after a treatment of 16 days. This reduction in tumor weight was found to be time and concentration-dependent [33].

Berberine binds to DNA or RNA to form the corresponding complexes [37,38]. Berberine also inhibits a number of enzymes, including cyclooxygenase-2 (COX-2), *N*-acetyltransferase (NAT) and telomerase [24]. It has many effects on tumor cells, which include cyclin-dependent kinase (CDK) regulation [24,37] and expression regulation of *B*-cell lymphoma 2 (Bcl2) proteins (Bax, Bcl-2, Bcl-xL) [24,33,37] and caspases [33,37]. Further, berberine has an inhibition activity on nuclear factor κ -light-chain enhancer of activated B cells (NF- κ B) and activation on the synthesis of intracellular ROS [24,33]. It is worth noting that berberine activity is selective for cancer cells [24]. Studies have shown that berberine affects tumor cell progression by the inhibition of focal adhesion kinase (FAK), urokinase, matrix metalloproteinase 9 (MMP-9), NF κ B and matrix metalloproteinase2 (MMP-2) [2,39]. In addition, it reduced Rho kinase-mediated Ezrin phosphorylation [36], inhibited COX-2 synthesis, prostaglandin receptors and prostaglandin E [40]. Other activities of berberine include inhibition of the synthesis of hypoxia-inducible factor 1 (HIF-1), proinflammatory mediators and vascular endothelial growth factor (VEGF) [41,42]. Berberine also activates P53 gene, which results in apoptosis and cell cycle arrest. It has been demonstrated that berberine also caused apoptosis by mitochondrial-dependent pathway and interactions with DNA, as shown in Figure 2 [32].

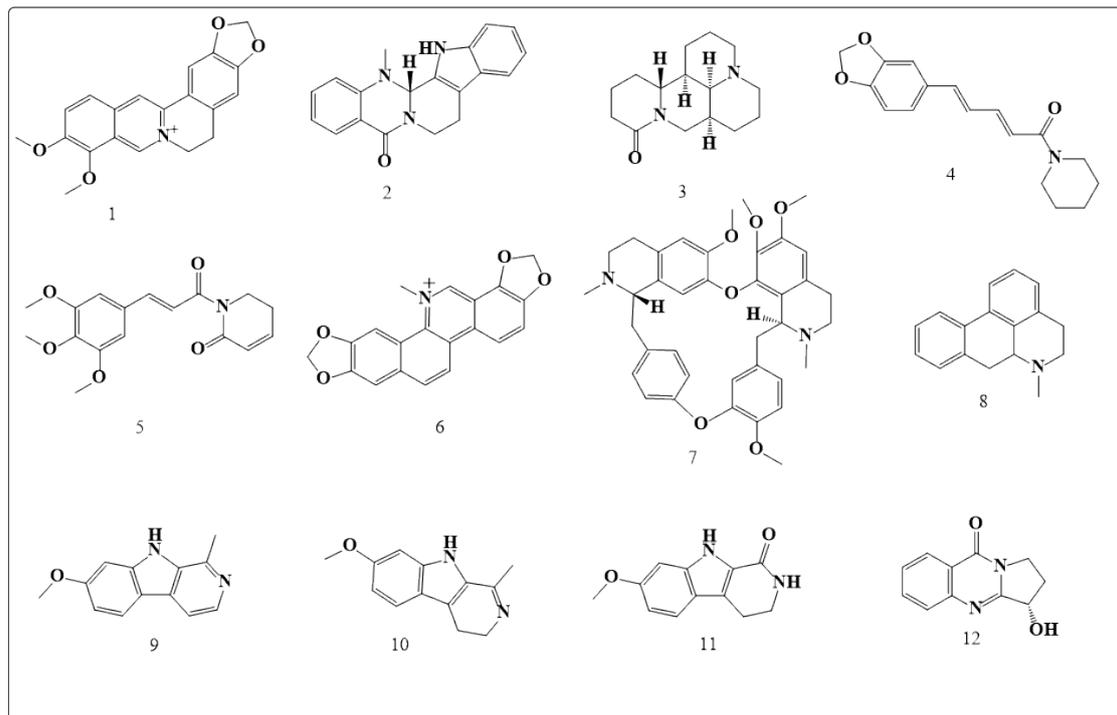


Figure 1. Chemical structures of anticancer natural alkaloids: Berberine (1), evodiamine (2), matrine (3), piperine (4), piplartine (5), sanguinarine (6), tetrandrine (7), aporphine (8), harmine (9), harmaline (10), harmalacidine (11) and vasicinone (12).

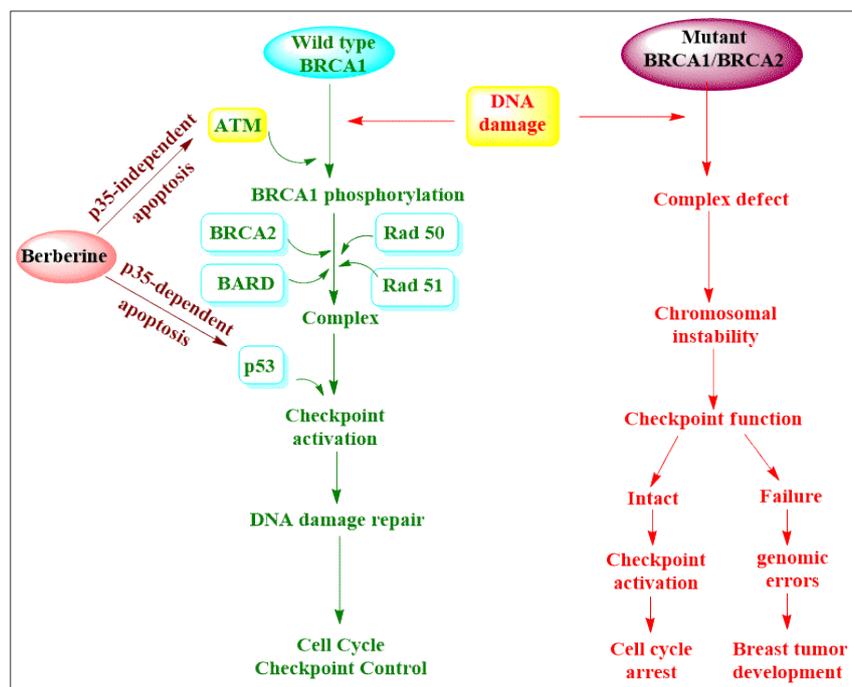


Figure 2. Anticancer mechanism of action.

Evodiamine (2 in Figure 1), a quinolone alkaloid, isolated from the Chinese plant *Evodia rutaecarpa* has a variety of pharmacological activities against obesity, allergy, inflammation, anxiety, nociception, cancer, thermoregulation. In addition, it is a vessel-relaxing activator and an excellent protector of myocardial ischemia-reperfusion injury [43–46]. It causes cell cycle arrest, apoptosis, inhibits the

angiogenesis, invasion, and metastasis in different cancer cells at G2/M phase in most cancer cell lines [47–51]. In vitro studies have shown evodiamine to be quite active against cancer cell progression at micromolar-nanomolar concentrations [52,53]. Additionally, evodiamine stimulates autophagy, which prolongs survival [54]. Evodiamine is selective for tumor cells and less toxic to normal human cells, such as human peripheral blood mononuclear cells. Studies have shown that it inhibits the proliferation of Adriamycin resistant human breast cancer NCI/ADR-RES cells, both in vitro and in vivo, and was found to be active when administered orally [49]. Moreover, it was found that the administration of 10 mg/kg evodiamine from the 6th day after tumor injection into mice reduced lung metastasis without affecting the mice weight [47]. Studies showed that evodiamine inhibits TopI enzyme, forms a DNA covalent complex with a close concentration, 2.4 μ M and 4.8 μ M, to that of CPT, and induces DNA damage [55–57]. It exhibited G2/M phase arrest [47,49,58] and not S phase arrest, which is not consistent with the mechanism of TopI inhibitors, such as CPT, which indicates that evodiamine has targeted other than TopI, such as tubulin polymerization [58]. Evodiamine was found to induce intracellular ROS production and cause mitochondrial depolarization [59]. Mitochondria apoptosis is caused by the generation of ROS and nitric oxide [54]. Evodiamine was also found to trigger caspases dependent and caspase-independent apoptosis, downregulates Bcl-2 expression, and upregulates Bax expression in some cancer cells [50,52]. The phosphatidylinositol 3kinase/Akt/caspase and Fas ligand (Fas-L)/NF- κ B and ubiquitin-proteasome pathway are considered the route in which evodiamine causes induction to cells death [53].

Matrine (3 in Figure 1) is an alkaloid isolated from *Sophora flavescens* Aiton plants [60]. It possesses a variety of pharmacological activities which include diuretic, choleric, hepatoprotective, nephroprotective, antibacterial, antiviral, anti-inflammatory, antiasthmatic, antiarrhythmic, antiobesity, cardioprotective and anticancer [61–67]. In the treatment of cancer matrine is used in high doses, but it has not shown any major effects on normal cells viability [61–71]. G1 cell cycle arrests mediation and apoptosis is the mechanism, by which matrine exerts its inhibition effects on the proliferation of different cancer cells [68,69,71–73]. Matrine triggers apoptosis and autophagy in cancer cells, such as hepatoma G2 cells and SGC7901 cells. Matrine also induces the differentiation of K562 tumor cells and has antiangiogenesis activity [74]. The in vivo anticancer effects of matrine has been tested in H22 cells, MNNG/HOS cells, 4T1 cells and BxPC-3 cells in BALB/c mice [70,71,74,75]. It was found that matrine at 50 mg/kg or 100 mg/kg inhibits MNNG/HOS *Xenograft* growth, and reduces the pancreatic tumor size compared to controls at similar doses [71]. Targets of matrine are still under study until now, but it was found that it affects many proteins involved in cell proliferation and apoptosis, such as E2F-1, Bax, Bcl-2, Fas, and Fas-L [68,70–73,76]. It also inhibits cancer cell progression by the inhibition of MMP-2 and MMP-9 expression and modulation of the NF- κ B signaling pathway [77–79].

Piperine (4 in Figure 1) is a piperidine alkaloid found in *Piper nigrum* and *Piper longum* [80]. It exhibits antioxidant, antidiarrheal, anti-inflammatory, anticonvulsant, anticancer and antihyperlipidemic properties in addition to being a trigger for bile secretion production [65,81] and suppressant to the CNS system [82,83]. An administration of 50 mg/kg or 100 mg/kg of piperine daily for a week significantly reduced the size of solid tumor in mice transplanted with sarcoma 180 cells. Recently, a study has revealed that piperine has managed to inhibit the progression of breast cancer in a selective manner [84]. It has been shown that this secondary metabolite triggered cell cycle arrest in G2/M phase and apoptosis in 4T1 cells [85,86]. Piperine in a concentration of 200 μ M/kg is also active against lung cancer metastasis induced by B16F-10 melanoma cells in mice [87] and causes suppression of phorbol-12-myristate-13acetate (PMA), which induce tumor cell invasion [88]. Piperine inhibits NF- κ B, c-Fos, cAMP response element-binding (CREB) and activated transcription factor 2 (ATF-2) [89]. It suppresses PMA-induced MMP-9 expression through the inhibition of PKC α /extracellular signal-regulated kinase (ERK) $\frac{1}{2}$ and reduction of NF- κ B/AP-1 activation [88]. Piperine also inhibits P-glycoprotein (P-gp) and CYP3A4 activity, which affects drug metabolism and also re-sensitizes multidrug resistant (MDR) cancer cells [90,91]. Piperine increases the effect of

docetaxel without inducing more side effects on the treated mice by inhibiting CYP3A4 which is the main metabolizing enzymes of docetaxel [92].

Piplartine, the less common name for piperlongumine, (5 in Figure 1) is an amide-alkaloid obtained from *Piper longum* L. It has resulted in tumor growth inhibition in *Sarcoma180* cells transplanted in mice. This antitumor activity was due to its antiproliferative effect [93].

Sanguinarine (6 in Figure 1) is a benzophenanthridine obtained from *Sanguinaria canadensis* L. and *Chelidoniummajus* L. [94,95]. It is active against bacterial, fungal and schistosomal infections, antiplatelet, and anti-inflammatory properties [96–98], it is also utilized for schistosomiasis control and cancer treatment. In vitro studies showed that it presents anticancer effects at concentrations less than ten micromoles. Sanguinarine triggers cell cycle arrest at different phases of apoptosis in many tumor cells [99–104]. It also is active against angiogenesis [105–107]. The administration of COX-2 inhibitors and sanguinarine has been recommended for prostate cancer treatment. Sanguinarine can also be used for the treatment of conditions caused by ultraviolet exposure, such as skin cancer [108]. The mechanism of its anticancer activity could be its interactions with glutathione (GSH). These interactions decrease cellular GSH and increase ROS generation [102,109]. Sanguinarine-induced ROS production and cytotoxicity can be blocked by pretreatment with N-acetyl cysteine or catalase. This mode of action is similar to that of TopII inhibitor salvicine [110,111]. Sanguinarine is considered a potent inhibitor of MKP-1 (mitogen-activated protein kinase phosphatase 1) [112]. It also interferes with microtubule assembling [113] and the nucleocytoplasmic trafficking of cyclin D1 and TopII, and causes DNA damage leading to anticancer activity. Sanguinarine suppresses NF- κ B activation triggered by TNF, interleukin-1, okadaic acid, and phorbol ester, but not that induced by hydrogen peroxide or ceramide [114]. It also inhibits the signal transducer and activator of transcription 3 activation (STAT-3) [115]; downregulates CDKs, cyclins, MMP-9 and MMP-2 [106,109]; upregulates p21, p27 [104,107] and the phosphorylation of p53 [99]; alters the members of the Bcl-2 family, including Bax, Bid, Bak Bcl-2, and Bcl-xL; activates caspases [101–103]; and upregulates death receptor 5 (DR-5) [101].

Tetrandrine (7 in Figure 1) is a bisbenzylisoquinoline alkaloid extracted from *Stephania tetrandra* S. Moore. It is used as an immune modulator, antihepatofibrogenetic, antiarrhythmic, anti-inflammatory, antiportal hypertension, anticancer and neuroprotective agent [116]. It is a potent anticancer agent. Tetrandrine triggers different phases of cell cycle arrest depending on the cancer cell type, and also induces apoptosis in many human cancer cells, including leukemia, colon, bladder, lung and hepatoma [117,118]. In vivo experiments demonstrated that the survival of mice subcutaneously injected with CT-26 cells was prolonged after daily treatment with tetrandrine [119]. Tetrandrine suppresses the expression of VEGF in glioma cells, has an anticancer effect on ECV304 human umbilical vein endothelial cells, and antiangiogenesis effects [120]. Tetrandrine had no acute toxicity were noticed [121]. Hence, tetrandrine has a great promise as an MDR modulator for the treatment of P-gp-mediated MDR cancers. Tetrandrine could be used in combination with 5-fluorouracil and cisplatin drugs [122,123]. If combined with tamoxifen it increases the efficacy by inhibiting phosphoinositide-dependent kinase 1 [124]. It also increases the radio-sensitivity of many cancer cells by affecting the radiation-induced cell cycle arrest and interfering with the cell cycle. So tetrandrine can be used in combination with cancer chemotherapy or radiotherapy. Activation of glycogen synthase kinase 3 β (GSK-3 β), generation of ROS, activation of p38 mitogen-activated protein kinase (p38 MAPK), and inhibition of Wnt/betacaten in signaling might cause the anticancer activity of tetrandrine [119,125]. Tetrandrine up-regulates p53, p21, p27, and Fas; down-regulates Akt phosphorylation, cyclins, and CDKs and activates caspases [120,125–127].

