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REVIEW

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Antibacterial activity of medicinal plants and their role in wound healing

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Abstract

Background The study of plant-based medications, or phytomedicine, involves a wide spectrum of biological activities. Due to the existence of secondary metabolites, herbal medicine has been used and practiced throughout history for the treatment of both acute and chronic conditions. Over the past century or so, numerous novel compounds with medicinal potential have been derived from plants. In the age of growing super infections and the emergence of resistant strains, natural medicines are inspiring optimism.

Main body of the abstract The review discusses the role of herbal medicine as antibacterial agents and their use in wound care and management of wounds and the critical role of secondary metabolites of herbal plants in fighting bacterial infections. Some medicinal plants such as St. John's wort (SJW) (*Hypericum perforatum*), Rosemary (*Rosmarinus officinalis*), Ginger (*Zingiber officinale*), and nopal cactus (*Opuntia ficusindica* (*L.*)) also possess wide range of biological activities and can give a synergistic effect if combined with antibiotics. In addition, natural biopolymers play an important role in the management of wounds as well as the physiological processes of the skin (hemostasis, inflammation, proliferation, and remodelling).

Method A narrative review of papers relevant to the use of phytomedicine in treating infections was conducted by using electronic databases PubMed, CrossREF, and Google Scholar.

Short conclusion Phytomedicine is one of the top options for the treatment of chronic illnesses for millions of people around the world. To learn about the bioactive components of medicinal plants, their medical benefits, and their synergistic or additive effects to enhance the action of medications, substantial new studies are still needed.

Keywords Phytomedicine, Secondary metabolites, Pathogens, Antibacterial

Highlights

- Phytomedicine involves a wide spectrum of biological activities.
- Bioactive compounds extracted from plants are used for the treatment of both acute and chronic conditions.
- Natural plant & secondary metabolites play a significant role in the treatment of bacterial infections.
- Natural biopolymers are used in wound care and restoring physiological processes of the skin.
- Substantial new studies are needed to learn about bioactive components medical benefits, and their synergistic or additive effects.

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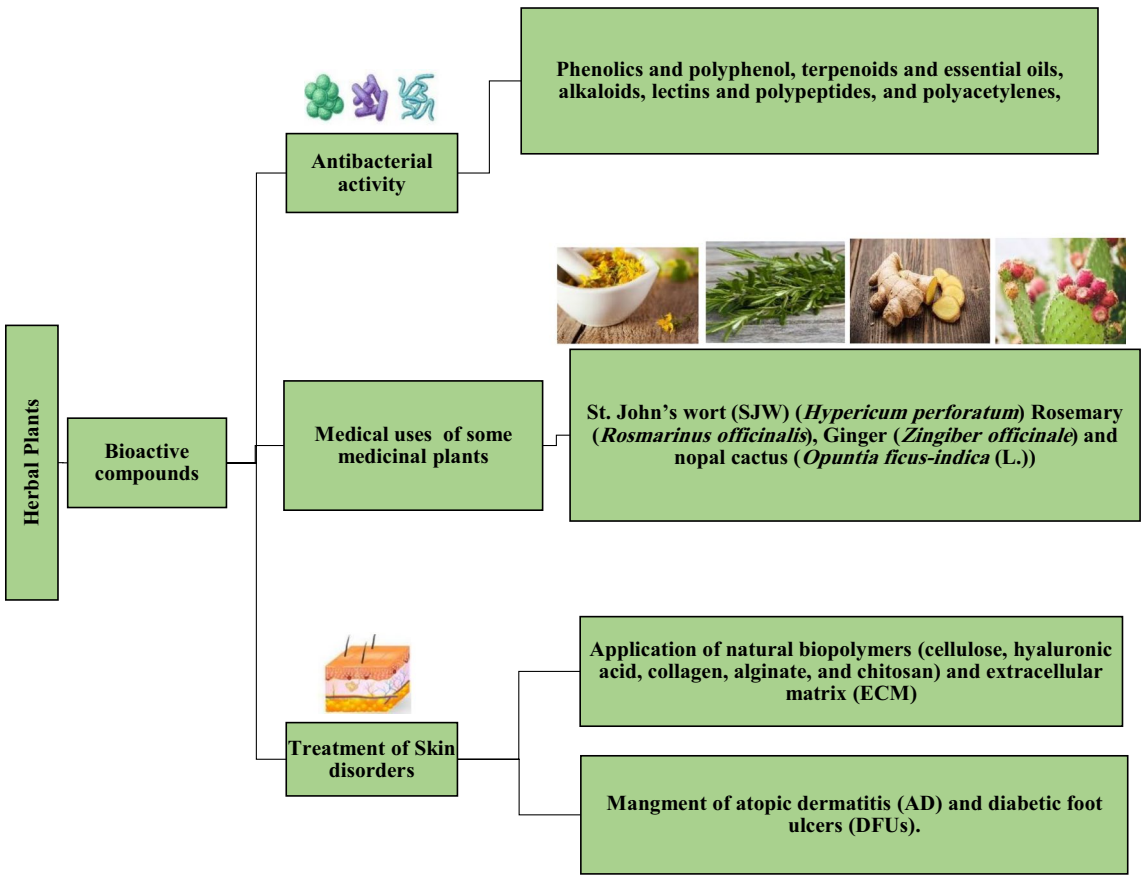
Graphical abstract