Aporphine alkaloids (8 in Figure 1) are extracted from the aerial part of *Pseuduvariasetosia*. These alkaloids demonstrated moderate antitumor activity against lung and breast cancer cells, in addition to their high antitumor activity against *epidermoid carcinoma* (KB) and breast cancer [36]. Mohamed et al. have studied *Magnolia grandiflora* L., characterized the isolated aporphine alkaloids and researched their cytotoxic activity. They found that the magnoflorine and lanuginosine alkaloids have cytotoxic activity against liver carcinoma cell lines [2].

Apomorphine alkaloids were isolated from *Nelumbo nucifera* Gaertn leaves and were demonstrated to have antioxidant and antiproliferative activities [41].

Peganum. Harmala has been used traditionally for cancer therapy, harmine (9 in Figure 1) and harmaline (10 in Figure 1) are the major alkaloids found in this plant in ratios of 4.3% and 5.6%, respectively [128]. Four alkaloids; harmine, (9 in Figure 1), harmaline (10 in Figure 1), harmalacidine (11 in Figure 1) and vasicinone (12 in Figure 1) were isolated from plant seeds and have shown a significant cytotoxic activity [128]. The mechanism of action of *P. harmala* seeds has been investigated by Sobhani et al.; it was found that these alkaloids inhibit topoisomerase 1, resulting in antiproliferation of cancer cells [129].

A concise summary of the anticancer activities of alkaloids 1–12 is depicted in Table 1.

Table 1. The anticancer compounds discussed in this section and their activities.

Alkaloids	Anticancer Activity
Berberine	Inhibits the proliferation of breast, lung, colon and liver cancer cell lines Inducing the cell cycle arrest or apoptosis in cancer cell
Matrine	Inhibits the proliferation of cancer cell by G1 cell cycle arrest or apoptosis
Piplartine	Antitumor related to its antiproliferative effect
Piperine	Antitumor and immunomodulatory
Sanguinarine	Induces cell cycle arrest at different phases or apoptosis in a variety of cancer cell
Tetrandrine	Induces different phases of cell cycle arrest depends on cancer cell types
Aporphine	Antitumor activity against small cell, lung cancer and breast cancer cells, in addition to a high antitumor activity against epidermoid carcinoma
Apomorphine	Antioxidant and antiproliferative activities
Harmine, harmaline harmalacidine, vasicinone	Inhibit topoisomerase 1 resulting in antiproliferation of cancer cells
Evodiamine Sanguinarine	Induce cell cycle arrest or apoptosis, inhibiting the angiogenesis, invasion, and metastasis in a variety of cancer cell lines
Matrine	Inhibits the proliferation of various types of cancer cells mainly through the mediation of G1 cell cycle arrest or apoptosis
Tetrandrine	Induces apoptosis in many human cancer cells, including leukemia, bladder, colon, hepatoma, and lung

4. Antibacterial Activities

Anti-bacterial agent is a chemical entity that has the potential to kill or inhibit the production of bacteria. Since antiquity several nations have been using different plants for healing and treating several kinds of diseases, like using, *Ayurveda*, in providing many medicines from the *Neem tree*, *Azadirachta indica* A.Juss.in India, and *Valerian (Valeriana officinalis)*, the medicinal plant endogenous to Europe and Asia and widely introduced in North America [37,39,130]. However, at the beginning of the 1980s this trend has declined, and the sights of researchers were turned into synthesizing new compounds. More recently the interest in using natural products has been renewed, due to the huge increase in antibiotics resistance, the limited availability of new synthetic antibacterials [37], and the discovery of many new natural products [38]. Finding new anti-infective agents is a necessity. Even with the careful use of antibiotics, each antibiotic has a limited life span [37]. Nothing can rule out the need for antibiotics, although biologics can sometimes be used in several cases, but they are usually accompanied by many limitations [39,40].

Several studies have demonstrated that much plant extracts containing alkaloids, flavonoids, phenolics and other compounds have significant antibacterial activity. However, in this section, we are specifically concerned with alkaloids as antibacterial agents.

Alkaloids have a reputation of being a natural curse and blessing [131]. They are a wide-range and diverse group of natural compounds that exist in plants, animals, bacteria, and fungi. The only thing they have in common is the occurrence of a basic nitrogen [132], which can be a primary, secondary or

tertiary amine. Currently, there are more than 18,000 discovered alkaloids [133]. The unique bioactivity of alkaloids is attributed to the presence of nitrogen, that capable of accepting a proton, and one or more amine donating hydrogen atoms, which is usually accompanied by proton-accepting and -donating functional [127].

Alkaloids have played a very important role in developing new antibacterial agents. Many interesting examples include the synthesis of quinolones from quinine, derivatization of azomycin to afford metronidazole, and alteration of the quinoline scaffold to furnish bedaquiline. In other antibacterial agents, alkaloids are utilized as scaffold substructures as seen with linezolid and trimethoprim [134–136].

4.1. Antibacterial Indole Alkaloids

Clausenine (**13** in Figure 3) extracted from the stem bark of *Clausena anisate* (Willd.) were shown to have antibacterial and antifungal activities [137]. *I*-Mahanine indole alkaloid (**14** in Figure 3) obtained from *Micromelum minutum* Wight and Arn. has demonstrated antimicrobial activity against *Bacillus cereus* (MIC100 values of 6.25 µg/mL) and *Staphylococcus aureus* (MIC100 values of 12.5 µg/mL) [138].

Hapalindole alkaloids, hapalindole X (**15** in Figure 3), deschlorohapalindole I (**16** in Figure 3), and 13-hydroxy dechlorofontonamide (**17** in Figure 3) and hapalindoles A, C, G, H, I, J, and U, hapalonamide H, anhydrohapaloxindole A, and fischerindole L were obtained from *cyanobacteria* *sp.* Results demonstrated that **15** and **18** possess a very strong activity against both *Mycobacterium tuberculosis* and *Candida albicans* with MIC values in the range of 0.6 to 2.5 µM [139].

The indolizidine alkaloid 2, 3-dihydro-1H-indolizinium chloride (**19** in Figure 3) isolated from *Prosopis glandulosa* Torr. var. *glandulosa* was found to be a strong antifungal and antibacterial agent against *Cryptococcus neoformans*, *Aspergillus fumigatus* with IC50 values of 0.4 and 3.0 µg/mL, respectively, and antibacterial activity against methicillin-resistant *Staphylococcus aureus* and *Mycobacterium* with IC50 values of 0.35 and 0.9 µg/mL respectively [140].

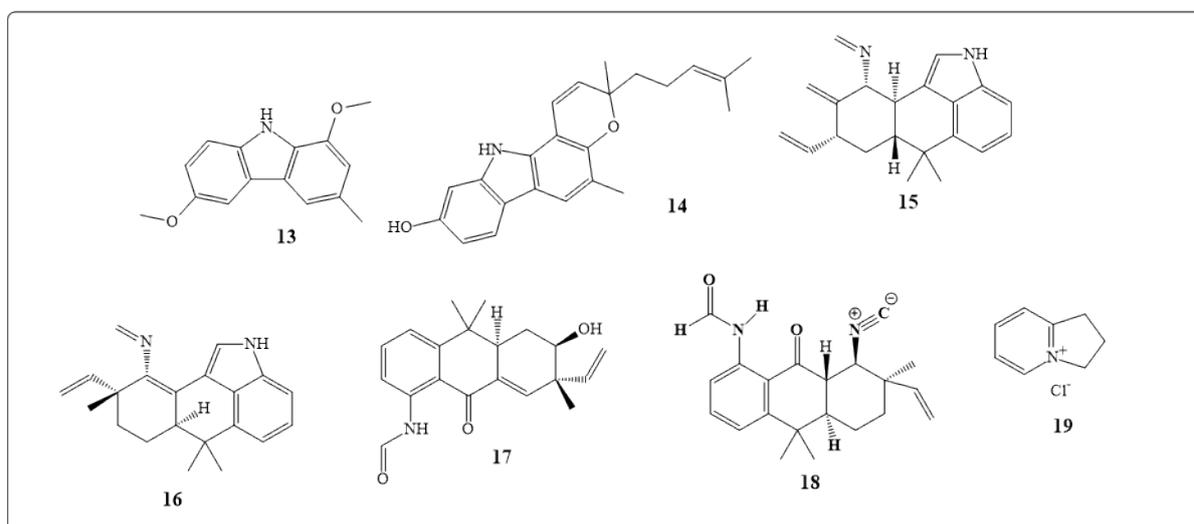


Figure 3. Chemical structures of natural antibacterial alkaloids: Clausenine (**13**), (*R*)-Mahanine (**14**), hapalindole X (**15**), deschlorohapalindole I (**16**), 13-hydroxy dechlorofontonamide (**17**), hapalonamide H (**18**) and 2,3-dihydro-1 H-indolizinium chloride (**19**).

The antimicrobial, antimalarial, cytotoxic, and anti-HIV activities of 26 isoquinolines were studied. The results showed that compound **20** (Figure 4) has antimicrobial effects, compounds **21**, **22** and **23** (Figure 4) have antimalarial effects, compounds **20** and **21** have cytotoxic effects and compounds **24** and **25** (Figure 4) have anti-HIV effects. It is expected that these compounds have the potential to be used as lead compounds for further research and investigation [141].

Berberine alkaloid (**1** in Figure 1) was tested against the oral pathogens *Fusobacterium nucleatum*, *Enterococcus faecalis*, and *Prevotella intermedia*. The MIC values of berberine against these pathogens were 31.25 µg/mL, 3.8 µg/mL and 500 µg/mL, respectively [142].

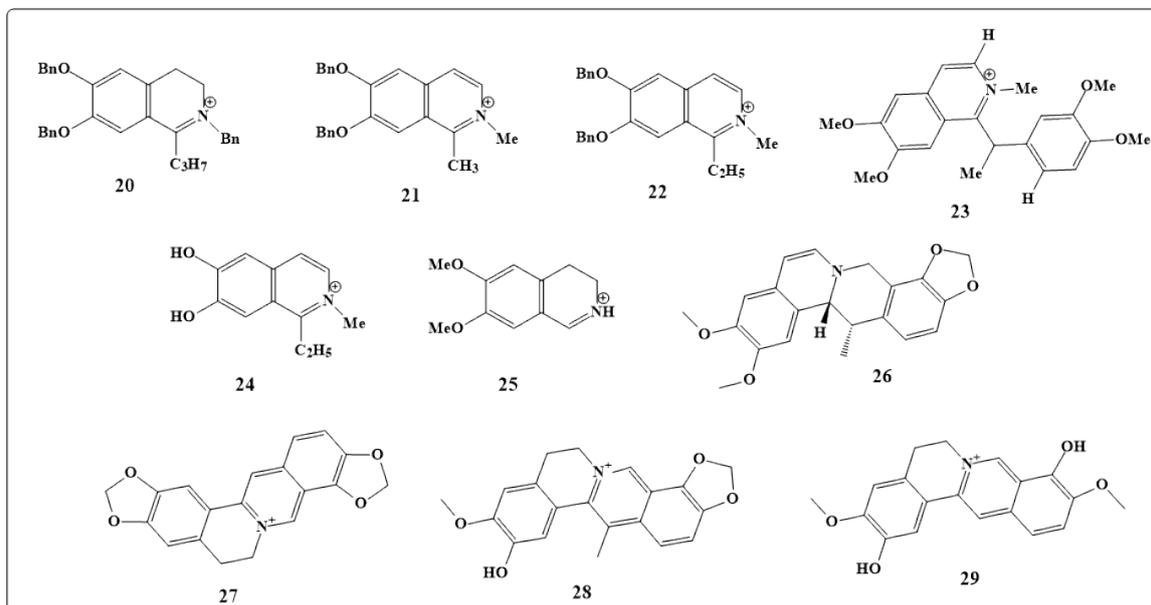


Figure 4. Chemical structures of isoquinolines alkaloids (antimicrobial, antimalarial, cytotoxic, and anti-HIV agents, **20–25**), 2-benzyl-6,7-bis(benzyloxy)-1-propyl-3,4-dihydroisoquinolin-2-ium (**20**), 6,7-bis(benzyloxy)-1,2-dimethylisoquinolin-2-ium (**21**), 6,7-bis(benzyloxy)-1-ethyl-2-methylisoquinolin-2-ium (**22**), 1-(1-(3,4-dimethoxyphenyl)ethyl)-6,7-dimethoxy-2-methylisoquinolin-2-ium (**23**), 1-ethyl-6,7-dihydroxy-2-methylisoquinolin-2-ium (**24**), 6,7-dimethoxy-3,4-dihydroisoquinolin-2-ium (**25**), dehydrocavidine (**26**), coptisine (**27**), dehydroapocavidine (**28**) and tetrahydroscoulerine (**29**).

Sanguinarine (**6** in Figure 1), a benzophenanthridine alkaloid obtained from the root of *Sanguinaria canadensis* L., has shown inhibition activity against methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria, an organism known for its resistance to almost all antibacterial agents. MRSA is responsible for a large number of life-threatening infections. MRSA infections that reach the bloodstream are responsible for numerous complications and fatalities, killing 10–30% of patients. An important predictor of morbidity and mortality in adults is the blood concentrations of vancomycin, the antibiotic of choice to treat this condition [18]. Many of them are skin-related conditions: Skin glands, and mucous membranes. Sanguinarine activity against MRSA strains is in the range of 3.12 to 6.25 µg/mL. Whereas, its MIC values against the two MRSA strains are 3.12 µg/mL and 1.56 µg/mL. Sanguinarine causes lysis of the cell by induction the release of autolytic enzymes [143]. Further, sanguinarine has shown to kill cells and destroy tissues when applied to the skin. The biosynthesis of sanguinarine in plants is via the action of dihydrobenzophenanthridineoxidase on dihydrosanguinarine.

Dehydrocavidine, coptisine, dehydroapocavidine and tetrahydroscoulerine (**26–29**, respectively, in Figure 4) represent the active compounds of Yanhuanglian that extracted from *Corydalis saxicola* Bunting and used in traditional Chinese medicine, and they have shown antibacterial, antiviral and anticancer activities in *in-vivo* studies [144].

Five new quinolone alkaloids, euocarpinines A–E (**30–35** in Figure 5), were isolated from the fruits of *Evodia ruticarpa* var. *officinalis* (Dode) C.C.Huang and were found to exhibit moderate antibacterial activities MIC values of 4–128 µg/mL. Compounds with thirteen carbons on side chain showed the highest antibacterial activity with favorable low cytotoxicity [145].



Figure 5. Chemical structures of alkaloids; euocarpines A–E, 30–35, respectively.

The three quinolone alkaloids kokusaginin, maculine, kolbisine (36–38 in Figure 6) were obtained from *Teclea afzelii* Engl. stem bark, and their antimicrobial and antifungal activities were studied. The results revealed that kokusaginine, 36, was active against Gram-positive and negative bacteria, fungi and *Mycobacterium smegmatis*. While the crude extracts maculine, 37, and kolbisine, 38, have resulted in inhibition of 87.5% of the microbes with an MIC value of 19.53 µg/mL. While maculine, 37, demonstrated a moderate activity against *M. smegmatis* with greater MIC value (156.25 µg/mL) [146].

Eight new quinolone alkaloids were extracted from the actinomycete *Pseudonocardia* sp. CL38489 were found to be potent and selective anti-*Helicobacter pylori* agents [147]. Diterpene alkaloids, such as agelasines O–U (39–45 in Figure 6), were obtained from Okinawan marine sponge *Agelas* sp. Studies have shown that agelasines O–R (39–42 in Figure 6) and T (44 in Figure 6) had antimicrobial activities against several bacteria and fungi [148].

The polyamine alkaloid squalamine (46 in Figure 6) which was extracted from tissues of the dogfish shark *Squalus acanthias* is now considered as a broad-spectrum steroidal antibiotic with potent bactericidal properties against both Gram-negative and Gram-positive bacteria [149].

Aptamine (47 in Figure 6) extracted from the Indonesian marine sponge of the genus *Xestospongia* has shown significant antibacterial activity against gram-negative bacteria [150]. Table 2 illustrates the antibacterial activity of the compounds discussed in this section.

Table 2. Antibacterial compounds, discussed in this section, and their antibacterial activity.

Alkaloids	Antibacterial Activity
Clausenol, Kokusaginine, Maculine, Kolbisine, squalamine, Aptamine	Active against Gram-positive and negative bacteria and fungi
R- Mahanine	Antimicrobial activity against <i>Bacillus cereus</i> and <i>Staphylococcus aureus</i>
hapalindole X, deschlorohapalin-dole I, 13-hydroxy dechlorofonto-namide, hapalonamide H	Potent activity against both <i>Mycobacterium tuberculosis</i> and <i>Candida albicans</i>
Indolizidine	Antibacterial activities against <i>Cryptococcus neoformans</i> , <i>Aspergillus fumigatus</i> , methicillin-resistant <i>Staphylococcus aureus</i> and <i>Mycobacterium intracellulare</i>
Isoquinolines	Antimalarial, cytotoxic, and anti-HIV effects.
Sanguinarine,	Antibacterial activity against methicillin-resistant <i>Staphylococcus aureus</i>

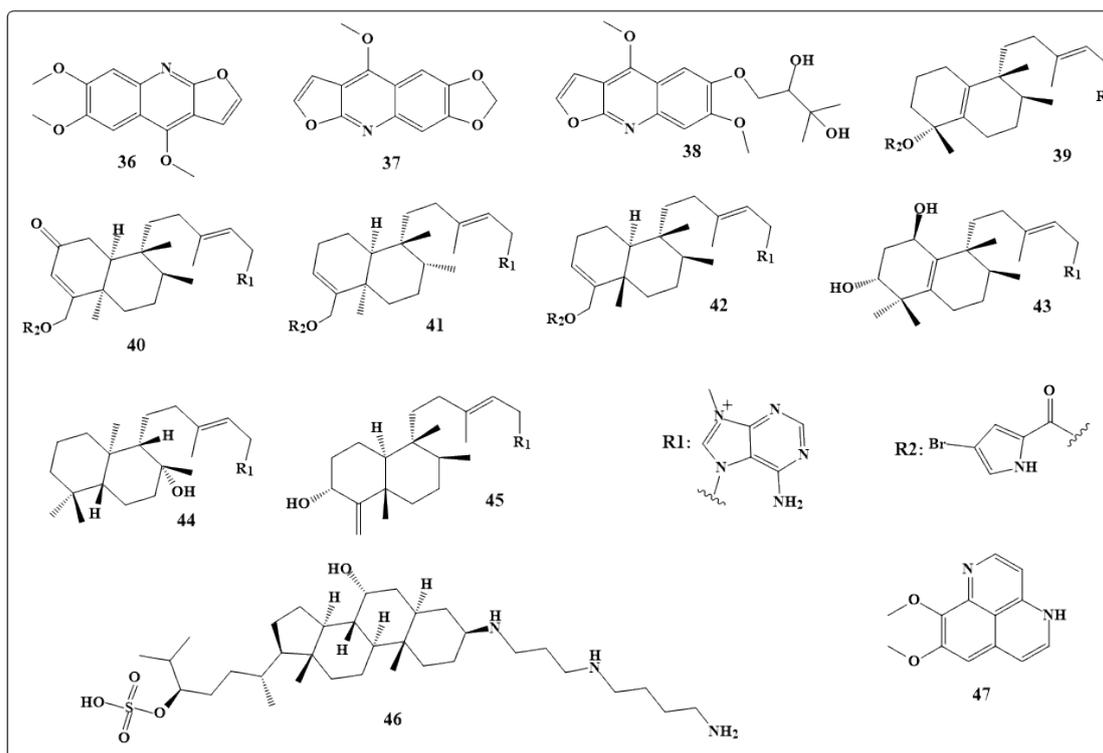


Figure 6. Chemical structures of natural antibacterial alkaloids: Kokusaginine (36), maculine (37), kolbisine (38), agelasines O–U (39–45), squalamine (46) and aptamine (47).

4.2. Antibacterial Mechanism of Action of Alkaloids

Most alkaloids are found to be bactericidal rather than being bacteriostatic. For example, squalamine, 42, was found to be with potent bactericidal properties killing *Gram-positive* and *Gram-negative* pathogens by $\geq 99.99\%$ in about 1–2 h [151]. The mechanism of action of squalamine, 42, is illustrated in Figure 7.

The alkaloids mechanism of action as antibacterial agents has been found to be different between each class. In the alkaloids pergularinine and tylophorinidine from the indolizine class, the antibacterial action is due to inhibition of the enzyme dihydrofolate reductase resulting in the inhibition of nucleic acid synthesis [152].

Within the isoquinolone class two mechanisms of bacterial inhibition were shown to occur; Ungereminea phenanthridine isoquinoline exerts its effect through the inhibition of nucleic acid synthesis, while from the studies with benzophenanthridine and protoberberine isoquinolines it was suggested that those agents act by the perturbation of the Z-ring and cell division inhibition, and this was further proved by many studies [97,153–155].

On the other hand, synthetic quinolones inhibit the type II topoisomerase enzymes, while the natural quinolone alkaloids lacking the 3-carboxyl function act as respiratory inhibitors by reducing oxygen consumption in the treated bacteria [156,157].

Agelasines alkaloids exert their antibacterial activity by the inhibition of the dioxygenase enzyme BCG 3185c, causing a disturbance in the bacterial hemostasis. This result was revealed from overexpression and binding affinity experiments on the anti-mycobacterial alkaloid agelasine D [158]. Squalamine from the polyamine alkaloid class acts by disturbing bacterial membrane integrity [158,159].

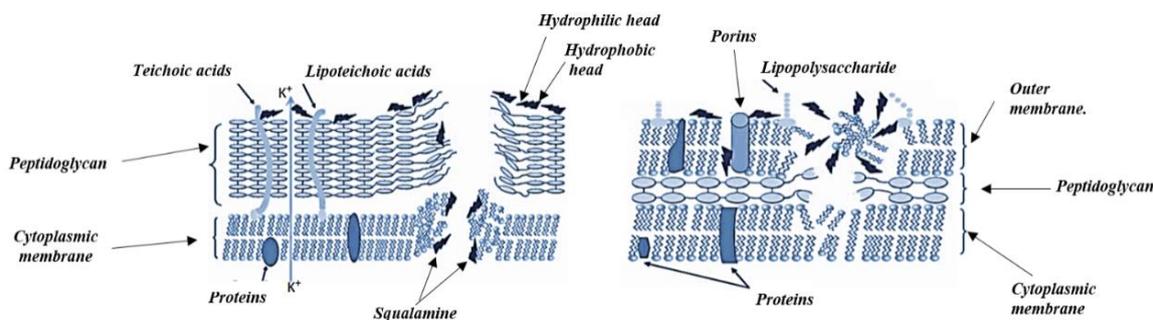


Figure 7. A representation of the mode of action of squalamine antibacterial agent; intracellular ion efflux in *Gram-positive* bacteria caused by the depolarization of the membranes, and membrane disruption in *Gram-negative* bacteria. PG is peptidoglycan, CM is cytoplasmic membrane, and OM is outer membrane.

5. Antiviral Activity

Plants and animals, host a vast number of viruses, often transmitted by insects, such as aphids and bugs. Viral infection resistance can be caused either by biochemical mechanisms that prevent the development and multiplication of the virus or by preventing vectors, such as aphids. The evaluation of the antiviral activity is relatively difficult. Several researchers have studied the effect of alkaloids on viral reproduction. The studies revealed that about 40 alkaloids possess antiviral properties.

Leurocristine, periformyline, perivine and vincalucoblastine (48–51 in Figure 8) are natural alkaloids obtained from *Catharanthus roseus* (L.) and *lanceus*Pich (Apocycaceae). Leurocristine, 48, is an active against *mengovirus* extracellular virucidal, poliovirus, *vaccinia*, and *influenza* viruses [160]. Periformyline, 49, inhibits poliovirus type viruses. Whereas, perivine, 50, exhibits polio extracellular virucidal activity against *vaccinia*, and vincalucoblastine, 51, possesses extracellular virucidal activity against *poliovirus vaccinia* and *influenza* virus.

The michellamines D and F (52 and 53 in Figure 8), naphthyl-isoquinoline alkaloids, obtained from the tropical liana *Ancistrocladus korupensis* have demonstrated HIV-inhibitory [161]. A series of isoquinoline alkaloids as lycorine, lycoricidine (54 in Figure 8), narciclasine, and cis-dihydronarciclasine, obtained from *Narcissus poeticus* (Amaryllidaceae), have shown significant in vitro activity against *flaviviruses* and *bunyaviruses*. Poliomyelitis virus inhibition by the above-mentioned compounds occurred at 1 mg/mL [162].

The alkaloids homonojirimycin (55 in Figure 9) and 1-deoxymanojirimycin (56 in Figure 9) were obtained from *Omphaleadiandra* (Euphorbiaceae). Homonojirimycin, 55, is an inhibitor of several α -glucosidases, glucosidase I and glucosidase II. Deoxymanojirimycin, 56, is an inhibitor of glycoprocessing mannosidase [163]. Castanospermine (57 in Figure 9) and australine (58 in Figure 9) are alkaloids present in seeds of *Castanospermum australe* A. Cunn. and C. Fraser (Leguminosae) and reduce the ability of HIV to infect cultured cells and have the potential for treating AIDS [164]. Sesquiterpene alkaloids obtained from *Tripterygium hypoglaucum* (H. Lév.) and *Tripterygium wilfordii* Hook. f. (Celastraceae) were found to possess anti-HIV activity [165].

The acridone alkaloids, 5-hydroxynoracronycine—same compound of 11-hydroxynoracronycine (59 in Figure 9) and Acrimarine F (60 in Figure 9) were extracted from *Citrus alata* (Tanaka) plants and were found to be very effective against Epstein-Barr virus [166–168]. Columbamine, palmitine (61, 62 in Figure 9), and berberine are alkaloids with potent activity against HIV-1 and can be found in many plants, including Annonaceae (Coelocline), *Berberis vulgaris* (Berberidaceae), Menispermaceae and Papaveraceae [169–171]. A concise summary of the antiviral activities of alkaloids 48–62 is depicted in Table 3.

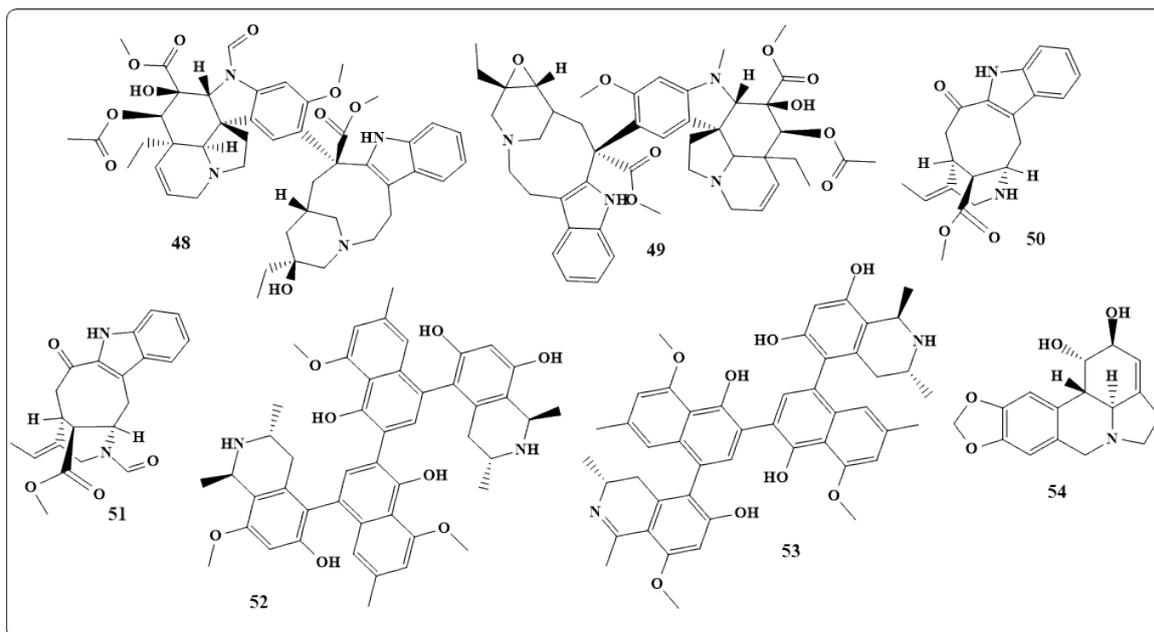


Figure 8. Chemical structures of the antiviral natural alkaloids: Leurocristine (48), periformyline (49), pervine (50), vincalucoblastine (51), michellamines D and F (52 and 53) and lycoricidine (54).

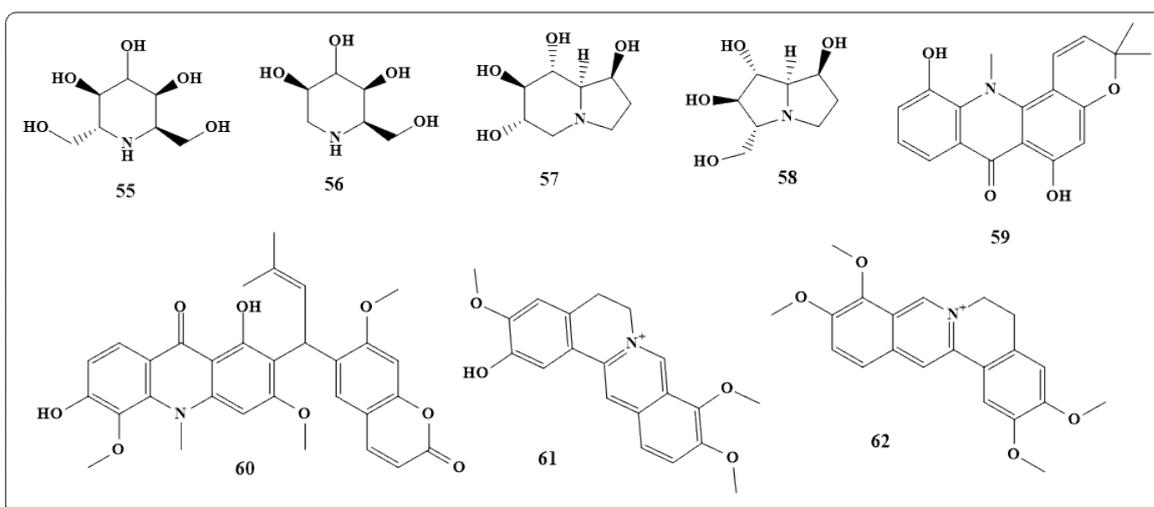


Figure 9. Chemical structures of antiviral natural alkaloid: Homonojirimycin (55), 1-deoxymanojirimycin (56), castanospermine (57), australine (58), 5-hydroxynoracronycine (59), acrimarine F (60), columbamine (61), palmitine (62).

Table 3. Antiviral compounds, discussed in this section, and their antiviral activity.

Alkaloids	Antiviral Activity
Leurocristine	Active against <i>mengovirus</i> extracellular virucidal, poliovirus, <i>vaccinia</i> , and <i>influenza</i> viruses
Periformyline	Inhibits poliovirus type viruses
Pervine	Exhibits polio extracellular virucidal activity against <i>vaccinia</i>
Vincalucoblastine	Possesses extracellular virucidal activity against poliovirus <i>vaccinia</i> and <i>influenza</i> virus.

Table 3. Cont.

Michellamines D and F	HIV-inhibitory
Homonojirimycin	Inhibitor of several α -glucosidases
Deoxymanojirimycin	Inhibitor of glycoprocessing mannosidase
Castanospermine, australine	Reduce the ability of the human immunodeficiency virus (HIV) to infect cultured cells, and have potential for treating AIDS
Sesquiterpene	Anti-HIV activity
5-hydroxynoracronycine, Acrimarine F	Remarkable inhibitory effects on <i>Epstein-Barr</i> virus activation
Columbamine, Berberine, Palmitine	Inhibitors alkaloids against HIV-1

6. Antifungal Activity

The spread of resistance to antifungal agents has accelerated in the recent few years. The rate of morbidity and mortality has enhanced, due to resistance to antifungal agents. Since the molecular processes in humans and fungi are similar, there is always a risk that the fungal cytotoxic substance is toxic to the host cells. Consequently, patients with a reduced immune system, such as those with transplants, cancer and diabetics who do not respond appropriately to the current medications have ignited the need for new antifungal medicines [93]. The current antifungal drugs suffer from many side effects as irritation, diarrhea, and vomiting; furthermore, it is less effective, due to the development of resistance to those drugs by the diverse available fungi. The potency and effectiveness of the antifungal medicines developed during 1980–1995, such as the imidazoles and triazoles, which inhibit the fungal cell processes have gradually decreased, due to the development of resistance by the microorganism [172]. Therefore, researchers are looking for new potent entities to replace the currently used antifungal agents. A respected number of biologically active compounds were isolated from medicinal plants and are widely used as mixtures or pure compounds to cure a variety of diseases. It is estimated that about 250,000 to 500,000 species of plants are growing on our planet. However, humans are using only 1 to 10% of those plants [173]. This treasure should be utilized to isolate and develop new antifungal agents by using new methods and techniques [174]. For example, chemical entities isolated from plants, such as the indole derivatives, dimethyl pyrrole and hydroxydihydrocornin-aglycones have shown promising antifungal activities [174]. However, pure medicines derived from these chemical entities still to be developed.

It should be emphasized that the annual mortality rate, due to fungi was constant through several decades, and the resistance to antifungal drugs has emerged only in the recent two to three decades [175–177]. Thus, a combined effort from chemists, biologists, pharmacologists and etc. is crucially needed to combat the issue of microorganisms' resistance to drugs. Consequently, great emphasis has been placed on developing a more detailed understanding of antimicrobial resistance mechanisms, improved methods for detecting resistance when they occur, new antimicrobial options for treating infections caused by resistant organisms, and ways to prevent the emergence and spread of resistance in the first place [174].

In this section of the review, we attempted to report on some important antifungal compounds obtained from plants.

Antifungal Activity of Alkaloids

Extraction of the opium poppy *Papaver somniferum* L. has resulted in the isolation of morphine which is considered the first member [156]. Recently, a new alkaloid, 2-(3,4-dimethyl-2,5-dihydro-1H-pyrrol-2-yl)-1-methylethyl pentanoate (**63** in Figure 10) was isolated from the plant *Datura metel* var. *fastuosa* (L.) *Saff.*, and has demonstrated activity against *Aspergillus* and *Candida* species when tested both in vitro and in vivo [178,179].

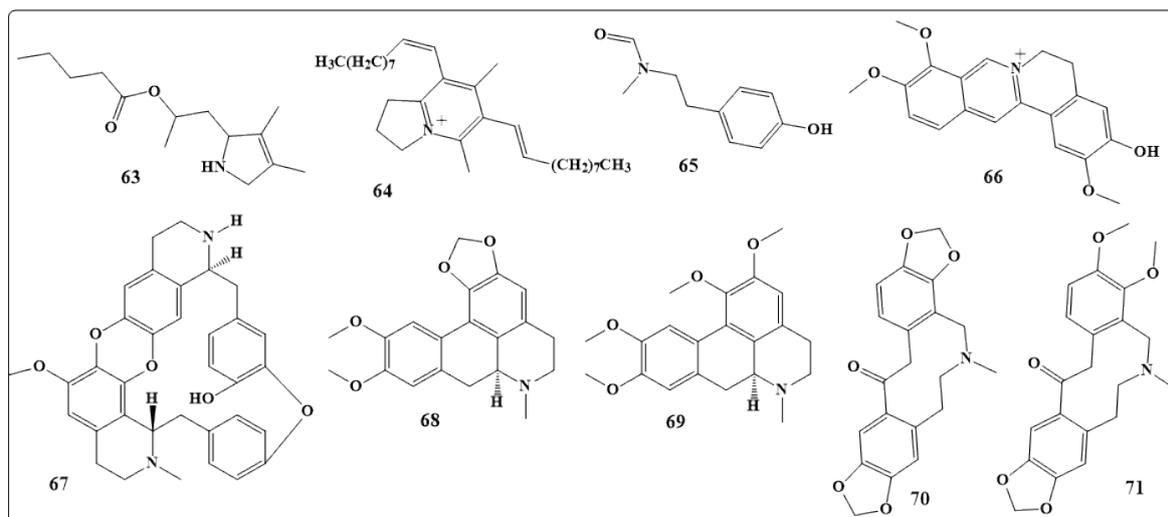


Figure 10. Chemical structures of antifungal natural alkaloids: 2-(3,4-dimethyl-2,5-dihydro-1H-pyrrol-2-yl)-1-methylethyl pentanoate (**63**), 6,8-didec-(1Z)-enyl-5,7-dimethyl-2,3-dihydro-1H-indolizinium (**64**), N-methyl-N-formyl-4-hydroxy-beta-phenylethylamine (**65**), Jatrorrhizine (**66**), (+)-Coccoline (**67**), dicentrine (**68**), glaucine (**69**), protopine (**70**) and alpha-allocryptopin (**71**).

Another alkaloid, 6,8-didec-(1Z)-enyl-5,7-dimethyl-2,3-dihydro-1H-indolizinium (**64** in Figure 10) was isolated from *Anibapanurensis* and demonstrated excellent activity against the strain of *C. albicans* [180].

β -Carboline, a tryptamine and twophenylethylamine-derived alkaloids along with N-methyl-N-formyl-4-hydroxy-beta-phenylethylamine (**65** in Figure 10) from *Cyathobasisfruticulosa* [20] and *haloxylinas A* and *B*, new piperidine from *Haloxylon schmittianum* Pomel have shown a potential antifungal activity [181].

Jatrorrhizine (**66** in Figure 10) isolated from *Mahonia aquifolium* (Pursh) Nutt. has shown the most potent antifungal inhibitory in all studied fungi with MIC between 62.5 to 125 $\mu\text{g/mL}$, while the crude extract, berberine, and palmatine showed reduced inhibitory activity with MIC of 500 to ≥ 1000 $\mu\text{g/mL}$ [182].

(+)-Coccoline (**67** in Figure 10) is a bisbenzylisoquinoline alkaloid isolated from *Epinetrum villosum* has demonstrated a good antifungal activity [183]. The alkaloids N-methylhydrasteinehydroxylactam and 1-methoxyberberine chloride isolated from *Corydalis longipes* D. Don demonstrated great inhibitory activity [184]. Four alkaloids, dicentrine (**68** in Figure 10), glaucine (**69** in Figure 10), protopine (**70** in Figure 10), and alpha-allocryptopin (**71** in Figure 10) were isolated from *Glaucium oxylobum* Boiss and Buhse have exhibited good activity against *Microsporium gypseum*, *Microsporium canis*, *T. mentagrophytes* and *Epidermophyton floccosum* [185].

Flindersine (**72** in Figure 11) and haplopin (**73** in Figure 11) obtained from *Haplophyllum sieversii* Fisch. were growth-inhibitory compounds against various fungi [186]. Canthin-6-one (**74** in Figure 11) and 5-methoxy-canthin-6-one (**75** in Figure 11) of *Zanthoxylum chiloperone* var. *angustifolium* exhibited antifungal activity against *C. albicans*, *A. fumigatus* and *T. mentagrophytes* [187]. Frangulanine (**76** in Figure 11), a cyclic peptide alkaloid and waltherione A (**77** in Figure 11), quinolinone alkaloids from leaves of *Melochia odorata* were reported to exhibit antifungal activities against a broad spectrum of pathogenic fungi [188].

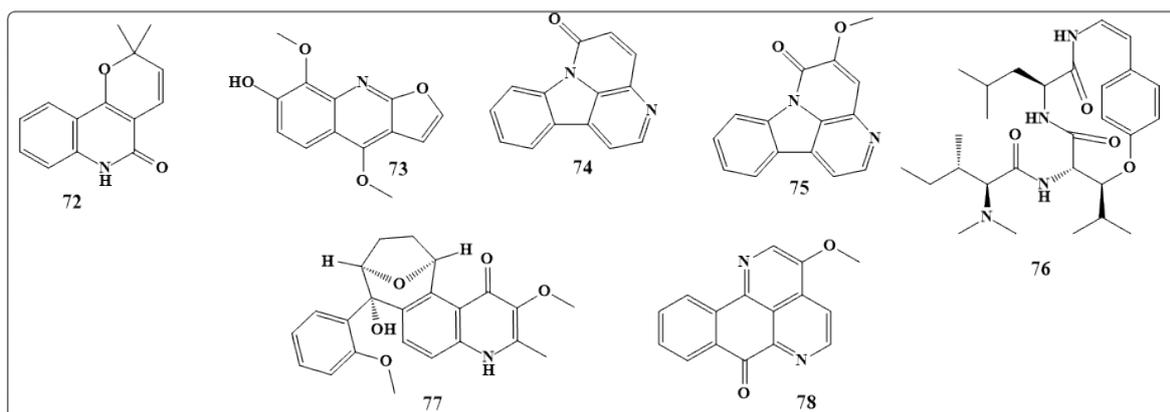


Figure 11. Chemical structures of antifungal natural alkaloids: Flindersine (72), haplopine (73), canthin-6-one (74), 5-methoxy-canthin-6-one (75), frangulanine (76), waltherione A (77) and 3-methoxisampangin (78).

Furthermore, anodic alkali aninolate has demonstrated inhibitory activity against all 10 fungi tested and demonstrated a particularly high sensitivity to this compound, showing germination levels of less than 10% [189]. From the root of *Dictamnus dasycarpus* two antifungal fructoxin alkaloids were isolated. 3-Methoxisampangin (78 in Figure 11) of *cleistopholispatens* showed vast inhibitory activity against each of *C. albicans*, *A. fumigatus*, and *C. neoformans* [190]. Table 4 lists the antifungal activity of the compounds discussed in this section.

Table 4. Antifungal compounds, discussed in this section, and their antifungal activity.

Alkaloids	Antifungal Activity
2-(3,4-dimethyl-2,5-dihydro-1H-pyrrol-2-yl)-1-methylethyl pentanoate	Activity against <i>Aspergillus</i> and <i>Candida</i> species
6,8-didec-(1Z)-enyl-5,7-dimethyl-2,3-dihydro-1H-indolizinium	Good activity against a drug-resistant strain of <i>C. albicans</i>
β -carboline, Cocsoline	Effective against all fungal species and marginal activity
Dicentrine, glaucine, Protopine, alpha-allocryptopin	Good activity against <i>Microsporiumgypseum</i> , <i>Microsporumcanis</i> , <i>T. mentagrophytes</i> and <i>Epidermophytonfloccosum</i>
Canthin-6-one, 5-methoxy-canthin-6-one	Antifungal activity against <i>C. albicans</i> , <i>A. fumigatus</i> and <i>T. mentagrophytes</i>
Frangulanine, Waltherione, quinolinone alkaloids	Exhibit antifungal activities against a broad spectrum of pathogenic fungi
3-methoxisampangin	Significant antifungal activity against <i>C. albicans</i> , <i>A. fumigatus</i> , and <i>C. neoformans</i>

7. Toxicity of Plant Secondary Metabolites

Through hundreds of years, people have been used plant extracts for the treatment of a variety of diseases, such as snakebite, fever and insanity. However, a number of plants containing alkaloids are classified as main plant toxins because of their vast structural diversity and different mechanism of actions. Inhalation or swallowing toxic alkaloids by humans or animals might result in a certain mechanism involving transporters, enzymes and receptors at certain cells and tissues, and therefore, causing musculoskeletal deformities and hepatotoxic effects. These toxic alkaloids include tropane, piperidine, pyrrolizidine and indolizidine. The most adverse effects of these entities are vomiting, mild gastrointestinal perturbation, teratogenicity, arrhythmias, itching, nausea, psychosis, paralysis, and death [188].

8. Conclusions

Secondary metabolites isolated from different plants have proven to be useful for humans and animals alike. Studies on a number of these alkaloids have demonstrated that a vast number of them possess many pharmacological activities. These activities include anticancer, antibacterial, antiviral, antioxidant and antifungal. However, when high doses of the secondary metabolites are consumed, toxic effects may be observed and in sometimes fatalities are imminent. For instance, some alkaloids have proven to lead to paralysis, asphyxia, and in sometimes to death. During the past few years researches have been conducted to make new derivatives of the isolated secondary metabolites aiming to obtain medicines with more potency, less toxicity, and more resistant to different microorganisms. It is hoped that the state-of-the-art methods and sophisticated techniques along with computational methods, will make the path for generating novel potent drugs, based on natural products, be shorter and beneficial.

Several plants contain secondary metabolites which are toxic and may cause danger to humans when administered. However, the cases in which fatal plant poisonings occur are negligible. The most common incidents of toxicity are those involving the abuse of plants for hallucinogenic purposes. Utilizing toxicological analysis of such secondary metabolites may help in the diagnosis of poisoning or abuse cases. Among the toxic secondary metabolites are harmaline, ibogaine, kawain, cytisine, dimethyltryptamine, harmine, aconitine, atropine, coniine, colchicine, taxine, mescaline, and scopolamine, which are often involved in fatal poisonings [190].

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References

1. Khan, M.T.H.; Ather, A.; Thompson, K.D.; Gambari, R. Extracts and molecules from medicinal plants against herpes simplex viruses. *Antivir. Res.* **2005**, *67*, 107–119. [[CrossRef](#)] [[PubMed](#)]
2. Mohamed, S.; Hassan, E.; Ibrahim, N. Cytotoxic and antiviral activities of aporphine alkaloids of *Magnolia Grandiflora* L. *Nat. Prod. Res.* **2010**, *24*, 1395–1402. [[CrossRef](#)] [[PubMed](#)]
3. Evers, D.L.; Chao, C.F.; Wang, X.; Zhang, Z.; Huong, S.M.; Huang, E.S. Human cytomegalovirus-inhibitory flavonoids: Studies on antiviral activity and mechanism of action. *Antivir. Res.* **2005**, *68*, 124–134. [[CrossRef](#)] [[PubMed](#)]
4. Peng, J.; Lin, T.; Wang, W.; Xin, Z.; Zhu, T.; Gu, Q.; Li, D. Antiviral alkaloids produced by the mangrove-derived fungus *Cladosporium* sp. PjX-41. *J. Nat. Prod.* **2013**, *76*, 1133–1140. [[CrossRef](#)] [[PubMed](#)]
5. Kainsa, S.; Kumar, P.; Rani, P. Medicinal plants of Asian origin having anticancer potential: Short review. *Asian J. Biomed. Pharm. Sci.* **2012**, *2*, 1–7.
6. Ziegler, J.; Facchini, P.J. Alkaloid biosynthesis: Metabolism and trafficking. *Annu. Rev. Plant Biol.* **2008**, *59*, 735–769. [[CrossRef](#)] [[PubMed](#)]
7. Marella, A.; Tanwar, O.P.; Saha, R.; Ali, M.R.; Srivastava, S.; Akhter, M.; Shaquiquzzaman, M.; Alam, M.M. Quinoline: A versatile heterocyclic. *Saudi Pharm. J.* **2013**, *21*, 1–12. [[CrossRef](#)] [[PubMed](#)]
8. Frick, S.; Kramell, R.; Schmidt, J.; Fist, A.J.; Kutchan, T.M. Comparative qualitative and quantitative determination of alkaloids in narcotic and condiment *Papaver s omniferum* cultivars. *J. Nat. Prod.* **2005**, *68*, 666–673. [[CrossRef](#)] [[PubMed](#)]
9. Nassiri, M. Simple, one-pot, and three-component coupling reactions of azaarenes (phenanthridine, isoquinoline, and quinoline), with acetylenic esters involving methyl propiolate or ethyl propiolate in the presence of nh-heterocyclic or 1, 3-dicarbonyl compounds. *Synth. Commun.* **2013**, *43*, 157–168. [[CrossRef](#)]
10. Herman, A.; Herman, A. Caffeine's mechanisms of action and its cosmetic use. *Skin Pharmacol. Physiol.* **2013**, *26*, 8–14. [[CrossRef](#)] [[PubMed](#)]

11. Li, S.; Lo, C.Y.; Pan, M.H.; Lai, C.S.; Ho, C.T. Black tea: Chemical analysis and stability. *Food Funct.* **2013**, *4*, 10–18. [[CrossRef](#)] [[PubMed](#)]
12. Singh, A.K.; Chawla, R.; Rai, A.; Yadav, L.D.S. NHC-catalysed diastereoselective synthesis of multifunctionalised piperidines via cascade reaction of enals with azalactones. *Chem. Commun.* **2012**, *48*, 3766–3768. [[CrossRef](#)] [[PubMed](#)]
13. Machado, P.A.; Hilário, F.F.; Carvalho, L.O.; Silveira, M.L.; Alves, R.B.; Freitas, R.P.; Coimbra, E.S. Effect of 3-Alkylpyridine Marine Alkaloid Analogues in Leishmania Species Related to American Cutaneous Leishmaniasis. *Chem. Biol. Drug Des.* **2012**, *80*, 745–751. [[CrossRef](#)] [[PubMed](#)]
14. Cronemberger, S.; Calixto, N.; Moraes, M.N.; Castro, I.D.; Lana, P.C.; Loredó, A.F. Efficacy of one drop of 2% pilocarpine to reverse the intraocular pressure peak at 6: 00 am in early glaucoma. *Vision Pan-Am. Pan-Am. J. Ophthalmol.* **2012**, *11*, 14–16.
15. Parmar, N.J.; Pansuriya, B.R.; Barad, H.A.; Kant, R.; Gupta, V.K. An improved microwave assisted one-pot synthesis, and biological investigations of some novel aryl diazenyl chromeno fused pyrrolidines. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4075–4079. [[CrossRef](#)] [[PubMed](#)]
16. Singh, K.S.; Das, B.; Naik, C.G. Quinolizidines alkaloids: Petrosin and xestospongins from the sponge *Oceanapia* sp. *J. Chem. Sci.* **2011**, *123*, 601–607. [[CrossRef](#)]
17. Kumar, P.; Sharma, B.; Bakshi, N. Biological activity of alkaloids from *Solanum dulcamara* L. *Nat. Prod. Res.* **2009**, *23*, 719–723. [[CrossRef](#)] [[PubMed](#)]
18. Zoraghi, R.; Worrall, L.; See, R.H.; Strangman, W.; Popplewell, W.L.; Gong, H.; Samaai, T.; Swayze, R.D.; Kaur, S.; Vuckovic, M. Methicillin-resistant *Staphylococcus aureus* (MRSA) pyruvate kinase as a target for bis-indole alkaloids with antibacterial activities. *J. Biol. Chem.* **2011**, *286*, 44716–44725. [[CrossRef](#)] [[PubMed](#)]
19. Villinski, J.; Dumas, E.; Chai, H.B.; Pezzuto, J.; Angerhofer, C.; Gafner, S. Antibacterial activity and alkaloid content of *Berberis thunbergii*, *Berberis vulgaris* and *Hydrastis canadensis*. *Pharm. Biol.* **2003**, *41*, 551–557. [[CrossRef](#)]
20. Otshudi, A.L.; Apers, S.; Pieters, L.; Claeys, M.; Pannecouque, C.; De Clercq, E.; Van Zeebroeck, A.; Lauwers, S.; Frederich, M.; Foriers, A. Biologically active bisbenzylisoquinoline alkaloids from the root bark of *Epinetrum villosum*. *J. Ethnopharmacol.* **2005**, *102*, 89–94. [[CrossRef](#)] [[PubMed](#)]
21. Oliva, A.; Meepagala, K.M.; Wedge, D.E.; Harries, D.; Hale, A.L.; Aliotta, G.; Duke, S.O. Natural fungicides from *Ruta graveolens* L. leaves, including a new quinolone alkaloid. *J. Agric. Food Chem.* **2003**, *51*, 890–896. [[CrossRef](#)] [[PubMed](#)]
22. Simons, V.; Morrissey, J.P.; Latijnhouwers, M.; Csukai, M.; Cleaver, A.; Yarrow, C.; Osbourn, A. Dual effects of plant steroidal alkaloids on *Saccharomyces cerevisiae*. *Antimicrob. Agents Chemother.* **2006**, *50*, 2732–2740. [[CrossRef](#)] [[PubMed](#)]
23. Cretton, S.; Dorsaz, S.; Azzollini, A.; Favre-Godal, Q.; Marcourt, L.; Ebrahimi, S.N.; Voinesco, F.; Michellod, E.; Sanglard, D.; Gindro, K. Antifungal quinoline alkaloids from *Waltheria indica*. *J. Nat. Prod.* **2016**, *79*, 300–307. [[CrossRef](#)] [[PubMed](#)]
24. Lou, C.; Yokoyama, S.; Saiki, I.; Hayakawa, Y. Selective anticancer activity of hirsutine against HER2-positive breast cancer cells by inducing DNA damage. *Oncol. Rep.* **2015**, *33*, 2072–2076. [[CrossRef](#)] [[PubMed](#)]
25. Li, M.; Su, B.S.; Chang, L.H.; Gao, Q.; Chen, K.L.; An, P.; Huang, C.; Yang, J.; Li, Z.F. Oxymatrine induces apoptosis in human cervical cancer cells through guanine nucleotide depletion. *Anti-Cancer Drugs* **2014**, *25*, 161–173. [[CrossRef](#)] [[PubMed](#)]
26. Marciniak, P.; Adamski, Z.; Bednarz, P.; Slocinska, M.; Ziemnicki, K.; Lelario, F.; Scrano, L.; Bufo, S.A. Cardioinhibitory properties of potato glycoalkaloids in beetles. *Bull. Environ. Contam. Toxicol.* **2010**, *84*, 153–156. [[CrossRef](#)] [[PubMed](#)]
27. Marciniak, P.; Kolińska, A.; Spochacz, M.; Chowański, S.; Adamski, Z.; Scrano, L.; Falabella, P.; Bufo, S.A.; Rosiński, G. Differentiated Effects of Secondary Metabolites from Solanaceae and Brassicaceae Plant Families on the Heartbeat of *Tenebrio molitor* Pupae. *Toxins* **2019**, *11*, 287. [[CrossRef](#)] [[PubMed](#)]
28. Büyükgüzel, E.; Büyükgüzel, K.; Erdem, M.; Adamski, Z.; Marciniak, P.; Ziemnicki, K.; Ventrella, E.; Scrano, L.; Bufo, S.A. The influence of dietary α -solanine on the waxmoth *Galleria mellonella* L. *Arch. Insect Biochem. Physiol.* **2013**, *83*, 15–24. [[CrossRef](#)] [[PubMed](#)]

29. Ventrella, E.; Adamski, Z.; Chudzińska, E.; Miądowicz-Kobielska, M.; Marciniak, P.; Büyükgüzel, E.; Büyükgüzel, K.; Erdem, M.; Falabella, P.; Scranò, L. Solanum tuberosum and Lycopersicon esculentum leaf extracts and single metabolites affect development and reproduction of *Drosophila melanogaster*. *PLoS ONE* **2016**, *11*, e0155958. [[CrossRef](#)] [[PubMed](#)]
30. Spochacz, M.; Chowański, S.; Szymczak, M.; Lelario, F.; Bufo, S.; Adamski, Z. Sublethal Effects of Solanum nigrum Fruit Extract and Its Pure Glycoalkaloids on the Physiology of *Tenebrio molitor* (Mealworm). *Toxins* **2018**, *10*, 504. [[CrossRef](#)] [[PubMed](#)]
31. Seo, Y.S.; Yim, M.J.; Kim, B.H.; Kang, K.R.; Lee, S.Y.; Oh, J.S.; You, J.S.; Kim, S.G.; Yu, S.J.; Lee, G.J. Berberine-induced anticancer activities in FaDu head and neck squamous cell carcinoma cells. *Oncol. Rep.* **2015**, *34*, 3025–3034. [[CrossRef](#)] [[PubMed](#)]
32. Kaboli, P.J.; Rahmat, A.; Ismail, P.; Ling, K.H. Targets and mechanisms of berberine, a natural drug with potential to treat cancer with special focus on breast cancer. *Eur. J. Pharmacol.* **2014**, *740*, 584–595. [[CrossRef](#)] [[PubMed](#)]
33. Letašiová, S.; Jantová, S.; Čipák, L.U.; Múčková, M. Berberine—Antiproliferative activity in vitro and induction of apoptosis/necrosis of the U937 and B16 cells. *Cancer Lett.* **2006**, *239*, 254–262. [[CrossRef](#)] [[PubMed](#)]
34. Bezerra, D.; Castro, F.; Alves, A.; Pessoa, C.; Moraes, M.; Silveira, E.; Lima, M.; Elmiro, F.; Costa-Lotufo, L. In vivo growth-inhibition of Sarcoma 180 by pipartine and piperine, two alkaloid amides from Piper. *Braz. J. Med. Biol. Res.* **2006**, *39*, 801–807. [[CrossRef](#)] [[PubMed](#)]
35. Sunila, E.; Kuttan, G. Immunomodulatory and antitumor activity of Piper longum Linn. and piperine. *J. Ethnopharmacol.* **2004**, *90*, 339–346. [[CrossRef](#)] [[PubMed](#)]
36. Wirasathien, L.; Boonarkart, C.; Pengsuparp, T.; Suttisri, R. Biological Activities of Alkaloids from Pseuduvaria setosa. *Pharm. Biol.* **2006**, *44*, 274–278. [[CrossRef](#)]
37. Chopra, I. The 2012 Garrod lecture: Discovery of antibacterial drugs in the 21st century. *J. Antimicrob. Chemother.* **2012**, *68*, 496–505. [[CrossRef](#)] [[PubMed](#)]
38. Imhoff, J.F.; Labes, A.; Wiese, J. Bio-mining the microbial treasures of the ocean: New natural products. *Biotechnol. Adv.* **2011**, *29*, 468–482. [[CrossRef](#)] [[PubMed](#)]
39. Oleksiewicz, M.B.; Nagy, G.; Nagy, E. Anti-bacterial monoclonal antibodies: Back to the future? *Arch. Insect Biochem.* **2012**, *526*, 124–131. [[CrossRef](#)] [[PubMed](#)]
40. Henein, A. What are the limitations on the wider therapeutic use of phage? *Bacteriophage* **2013**, *3*, e24872. [[CrossRef](#)] [[PubMed](#)]
41. Liu, C.M.; Kao, C.L.; Wu, H.M.; Li, W.J.; Huang, C.T.; Li, H.T.; Chen, C.Y. Antioxidant and anticancer aporphine alkaloids from the leaves of *Nelumbo nucifera* Gaertn. cv. *Rosa-plena*. *Molecules* **2014**, *19*, 17829–17838. [[CrossRef](#)] [[PubMed](#)]
42. Lamchouri, F.; Zemzami, M.; Jossang, A.; Abdellatif, A.; Israili, Z.H.; Lyoussi, B. Cytotoxicity of alkaloids isolated from *Peganum harmala* seeds. *Pak. J. Pharm. Sci.* **2013**, *26*, 699–706. [[PubMed](#)]
43. Kobayashi, Y.; Nakano, Y.; Kizaki, M.; Hoshikuma, K.; Yokoo, Y.; Kamiya, T. Capsaicin-like anti-obese activities of evodiamine from fruits of *Evodia rutaecarpa*, a vanilloid receptor agonist. *Planta Med.* **2001**, *67*, 628–633. [[CrossRef](#)] [[PubMed](#)]
44. Kobayashi, Y. The nociceptive and anti-nociceptive effects of evodiamine from fruits of *Evodia rutaecarpa* in mice. *Planta. Med.* **2003**, *69*, 425–428. [[PubMed](#)]
45. Shin, Y.W.; Bae, E.A.; Cai, X.F.; Lee, J.J.; Kim, D.H. In vitro and in vivo antiallergic effect of the fructus of *Evodia rutaecarpa* and its constituents. *Biol. Pharm. Bull.* **2007**, *30*, 197–199. [[CrossRef](#)] [[PubMed](#)]
46. Ko, H.C.; Wang, Y.H.; Liou, K.T.; Chen, C.M.; Chen, C.H.; Wang, W.Y.; Chang, S.; Hou, Y.C.; Chen, K.T.; Chen, C.F. Anti-inflammatory effects and mechanisms of the ethanol extract of *Evodia rutaecarpa* and its bioactive components on neutrophils and microglial cells. *Eur. J. Pharmacol.* **2007**, *555*, 211–217. [[CrossRef](#)] [[PubMed](#)]
47. Du, J.; Wang, X.F.; Zhou, Q.M.; Zhang, T.L.; Lu, Y.Y.; Zhang, H.; Su, S.B. Evodiamine induces apoptosis and inhibits metastasis in MDA-MB-231 human breast cancer cells in vitro and in vivo. *Oncol. Rep.* **2013**, *30*, 685–694. [[CrossRef](#)] [[PubMed](#)]
48. Ogasawara, M.; Matsunaga, T.; Takahashi, S.; Saiki, I.; Suzuki, H. Anti-invasive and metastatic activities of evodiamine. *Biol. Pharm. Bull.* **2002**, *25*, 1491–1493. [[CrossRef](#)] [[PubMed](#)]

49. Fei, X.F.; Wang, B.X.; Li, T.J.; Tashiro, S. i.; Minami, M.; Xing, D.J.; Ikejima, T. Evodiamine, a constituent of *Evodiae Fructus*, induces anti-proliferating effects in tumor cells. *Cancer Sci.* **2003**, *94*, 92–98. [[CrossRef](#)] [[PubMed](#)]
50. Zhang, Y.; Wu, L.J.; Tashiro, S.I.; Onodera, S.; Ikejima, T. Intracellular regulation of evodiamine-induced A375-S2 cell death. *Biol. Pharm. Bull.* **2003**, *26*, 1543–1547. [[CrossRef](#)] [[PubMed](#)]
51. Shyu, K.G.; Lin, S.; Lee, C.C.; Chen, E.; Lin, L.C.; Wang, B.W.; Tsai, S.C. Evodiamine inhibits in vitro angiogenesis: Implication for antitumorogenicity. *Life Sci.* **2006**, *78*, 2234–2243. [[CrossRef](#)] [[PubMed](#)]
52. Lee, T.J.; Kim, E.J.; Kim, S.; Jung, E.M.; Park, J.W.; Jeong, S.H.; Park, S.E.; Yoo, Y.H.; Kwon, T.K. Caspase-dependent and caspase-independent apoptosis induced by evodiamine in human leukemic U937 cells. *Mol. Cancer Ther.* **2006**, *5*, 2398–2407. [[CrossRef](#)] [[PubMed](#)]
53. Wang, C.; Li, S.; Wang, M.W. Evodiamine-induced human melanoma A375-S2 cell death was mediated by PI3K/Akt/caspase and Fas-L/NF- κ B signaling pathways and augmented by ubiquitin—Proteasome inhibition. *Toxicol. Vitro.* **2010**, *24*, 898–904. [[CrossRef](#)] [[PubMed](#)]
54. Yang, J.; Wu, L.J.; Tashino, S.I.; Onodera, S.; Ikejima, T. Reactive oxygen species and nitric oxide regulate mitochondria-dependent apoptosis and autophagy in evodiamine-treated human cervix carcinoma HeLa cells. *Free Radic. Res.* **2008**, *42*, 492–504. [[CrossRef](#)] [[PubMed](#)]
55. Tsai, H.P.; Lin, L.W.; Lai, Z.Y.; Wu, J.Y.; Chen, C.E.; Hwang, J.; Chen, C.S.; Lin, C.M. Immobilizing topoisomerase I on a surface plasmon resonance biosensor chip to screen for inhibitors. *J. Biomed. Sci.* **2010**, *17*, 49. [[CrossRef](#)] [[PubMed](#)]
56. Chan, A.; Chang, W.S.; Chen, L.M.; Lee, C.M.; Chen, C.E.; Lin, C.M.; Hwang, J.L. Evodiamine stabilizes topoisomerase I-DNA cleavable complex to inhibit topoisomerase I activity. *Molecules* **2009**, *14*, 1342–1352. [[CrossRef](#)] [[PubMed](#)]
57. Dong, G.; Sheng, C.; Wang, S.; Miao, Z.; Yao, J.; Zhang, W. Selection of evodiamine as a novel topoisomerase I inhibitor by structure-based virtual screening and hit optimization of evodiamine derivatives as antitumor agents. *J. Med. Chem.* **2010**, *53*, 7521–7531. [[CrossRef](#)] [[PubMed](#)]
58. Huang, Y.C.; Guh, J.H.; Teng, C.M. Induction of mitotic arrest and apoptosis by evodiamine in human leukemic T-lymphocytes. *Life Sci.* **2004**, *75*, 35–49. [[CrossRef](#)] [[PubMed](#)]
59. Yang, J.; Wu, L.J.; Tashino, S.I.; Onodera, S.; Ikejima, T. Critical roles of reactive oxygen species in mitochondrial permeability transition in mediating evodiamine-induced human melanoma A375-S2 cell apoptosis. *Free Radic. Res.* **2007**, *41*, 1099–1108. [[CrossRef](#)] [[PubMed](#)]
60. Lai, J.P.; He, X.W.; Jiang, Y.; Chen, F. Preparative separation and determination of matrine from the Chinese medicinal plant *Sophora flavescens* Ait by molecularly imprinted solid-phase extraction. *Anal. Bioanal. Chem.* **2003**, *375*, 264–269. [[CrossRef](#)] [[PubMed](#)]
61. Li, X.; Zhou, R.; Zheng, P.; Yan, L.; Wu, Y.; Xiao, X.; Dai, G. Cardioprotective effect of matrine on isoproterenol-induced cardiotoxicity in rats. *J. Pharm. Pharmacol.* **2010**, *62*, 514–520. [[CrossRef](#)] [[PubMed](#)]
62. Xing, Y.; Yan, F.; Liu, Y.; Liu, Y.; Zhao, Y. Matrine inhibits 3T3-L1 preadipocyte differentiation associated with suppression of ERK1/2 phosphorylation. *Bio. Chem. Bioph Res. Commun.* **2010**, *396*, 691–695. [[CrossRef](#)] [[PubMed](#)]
63. Zheng, J.; Zheng, P.; Zhou, X.; Yan, L.; Zhou, R.; Fu, X.Y.; Dai, G.D. Relaxant effects of matrine on aortic smooth muscles of guinea pigs. *Biomed. Environ. Sci.* **2009**, *22*, 327–332. [[CrossRef](#)]
64. Long, Y.; Lin, X.; Zeng, K.; Zhang, L. Efficacy of intramuscular matrine in the treatment of chronic hepatitis B. *Hepatobiliary Pancreat. Dis. Int.* **2004**, *3*, 69–72. [[PubMed](#)]
65. Yadav, V.; Krishnan, A.; Vohora, D. A systematic review on *Piper longum* L.: Bridging traditional knowledge and pharmacological evidence for future translational research. *J. Ethnopharmacol.* **2019**. [[CrossRef](#)] [[PubMed](#)]
66. Yixiang, H.; Shenghui, Z.; Jianbo, W.; Kang, Y.; Yu, Z.; Lihui, Y.; Laixi, B. Matrine induces apoptosis of human multiple myeloma cells via activation of the mitochondrial pathway. *Leuk. Lymphoma* **2010**, *51*, 1337–1346. [[CrossRef](#)] [[PubMed](#)]
67. Zhang, L.; Wang, T.; Wen, X.; Wei, Y.; Peng, X.; Li, H.; Wei, L. Effect of matrine on HeLa cell adhesion and migration. *Eur. J. Pharmacol.* **2007**, *563*, 69–76. [[CrossRef](#)] [[PubMed](#)]
68. Dai, Z.J.; Gao, J.; Ji, Z.Z.; Wang, X.J.; Ren, H.T.; Liu, X.X.; Wu, W.Y.; Kang, H.F.; Guan, H.T. Matrine induces apoptosis in gastric carcinoma cells via alteration of Fas/FasL and activation of caspase-3. *J. Ethnopharmacol.* **2009**, *123*, 91–96. [[CrossRef](#)] [[PubMed](#)]

69. Zhang, P.; Wang, Z.; Chong, T.; Ji, Z. Matrine inhibits proliferation and induces apoptosis of the androgen-independent prostate cancer cell line PC-3. *Mol. Med. Rep.* **2012**, *5*, 783–787. [[CrossRef](#)] [[PubMed](#)]
70. Liang, C.Z.; Zhang, J.K.; Shi, Z.; Liu, B.; Shen, C.Q.; Tao, H.M. Matrine induces caspase-dependent apoptosis in human osteosarcoma cells in vitro and in vivo through the upregulation of Bax and Fas/FasL and downregulation of Bcl-2. *Cancer Chemother. Pharmacol.* **2012**, *69*, 317–331. [[CrossRef](#)] [[PubMed](#)]
71. Liu, T.; Song, Y.; Chen, H.; Pan, S.; Sun, X. Matrine inhibits proliferation and induces apoptosis of pancreatic cancer cells in vitro and in vivo. *Biol. Pharm. Bull.* **2010**, *33*, 1740–1745. [[CrossRef](#)] [[PubMed](#)]
72. Zhang, Z.; Wang, X.; Wu, W.; Wang, J.; Wang, Y.; Wu, X.; Fei, X.; Li, S.; Zhang, J.; Dong, P. Effects of Matrine on Proliferation and Apoptosis in Gallbladder Carcinoma Cells (GBC-SD). *Phytother. Res.* **2012**, *26*, 932–937. [[CrossRef](#)] [[PubMed](#)]
73. Jiang, H.; Hou, C.; Zhang, S.; Xie, H.; Zhou, W.; Jin, Q.; Cheng, X.; Qian, R.; Zhang, X. Matrine upregulates the cell cycle protein E2F-1 and triggers apoptosis via the mitochondrial pathway in K562 cells. *Eur. J. Pharmacol.* **2007**, *559*, 98–108. [[CrossRef](#)] [[PubMed](#)]
74. Li, H.; Tan, G.; Jiang, X.; Qiao, H.; Pan, S.; Jiang, H.; Kanwar, J.R.; Sun, X. Therapeutic effects of matrine on primary and metastatic breast cancer. *Am. J. Chin. Med.* **2010**, *38*, 1115–1130. [[CrossRef](#)] [[PubMed](#)]
75. Ma, L.; Wen, S.; Zhan, Y.; He, Y.; Liu, X.; Jiang, J. Anticancer effects of the Chinese medicine matrine on murine hepatocellular carcinoma cells. *Planta Med.* **2008**, *74*, 245–251. [[CrossRef](#)] [[PubMed](#)]
76. Zhang, W.; Dai, B.T.; Xu, Y.H. Effects of matrine on invasion and metastasis of leukemia cell line Jurkat. *Chin. J. Integr. Tradit. West. Med.* **2008**, *28*, 907–911. [[CrossRef](#)] [[PubMed](#)]
77. Yu, P.; Liu, Q.; Liu, K.; Yagasaki, K.; Wu, E.; Zhang, G. Matrine suppresses breast cancer cell proliferation and invasion via VEGF-Akt-NF- κ B signaling. *Cytotechnology* **2009**, *59*, 219–229. [[CrossRef](#)] [[PubMed](#)]
78. Yu, H.B.; Zhang, H.F.; Li, D.Y.; Zhang, X.; Xue, H.Z.; Zhao, S.H. Matrine inhibits matrix metalloproteinase-9 expression and invasion of human hepatocellular carcinoma cells. *J. Asian Nat. Prod. Res.* **2011**, *13*, 242–250. [[CrossRef](#)] [[PubMed](#)]
79. Luo, C.; Zhong, H.J.; Zhu, L.M.; Wu, X.G.; Ying, J.E.; Wang, X.H.; Lü, W.X.; Xu, Q.; Zhu, Y.L.; Huang, J. Inhibition of matrine against gastric cancer cell line MNK45 growth and its anti-tumor mechanism. *Mol. Biol. Rep.* **2012**, *39*, 5459–5464. [[CrossRef](#)] [[PubMed](#)]
80. Szallasi, A. Piperine: Researchers discover new flavor in an ancient spice. *Trends Pharmacol. Sci.* **2005**, *26*, 437–439. [[CrossRef](#)] [[PubMed](#)]
81. Srinivasan, K. Black pepper and its pungent principle-piperine: A review of diverse physiological effects. *Crit. Rev. Food Sci.* **2007**, *47*, 735–748. [[CrossRef](#)] [[PubMed](#)]
82. Lee, S.A.; Hong, S.S.; Han, X.H.; Hwang, J.S.; Oh, G.J.; Lee, K.S.; Lee, M.K.; Hwang, B.Y.; Ro, J.S. Piperine from the fruits of *Piper longum* with inhibitory effect on monoamine oxidase and antidepressant-like activity. *Chem. Pharm. Bull.* **2005**, *53*, 832–835. [[CrossRef](#)] [[PubMed](#)]
83. Li, S.; Wang, C.; Wang, M.; Li, W.; Matsumoto, K.; Tang, Y. Antidepressant like effects of piperine in chronic mild stress treated mice and its possible mechanisms. *Life Sci.* **2007**, *80*, 1373–1381. [[CrossRef](#)] [[PubMed](#)]
84. Kakarala, M.; Brenner, D.E.; Korkaya, H.; Cheng, C.; Tazi, K.; Ginestier, C.; Liu, S.; Dontu, G.; Wicha, M.S. Targeting breast stem cells with the cancer preventive compounds curcumin and piperine. *Breast Cancer Res. Treat.* **2010**, *122*, 777–785. [[CrossRef](#)] [[PubMed](#)]
85. Lai, L.H.; Fu, Q.H.; Liu, Y.; Jiang, K.; Guo, Q.M.; Chen, Q.Y.; Yan, B.; Wang, Q.Q.; Shen, J.G. Piperine suppresses tumor growth and metastasis in vitro and in vivo in a 4T1 murine breast cancer model. *Acta Pharmacol. Sin.* **2012**, *33*, 523. [[CrossRef](#)] [[PubMed](#)]
86. Song, Q.; Qu, Y.; Zheng, H.; Zhang, G.; Lin, H.; Yang, J. Differentiation of erythroleukemia K562 cells induced by piperine. *Chin. J. Cancer* **2008**, *27*, 571–574.
87. Pradeep, C.; Kuttan, G. Effect of piperine on the inhibition of lung metastasis induced B16F-10 melanoma cells in mice. *Clin. Exp. Metastasis* **2002**, *19*, 703–708. [[CrossRef](#)] [[PubMed](#)]
88. Hwang, Y.P.; Yun, H.J.; Kim, H.G.; Han, E.H.; Choi, J.H.; Chung, Y.C.; Jeong, H.G. Suppression of phorbol-12-myristate-13-acetate-induced tumor cell invasion by piperine via the inhibition of PKC α /ERK1/2-dependent matrix metalloproteinase-9 expression. *Toxicol. Lett.* **2011**, *203*, 9–19. [[CrossRef](#)] [[PubMed](#)]
89. Pradeep, C.; Kuttan, G. Piperine is a potent inhibitor of nuclear factor- κ B (NF- κ B), c-Fos, CREB, ATF-2 and proinflammatory cytokine gene expression in B16F-10 melanoma cells. *Int. Immunopharmacol.* **2004**, *4*, 1795–1803. [[CrossRef](#)] [[PubMed](#)]

90. Bhardwaj, R.K.; Glaeser, H.; Becquemont, L.; Klotz, U.; Gupta, S.K.; Fromm, M.F. Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. *J. Pharmacol. Exp. Ther.* **2002**, *302*, 645–650. [[CrossRef](#)] [[PubMed](#)]
91. Li, S.; Lei, Y.; Jia, Y.; Li, N.; Wink, M.; Ma, Y. Piperine, a piperidine alkaloid from *Piper nigrum* re-sensitizes P-gp, MRP1 and BCRP dependent multidrug resistant cancer cells. *Phytomedicine* **2011**, *19*, 83–87. [[CrossRef](#)] [[PubMed](#)]
92. Makhov, P.; Golovine, K.; Canter, D.; Kutikov, A.; Simhan, J.; Corlew, M.M.; Uzzo, R.G.; Kolenko, V.M. Co-administration of piperine and docetaxel results in improved anti-tumor efficacy via inhibition of CYP3A4 activity. *Prostate* **2012**, *72*, 661–667. [[CrossRef](#)] [[PubMed](#)]
93. Wang, Y.H.; Morris-Natschke, S.L.; Yang, J.; Niu, H.M.; Long, C.L.; Lee, K.H. Anticancer principles from medicinal Piper plants. *J. Tradit. Complement. Med.* **2014**, *4*, 8–16. [[CrossRef](#)] [[PubMed](#)]
94. Mahady, G.B.; Beecher, C. Quercetin-induced benzophenanthridine alkaloid production in suspension cell cultures of *Sanguinaria canadensis*. *Planta Med.* **1994**, *60*, 553–557. [[CrossRef](#)] [[PubMed](#)]
95. Vavrečková, C.; Gawlik, I.; Müller, K. Benzophenanthridine alkaloids of *Chelidonium majus*; I. Inhibition of 5- and 12-lipoxygenase by a non-redox mechanism. *Planta. Med.* **1996**, *62*, 397–401. [[CrossRef](#)] [[PubMed](#)]
96. Lenfeld, J.; Kroutil, M.; Maršálek, E.; Slavik, J.; Preininger, V.; Šimánek, V. Antiinflammatory activity of quaternary benzophenanthridine alkaloids from *Chelidonium majus*. *Planta Med.* **1981**, *43*, 161–165. [[CrossRef](#)] [[PubMed](#)]
97. Beuria, T.K.; Santra, M.K.; Panda, D. Sanguinarine blocks cytokinesis in bacteria by inhibiting FtsZ assembly and bundling. *Biochemistry* **2005**, *44*, 16584–16593. [[CrossRef](#)] [[PubMed](#)]
98. Jeng, J.H.; Wu, H.L.; Lin, B.R.; Lan, W.H.; Chang, H.H.; Ho, Y.S.; Lee, P.H.; Wang, Y.J.; Wang, J.S.; Chen, Y.J. Antiplatelet effect of sanguinarine is correlated to calcium mobilization, thromboxane and cAMP production. *Atherosclerosis* **2007**, *191*, 250–258. [[CrossRef](#)] [[PubMed](#)]
99. Ahsan, H.; Reagan-Shaw, S.; Breur, J.; Ahmad, N. Sanguinarine induces apoptosis of human pancreatic carcinoma AsPC-1 and BxPC-3 cells via modulations in Bcl-2 family proteins. *Cancer Lett.* **2007**, *249*, 198–208. [[CrossRef](#)] [[PubMed](#)]
100. Chang, M.C.; Chan, C.P.; Wang, Y.J.; Lee, P.H.; Chen, L.I.; Tsai, Y.L.; Lin, B.R.; Wang, Y.L.; Jeng, J.H. Induction of necrosis and apoptosis to KB cancer cells by sanguinarine is associated with reactive oxygen species production and mitochondrial membrane depolarization. *Toxicol. Appl. Pharm.* **2007**, *218*, 143–151. [[CrossRef](#)] [[PubMed](#)]
101. Hussain, A.R.; Al-Jomah, N.A.; Siraj, A.K.; Manogaran, P.; Al-Hussein, K.; Abubaker, J.; Plataniias, L.C.; Al-Kuraya, K.S.; Uddin, S. Sanguinarine-dependent induction of apoptosis in primary effusion lymphoma cells. *Cancer. Res.* **2007**, *67*, 3888–3897. [[CrossRef](#)] [[PubMed](#)]
102. Kim, S.; Lee, T.J.; Leem, J.; Choi, K.S.; Park, J.W.; Kwon, T.K. Sanguinarine-induced apoptosis: Generation of ROS, down-regulation of Bcl-2, c-FLIP, and synergy with TRAIL. *J. Cell Biochem.* **2008**, *104*, 895–907. [[CrossRef](#)] [[PubMed](#)]
103. Adhami, V.M.; Aziz, M.H.; Mukhtar, H.; Ahmad, N. Activation of prodeath Bcl-2 family proteins and mitochondrial apoptosis pathway by sanguinarine in immortalized human HaCaT keratinocytes. *Clin. Cancer Res.* **2003**, *9*, 3176–3182. [[PubMed](#)]
104. Adhami, V.M.; Aziz, M.H.; Reagan-Shaw, S.R.; Nihal, M.; Mukhtar, H.; Ahmad, N. Sanguinarine causes cell cycle blockade and apoptosis of human prostate carcinoma cells via modulation of cyclin kinase inhibitor-cyclin-cyclin-dependent kinase machinery. *Mol. Cancer Ther.* **2004**, *3*, 933–940. [[PubMed](#)]
105. Weerasinghe, P.; Hallock, S.; Tang, S.C.; Trump, B.; Liepins, A. Sanguinarine overcomes P-glycoprotein-mediated multidrug-resistance via induction of apoptosis and oncosis in CEM-VLB 1000 cells. *Exp. Toxicol. Pathol.* **2006**, *58*, 21–30. [[CrossRef](#)] [[PubMed](#)]
106. De Stefano, I.; Raspaglio, G.; Zannoni, G.F.; Travaglia, D.; Prisco, M.G.; Mosca, M.; Ferlini, C.; Scambia, G.; Gallo, D. Antiproliferative and antiangiogenic effects of the benzophenanthridine alkaloid sanguinarine in melanoma. *Biochem. Pharmacol.* **2009**, *78*, 1374–1381. [[CrossRef](#)] [[PubMed](#)]
107. Choi, Y.H.; Choi, W.Y.; Hong, S.H.; Kim, S.O.; Kim, G.Y.; Lee, W.H.; Yoo, Y.H. Anti-invasive activity of sanguinarine through modulation of tight junctions and matrix metalloproteinase activities in MDA-MB-231 human breast carcinoma cells. *Chem. Biol. Interact.* **2009**, *179*, 185–191. [[CrossRef](#)] [[PubMed](#)]

108. Ahsan, H.; Reagan-Shaw, S.; Eggert, D.M.; Tan, T.C.; Afaq, F.; Mukhtar, H.; Ahmad, N. Protective effect of sanguinarine on ultraviolet B-mediated damages in SKH-1 hairless mouse skin: Implications for prevention of skin cancer. *Photochem. Photobiol.* **2007**, *83*, 986–993. [[CrossRef](#)] [[PubMed](#)]
109. Jang, B.C.; Park, J.G.; Song, D.K.; Baek, W.K.; Yoo, S.K.; Jung, K.H.; Park, G.Y.; Lee, T.Y.; Suh, S.I. Sanguinarine induces apoptosis in A549 human lung cancer cells primarily via cellular glutathione depletion. *Toxicol. Vitr.* **2009**, *23*, 281–287. [[CrossRef](#)] [[PubMed](#)]
110. Cai, Y.J.; Lu, J.J.; Zhu, H.; Xie, H.; Huang, M.; Lin, L.P.; Zhang, X.W.; Ding, J. Salvicine triggers DNA double-strand breaks and apoptosis by GSH-depletion-driven H₂O₂ generation and topoisomerase II inhibition. *Free Radic. Bio. Med.* **2008**, *45*, 627–635. [[CrossRef](#)] [[PubMed](#)]
111. Cai, Y.; Lu, J.; Miao, Z.; Lin, L.; Ding, J. Reactive oxygen species contribute to cell killing and P-glycoprotein downregulation by salvicine in multidrug resistant K562/A02 cells. *Cancer Biol. Ther.* **2007**, *6*, 1794–1799. [[CrossRef](#)] [[PubMed](#)]
112. Vogt, A.; Tamewitz, A.; Skoko, J.; Sikorski, R.P.; Giuliano, K.A.; Lazo, J.S. The benzo [c] phenanthridine alkaloid, sanguinarine, is a selective, cell-active inhibitor of mitogen-activated protein kinase phosphatase-1. *J. Biol. Chem.* **2005**, *280*, 19078–19086. [[CrossRef](#)] [[PubMed](#)]
113. Lopus, M.; Panda, D. The benzophenanthridine alkaloid sanguinarine perturbs microtubule assembly dynamics through tubulin binding: A possible mechanism for its antiproliferative activity. *J. FEBS* **2006**, *273*, 2139–2150. [[CrossRef](#)] [[PubMed](#)]
114. Chaturvedi, M.M.; Kumar, A.; Darnay, B.G.; Chainy, G.B.; Agarwal, S.; Aggarwal, B.B. Sanguinarine (pseudocheleerythrine) is a potent inhibitor of NF- κ B activation, I κ B α phosphorylation, and degradation. *J. Biol. Chem.* **1997**, *272*, 30129–30134. [[CrossRef](#)] [[PubMed](#)]
115. Sun, M.; Liu, C.; Nadiminty, N.; Lou, W.; Zhu, Y.; Yang, J.; Evans, C.P.; Zhou, Q.; Gao, A.C. Inhibition of Stat3 activation by sanguinarine suppresses prostate cancer cell growth and invasion. *Prostate* **2012**, *72*, 82–89. [[CrossRef](#)] [[PubMed](#)]
116. Li, D.G.; Wang, Z.R.; Lu, H.M. Pharmacology of tetrandrine and its therapeutic use in digestive diseases. *World J. Gastroenterol.* **2001**, *7*, 627. [[CrossRef](#)] [[PubMed](#)]
117. Ng, L.T.; Chiang, L.C.; Lin, Y.T.; Lin, C.C. Antiproliferative and apoptotic effects of tetrandrine on different human hepatoma cell lines. *Am. J. Chin. Med.* **2006**, *34*, 125–135. [[CrossRef](#)] [[PubMed](#)]
118. Meng, L.H.; Zhang, H.; Hayward, L.; Takemura, H.; Shao, R.G.; Pommier, Y. Tetrandrine induces early G1 arrest in human colon carcinoma cells by down-regulating the activity and inducing the degradation of G1-S-specific cyclin-dependent kinases and by inducing p53 and p21Cip1. *Cancer Res.* **2004**, *64*, 9086–9092. [[CrossRef](#)] [[PubMed](#)]
119. Wu, J.M.; Chen, Y.; Chen, J.C.; Lin, T.Y.; Tseng, S.H. Tetrandrine induces apoptosis and growth suppression of colon cancer cells in mice. *Cancer Lett.* **2010**, *287*, 187–195. [[CrossRef](#)] [[PubMed](#)]
120. Chen, Y.; Chen, J.C.; Tseng, S.H. Tetrandrine suppresses tumor growth and angiogenesis of gliomas in rats. *Int. J. Cancer* **2009**, *124*, 2260–2269. [[CrossRef](#)] [[PubMed](#)]
121. Chang, K.H.; Liao, H.F.; Chang, H.H.; Chen, Y.Y.; Yu, M.C.; Chou, C.J.; Chen, Y.J. Inhibitory effect of tetrandrine on pulmonary metastases in CT26 colorectal adenocarcinoma-bearing BALB/c mice. *Am. J. Chin. Med.* **2004**, *32*, 863–872. [[CrossRef](#)] [[PubMed](#)]
122. Zhang, Y.; Wang, C.; Wang, H.; Wang, K.; Du, Y.; Zhang, J. Combination of Tetrandrine with cisplatin enhances cytotoxicity through growth suppression and apoptosis in ovarian cancer in vitro and in vivo. *Cancer Lett.* **2011**, *304*, 21–32. [[CrossRef](#)] [[PubMed](#)]
123. Wei, J.; Liu, B.; Wang, L.; Qian, X.; Ding, Y.; Yu, L. Synergistic interaction between tetrandrine and chemotherapeutic agents and influence of tetrandrine on chemotherapeutic agent-associated genes in human gastric cancer cell lines. *Cancer Chemother. Pharmacol.* **2007**, *60*, 703–711. [[CrossRef](#)] [[PubMed](#)]
124. Iorns, E.; Lord, C.J.; Ashworth, A. Parallel RNAi and compound screens identify the PDK1 pathway as a target for tamoxifen sensitization. *Biochem. J.* **2009**, *417*, 361–371. [[CrossRef](#)] [[PubMed](#)]
125. Li, C.X.; Huan Ren, K.; He, H.W.; Shao, R.G. Involvement of PI3K/AKT/GSK3 β pathway in tetrandrine-induced G1 arrest and apoptosis. *Cancer Biol. Ther.* **2008**, *7*, 1073–1078.
126. Oh, S.H.; Lee, B.H. Induction of apoptosis in human hepatoblastoma cells by tetrandrine via caspase-dependent Bid cleavage and cytochrome c release. *Biochem. Pharmacol.* **2003**, *66*, 725–731. [[CrossRef](#)]

127. Cho, H.S.; Chang, S.H.; Chung, Y.S.; Shin, J.Y.; Park, S.J.; Lee, E.S.; Hwang, S.K.; Kwon, J.T.; Tehrani, A.M.; Woo, M. Synergistic effect of ERK inhibition on tetrandrine-induced apoptosis in A549 human lung carcinoma cells. *J. Vet. Sci.* **2009**, *10*, 23–28. [[CrossRef](#)] [[PubMed](#)]
128. Kittakoop, P.; Mahidol, C.; Ruchirawat, S. Alkaloids as important scaffolds in therapeutic drugs for the treatments of cancer, tuberculosis, and smoking cessation. *Curr. Top. Med. Chem.* **2014**, *14*, 239–252. [[CrossRef](#)] [[PubMed](#)]
129. Sobhani, A.M.; Ebrahimi, S.A.; Mahmoudian, M. An in vitro evaluation of human DNA topoisomerase I inhibition by *Peganum harmala* L. seeds extract and its beta-carboline alkaloids. *J. Pharm. Pharm. Sci.* **2002**, *5*, 19–23. [[PubMed](#)]
130. Heinrich, M.; Barnes, J.; Gibbons, S.; Williamson, E. *A Text Book of Fundamentals of Pharmacognosy and Phytotherapy*; Elsevier: New York, NY, USA, 2004; Volume 8, pp. 60–105.
131. Hesse, M. *Alkaloids: Nature's Curse or Blessing*; John Wiley & Sons: zürich, Switzerland, 2002.
132. Evans, W.C. *Trease and Evans' Pharmacognosy E-Book*; Elsevier Health Sciences: Edinburgh, UK, 2009.
133. Robbers, J.E.; Speedie, M.K.; Tyler, V.E. *Pharmacognosy and Pharmacobiotechnology*; Williams & Wilkins: Baltimore, MD, USA, 1996.
134. Hraiech, S.; Brégeon, F.; Brunel, J.M.; Rolain, J.-M.; Lepidi, H.; Andrieu, V.; Raoult, D.; Papazian, L.; Roch, A. Antibacterial efficacy of inhaled squalamine in a rat model of chronic *Pseudomonas aeruginosa* pneumonia. *J. Antimicrob. Chemother.* **2012**, *67*, 2452–2458. [[CrossRef](#)] [[PubMed](#)]
135. Bogatcheva, E.; Hanrahan, C.; Nikonenko, B.; De los Santos, G.; Reddy, V.; Chen, P.; Barbosa, F.; Einck, L.; Nacy, C.; Protopopova, M. Identification of SQ609 as a lead compound from a library of dipiperidines. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5353–5357. [[CrossRef](#)] [[PubMed](#)]
136. Parhi, A.; Kelley, C.; Kaul, M.; Pilch, D.S.; LaVoie, E.J. Antibacterial activity of substituted 5-methylbenzo [c] phenanthridinium derivatives. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7080–7083. [[CrossRef](#)] [[PubMed](#)]
137. Chakraborty, A.; Chowdhury, B.; Bhattacharyya, P. Clausenol and clausenine—Two carbazole alkaloids from *Clausena anisata*. *Phytochemistry* **1995**, *40*, 295–298. [[CrossRef](#)]
138. Nakahara, K.; Trakoontivakorn, G.; Alzoreky, N.S.; Ono, H.; Onishi-Kameyama, M.; Yoshida, M. Antimutagenicity of some edible Thai plants, and a bioactive carbazole alkaloid, mahanine, isolated from *Micromelum minutum*. *J. Agric. Food Chem.* **2002**, *50*, 4796–4802. [[CrossRef](#)] [[PubMed](#)]
139. Kim, H.; Lantvit, D.; Hwang, C.H.; Kroll, D.J.; Swanson, S.M.; Franzblau, S.G.; Orjala, J. Indole alkaloids from two cultured cyanobacteria, *Westiellopsis* sp. and *Fischerella muscicola*. *Bioorgan. Med. Chem.* **2012**, *20*, 5290–5295. [[CrossRef](#)] [[PubMed](#)]
140. Samoylenko, V.; Ashfaq, M.K.; Jacob, M.R.; Tekwani, B.L.; Khan, S.I.; Manly, S.P.; Joshi, V.C.; Walker, L.A.; Muhammad, I. Indolizidine, antiinfective and antiparasitic compounds from *Prosopis glandulosa* Torr. var. *glandulosa*. *Planta med.* **2009**, *75*, 48. [[CrossRef](#)]
141. Iwasa, K.; Moriyasu, M.; Tachibana, Y.; Kim, H.S.; Wataya, Y.; Wiegrebe, W.; Bastow, K.F.; Cosentino, L.M.; Kozuka, M.; Lee, K.H. Simple isoquinoline and benzyloisoquinoline alkaloids as potential antimicrobial, antimalarial, cytotoxic, and anti-HIV agents. *Bioorgan. Med. Chem.* **2001**, *9*, 2871–2884. [[CrossRef](#)]
142. Xie, Q.; Johnson, B.R.; Wenckus, C.S.; Fayad, M.I.; Wu, C.D. Efficacy of berberine, an antimicrobial plant alkaloid, as an endodontic irrigant against a mixed-culture biofilm in an in vitro tooth model. *J. Endod.* **2012**, *38*, 1114–1117. [[CrossRef](#)] [[PubMed](#)]
143. Obiang-Obounou, B.W.; Kang, O.H.; Choi, J.G.; Keum, J.H.; Kim, S.B.; Mun, S.H.; Shin, D.W.; Kim, K.W.; Park, C.B.; Kim, Y.G. The mechanism of action of sanguinarine against methicillin-resistant *Staphylococcus aureus*. *J. Toxicol. Sci.* **2011**, *36*, 277–283. [[CrossRef](#)] [[PubMed](#)]
144. Li, H.L.; Zhang, W.D.; Zhang, C.; Liu, R.H.; Wang, X.W.; Wang, X.L.; Zhu, J.B.; Chen, C.L. Bioavailability and pharmacokinetics of four active alkaloids of traditional Chinese medicine Yanhuanglian in rats following intravenous and oral administration. *J. Pharma. Biomed.* **2006**, *41*, 1342–1346. [[CrossRef](#)] [[PubMed](#)]
145. Wang, X.X.; Zan, K.; Shi, S.P.; Zeng, K.W.; Jiang, Y.; Guan, Y.; Xiao, C.L.; Gao, H.Y.; Wu, L.J.; Tu, P.F. Quinolone alkaloids with antibacterial and cytotoxic activities from the fruits of *Evodia rutaecarpa*. *Fitoterapia* **2013**, *89*, 1–7. [[CrossRef](#)] [[PubMed](#)]
146. Kuete, V.; Wansi, J.; Mbaveng, A.; Sop, M.K.; Tadjong, A.T.; Beng, V.P.; Etoa, F.X.; Wandji, J.; Meyer, J.M.; Lall, N. Antimicrobial activity of the methanolic extract and compounds from *Teclea afzelii* (Rutaceae). *S. Afr. J. Bot.* **2008**, *74*, 572–576. [[CrossRef](#)]

147. Dekker, K.A.; Inagaki, T.; Gootz, T.D.; Huang, L.H.; Kojima, Y.; Kohlbrenner, W.E.; Matsunaga, Y.; McGuirk, P.R.; Nomura, E.; Sakakibara, T. New Quinolone Compounds from *Pseudonocardia* sp. with Selective and Potent Anti-*Helicobacter pylori* Activity. *Jpn. J. Antibiot.* **1998**, *51*, 145–152. [[CrossRef](#)] [[PubMed](#)]
148. Kubota, T.; Iwai, T.; Takahashi-Nakaguchi, A.; Fromont, J.; Gonoi, T.; Kobayashi, J.I. Agelasines O–U, new diterpene alkaloids with a 9-N-methyladenine unit from a marine sponge *Agelas* sp. *Tetrahedron* **2012**, *68*, 9738–9744. [[CrossRef](#)]
149. Moore, K.S.; Wehrli, S.; Roder, H.; Rogers, M.; Forrest, J.N.; McCrimmon, D.; Zasloff, M. Squalamine: An aminosterol antibiotic from the shark. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 1354–1358. [[CrossRef](#)] [[PubMed](#)]
150. Calcul, L.; Longeon, A.; Al Mourabit, A.; Guyot, M.; Bourguet-Kondracki, M.L. Novel alkaloids of the aaptamine class from an Indonesian marine sponge of the genus *Xestospongia*. *Tetrahedron* **2003**, *59*, 6539–6544. [[CrossRef](#)]
151. Alhanout, K.; Malesinki, S.; Vidal, N.; Peyrot, V.; Rolain, J.M.; Brunel, J.M. New insights into the antibacterial mechanism of action of squalamine. *J. Antimicrob. Chemother.* **2010**, *65*, 1688–1693. [[CrossRef](#)] [[PubMed](#)]
152. Rao, K.N.; Venkatachalam, S. Inhibition of dihydrofolate reductase and cell growth activity by the phenanthroindolizidine alkaloids pergularinine and tylophorinidine: The in vitro cytotoxicity of these plant alkaloids and their potential as antimicrobial and anticancer agents. *Toxicol. Vitro.* **2000**, *14*, 53–59. [[CrossRef](#)]
153. Casu, L.; Cottiglia, F.; Leonti, M.; De Logu, A.; Agus, E.; Tse-Dinh, Y.-C.; Lombardo, V.; Sissi, C. Ungeremine effectively targets mammalian as well as bacterial type I and type II topoisomerases. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7041–7044. [[CrossRef](#)] [[PubMed](#)]
154. Domadia, P.N.; Bhunia, A.; Sivaraman, J.; Swarup, S.; Dasgupta, D. Berberine targets assembly of *Escherichia coli* cell division protein FtsZ. *Biochemistry* **2008**, *47*, 3225–3234. [[CrossRef](#)] [[PubMed](#)]
155. Boberek, J.M.; Stach, J.; Good, L. Genetic evidence for inhibition of bacterial division protein FtsZ by berberine. *PLoS ONE* **2010**, *5*, e13745. [[CrossRef](#)] [[PubMed](#)]
156. Heeb, S.; Fletcher, M.P.; Chhabra, S.R.; Diggle, S.P.; Williams, P.; Cámara, M. Quinolones: From antibiotics to autoinducers. *FEMS Microbiol. Rev.* **2011**, *35*, 247–274. [[CrossRef](#)] [[PubMed](#)]
157. Tominaga, K.; Higuchi, K.; Hamasaki, N.; Hamaguchi, M.; Takashima, T.; Tanigawa, T.; Watanabe, T.; Fujiwara, Y.; Tezuka, Y.; Nagaoka, T. In vivo action of novel alkyl methyl quinolone alkaloids against *Helicobacter pylori*. *J. Antimicrob. Chemother.* **2002**, *50*, 547–552. [[CrossRef](#)] [[PubMed](#)]
158. Arai, M.; Yamano, Y.; Setiawan, A.; Kobayashi, M. Identification of the Target Protein of Agelasine D, a Marine Sponge Diterpene Alkaloid, as an Anti-dormant Mycobacterial Substance. *ChemBioChem* **2014**, *15*, 117–123. [[CrossRef](#)] [[PubMed](#)]
159. Salmi, C.; Loncle, C.; Vidal, N.; Letourneux, Y.; Fantini, J.; Maresca, M.; Taïeb, N.; Pagès, J.M.; Brunel, J.M. Squalamine: An appropriate strategy against the emergence of multidrug resistant gram-negative bacteria? *PLoS ONE* **2008**, *3*, e2765. [[CrossRef](#)] [[PubMed](#)]
160. Patil, P.J.; Ghosh, J.S. Antimicrobial activity of *Catharanthus roseus*—A detailed study. *Br. J. Pharmacol. Toxicol.* **2010**, *1*, 40–44.
161. Hallock, Y.F.; Manfredi, K.P.; Dai, J.R.; Cardellina, J.H.; Gulakowski, R.J.; McMahon, J.B.; Schäffer, M.; Stahl, M.; Gulden, K.P.; Bringmann, G. Michellamines D–F, new HIV-inhibitory dimeric naphthylisoquinoline alkaloids, and korupensamine E, a new antimalarial monomer, from *Ancistrocladus korupensis*. *J. Nat. Prod.* **1997**, *60*, 677–683. [[CrossRef](#)] [[PubMed](#)]
162. Song, B.; Yang, S.; Jin, L.H.; Bhadury, P.S. *Environment-Friendly Antiviral Agents for Plants*; Springer Science & Business Media: Guizhou, China, 2011.
163. Sasidharan, S.; Chen, Y.; Saravanan, D.; Sundram, K.; Latha, L.Y. Extraction, isolation and characterization of bioactive compounds from plants' extracts. *Afr. J. Tradit. Complement. Altern. Med.* **2011**, *8*, 1–10. [[CrossRef](#)] [[PubMed](#)]
164. Watson, A.A.; Fleet, G.W.; Asano, N.; Molyneux, R.J.; Nash, R.J. Polyhydroxylated alkaloids—Natural occurrence and therapeutic applications. *Phytochemistry* **2001**, *56*, 265295. [[CrossRef](#)]
165. Duan, H.; Takaishi, Y.; Imakura, Y.; Jia, Y.; Li, D.; Cosentino, L.M.; Lee, K.H. Sesquiterpene Alkaloids from *Tripterygium hypoglaucum* and *Tripterygium wilfordii*: A New Class of Potent Anti-HIV Agents. *J. Nat. Prod.* **2000**, *63*, 357–361. [[CrossRef](#)] [[PubMed](#)]
166. Rahman, M.M.; Gray, A.I. Antimicrobial constituents from the stem bark of *Feronia limonia*. *Phytochemistry* **2002**, *59*, 73–77. [[CrossRef](#)]

167. Tabarrini, O.; Manfroni, G.; Fravolini, A.; Cecchetti, V.; Sabatini, S.; De Clercq, E.; Rozenski, J.; Canard, B.; Dutartre, H.; Paeshuysse, J. Synthesis and anti-BVDV activity of acridones as new potential antiviral agents. *J. Med. Chem.* **2006**, *49*, 2621–2627. [[CrossRef](#)] [[PubMed](#)]
168. Ito, C.; Itoigawa, M.; Sato, A.; Hasan, C.M.; Rashid, M.A.; Tokuda, H.; Mukainaka, T.; Nishino, H.; Furukawa, H. Chemical Constituents of Glycosmia a rborea: Three New Carbazole Alkaloids and Their Biological Activity. *J. Nat. Prod.* **2004**, *67*, 1488–1491. [[CrossRef](#)] [[PubMed](#)]
169. Manske, R.H.F.; Holmes, H.L. *The Alkaloids: Chemistry and Physiology*; Elsevier: New York, NY, USA, 2014.
170. Ududua, U.O.; Monanu, M.O.; Chuku, L.C. Proximate Analysis and Phytochemical Profile of *Brachystegia eurycoma* Leaves. *Asian J. Res. Biochem.* **2019**, *4*, 1–11. [[CrossRef](#)]
171. Petrov, N.M. Antiviral Activity of Plant Extract from *Tanacetum Vulgare* Against Cucumber Mosaic Virus and Potato Virus Y. *J. Biomed Biotechnol.* **2016**, *5*, 189–194.
172. Rex, J.H.; Rinaldi, M.; Pfaller, M. Resistance of *Candida* species to fluconazole. *Antimicrob. Agents. Chemother.* **1995**, *39*, 1. [[CrossRef](#)] [[PubMed](#)]
173. Borris, R.P. Natural products research: Perspectives from a major pharmaceutical company. *J. Ethnopharmacol.* **1996**, *51*, 29–38. [[CrossRef](#)]
174. Lewis, W.H.; Elvin-Lewis, M.P. Medicinal plants as sources of new therapeutics. *Ann. Mo. Bot. Gard.* **1995**, *82*, 16–24. [[CrossRef](#)]
175. Anaissie, E.; Bodey, G.; Rinaldi, M. Emerging fungal pathogens. *Eur. J. Clin. Microbiol. Infect. Dis.* **1989**, *8*, 323–330. [[CrossRef](#)] [[PubMed](#)]
176. Wey, S.B.; Mori, M.; Pfaller, M.A.; Woolson, R.F.; Wenzel, R.P. Hospital-acquired candidemia: The attributable mortality and excess length of stay. *Arch. Intern. Med.* **1988**, *148*, 2642–2645. [[CrossRef](#)] [[PubMed](#)]
177. Beck-Sague, C.; Banerjee, S.; Jarvis, W.R. Infectious diseases and mortality among US nursing home residents. *Am. J. Public Health* **1993**, *83*, 1739–1742. [[CrossRef](#)] [[PubMed](#)]
178. Schultes, R.E. Plants and plant constituents as mind-altering agents throughout history. In *Stimulants*; Springer: Boston, MA, USA, 1978; pp. 219–241.
179. Küçükosmanoğlu Bahçeevli, A.; Kurucu, S.; Kolak, U.; Topçu, G.; Adou, E.; Kingston, D.G. Alkaloids and Aromatics of *Cyathobasis f rutilculosa* (Bunge) Aellen. *J. Nat. Prod.* **2005**, *68*, 956–958. [[CrossRef](#)] [[PubMed](#)]
180. Ferheen, S.; Ahmed, E.; Afza, N.; Malik, A.; Shah, M.R.; Nawaz, S.A.; Choudhary, M.I. Haloxylinines A and B, antifungal and cholinesterase inhibiting piperidine alkaloids from *Haloxylon salicornicum*. *Chem. Pharm. Bull.* **2005**, *53*, 570–572. [[CrossRef](#)] [[PubMed](#)]
181. Singh, N.; Azmi, S.; Maurya, S.; Singh, U.; Jha, R.; Pandey, V. Two plant alkaloids isolated from *Corydalis longipes* as potential antifungal agents. *Folia Microbiol.* **2003**, *48*, 605–609. [[CrossRef](#)] [[PubMed](#)]
182. Jung, H.J.; Sung, W.S.; Yeo, S.H.; Kim, H.S.; Lee, I.S.; Woo, E.R.; Lee, D.G. Antifungal effect of amentoflavone derived from *Selaginella tamariscina*. *Arch. Pharm. Res.* **2006**, *29*, 746. [[CrossRef](#)] [[PubMed](#)]
183. Morteza-Semnani, K.; Amin, G.; Shidfar, M.; Hadizadeh, H.; Shafiee, A. Antifungal activity of the methanolic extract and alkaloids of *Glaucium oxylobum*. *Fitoterapia* **2003**, *74*, 493–496. [[CrossRef](#)]
184. Thouvenel, C.; Gantier, J.C.; Duret, P.; Fourneau, C.; Hocquemiller, R.; Ferreira, M.E.; de Arias, A.R.; Fournet, A. Antifungal compounds from *Zanthoxylum chiloperone* var. *angustifolium*. *Phytother. Res.* **2003**, *17*, 678–680. [[CrossRef](#)] [[PubMed](#)]
185. Singh, U.; Sarma, B.; Mishra, P.; Ray, A. Antifungal activity of venenatine, an indole alkaloid isolated from *Alstonia venenata*. *Folia Microbiol.* **2000**, *45*, 173. [[CrossRef](#)] [[PubMed](#)]
186. Balls, A.; Hale, W.; Harris, T. A crystalline protein obtained from a lipoprotein of wheat flour. *Cereal Chem.* **1942**, *19*, 279–288.
187. Liu, S.; Oguntimein, B.; Hufford, C.; Clark, A. 3-Methoxysampangine, a novel antifungal copyrine alkaloid from *Cleistopholis patens*. *Antimicrob. Agents Chemother.* **1990**, *34*, 529–533. [[CrossRef](#)] [[PubMed](#)]
188. Emile, A.; Waikedre, J.; Herrenknecht, C.; Fourneau, C.; Gantier, J.C.; Hnawia, E.; Cabalion, P.; Hocquemiller, R.; Fournet, A. Bioassay-guided isolation of antifungal alkaloids from *Melochia odorata*. *Phytother. Res.* **2007**, *21*, 398–400. [[CrossRef](#)] [[PubMed](#)]
189. Cantrell, C.; Schrader, K.; Mamonov, L.; Sitpaeva, G.; Kustova, T.; Dunbar, C.; Wedge, D. Isolation and identification of antifungal and antialgal alkaloids from *Haplophyllum sieversii*. *J. Agric. Food Chem.* **2005**, *53*, 7741–7748. [[CrossRef](#)] [[PubMed](#)]

190. Salehi, B.; Sharopov, F.; Boyunegmez Tumer, T.; Ozleyen, A.; Rodríguez-Pérez, C.; M Ezzat, S.; Azzini, E.; Hosseinabadi, T.; Butnariu, M.; Sarac, I. Symphytum Species: A Comprehensive Review on Chemical Composition, Food Applications and Phytopharmacology. *Molecules* **2019**, *24*, 2272. [[CrossRef](#)] [[PubMed](#)]



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