Background

An herbal remedy known as phytomedicine is utilized all over the world to treat or prevent physical and mental illnesses [1]. Herbal medicine or a phytopharmaceutical preparation is a type of medication that is made in a crude form solely from whole plants or specific plant parts [2]. Herbal medicine, which has a history spanning more than 3000 years and was enumerated in Sheng Nong's herbal book "*The Devine Farmer's Classic of Herbalism*" [3], is the foundation of traditional Chinese medicine (TCM). Herbal medicine is one of the most sought-after treatments by 3.5–4 billion people worldwide, mainly in Africa, India, and China, according to the World Health Organization (WHO) [4]. Products made from medicinal plants have greatly increased over the past 10 years, which has revolutionized and improved phytomedicine. There are about 35,000 plant species that are utilized as medicines, but only 20% of them go through the phytochemical analysis stage and only 10% make it to the biological screening stage, leaving the rest in need of further study [5]. As herbal medicine becomes more and more popular, it is important to maintain quality, safety, and to prevent potential toxicity [6–8]. In addition to long-term boiled extract and cold infusion of plants, plants can be extracted using alcoholic, vinegar, and hot water as well as other solvents, times, and temperatures [1]. Due to the existence of secondary metabolites, which are abundant in bioactive substances, herbs are used to treat both acute and chronic illnesses, including depression, cardiovascular disease, inflammation, and others [9, 10]. Plant constitutes are used directly as therapeutic agents or as models for pharmacologically active compounds or as starting materials for the synthesis of drugs (Table 1) such as morphine which was produced from opium extracted from *Papaver somniferum,* digoxin from *Digitalis purpurea*, antimalarials such as quinine from *Cinchona* bark, and over 60% of cancer therapeutics are based on natural products such as paclitaxel from the Pacific yew tree [11–15]. Due to inadequate research methodologies, time-consuming, and expensive isolation

Table 1 List of drugs derived from plant origin and their clinical use

Drug	Plant origin	Clinical uses	References
Aescin (Fig. 1)	*Aesculus hippocastanum*	Aescin has potent anti-inflammatory, antioxidant, antiedematous, and vaso-protective effects. It is used in the management of haemorrhoids and hematoma	[16]
Aesculetin (Fig. 1)	*Fraxinus rhynchophylla*	Aesculetin is a phenolic coumarin derivative compound that has anti-inflammatory, antinociceptive, antioxidative, and anticancer effects, in addition to its effectiveness against allergic asthma	[17]
Agrimophol (Fig. 1)	*Agrimonia Pilosa*	Agrimophol is a phloroglucinol compound identified by high-throughput screening (HTS) method. It acts by disturbing pH_{IB} homeostasis of *Mycobacterium tuberculosis*	[18, 19]
Allyl isothiocyanate (Fig. 1)	*Brassica nigra*	A black mustard volatile oil responsible for the bitter taste and pungent odour. It has the potential to be used as antibacterial, anticancer, antifungal, and antihelminthic, in addition to its antifermentative and antibrowning in food industry	[20, 21]
Anisodamine (Fig. 1)	*Anisodus tanguticus*	An atropine derivative with nonspecific cholinergic antagonist activity. It has a cardiovascular properties that include depression of cardiac conduction and protection against arrhythmia	[22, 23]
Artemisinin (Fig. 1)	*Artemisia annua* L	A sesquiterpene lactone with potent antimalarial activity in addition to its ability to treat some viral infections and various neoplasms	[24]
Aspirin (Fig. 1)	Willow tree bark	Anti-inflammatory and antiplatelet agent	[25, 26]
Atropine (Fig. 1)	*Atropa belladonna*	An Anticholinergic and Cholinergic Muscarinic Antagonist	[27]
Berberine (Fig. 1)	*Berberis vulgaris*	A nonbasic and quaternary benzylisoquinoline alkaloid used for the treatment of skin diseases, inflammatory disorders, respiratory diseases affections of eyes, tumours, microbial pathologies and for wound healing	[28]
Bromelain (Fig. 1)	*Ananas comosus*	Anti-inflammatory, antiedematous, antithrombotic, fibrinolytic, anticancerous, and facilitate the death of apoptotic cells	[29]
Camphor (Fig. 1)	*Cinnamomum camphora*	Camphor used for the treatment of various symptoms such as infection, inflammation, muscle pain, congestion, and irritation in various regions	[30]
Camptothecin (Fig. 1)	*Camptotheca acuminata*	A natural alkaloid acts as a DNA topoisomerase 1 poison with antitumour activity	[31]
Catechin (Fig. 1)	*Camellia sinensis*	Catechins are polyphenol compounds from tea leaves and have a strong antioxidants activity. They can prevent or reduce skin damage	[32]
Cocaine (Fig. 1)	*Erythroxylum coca*	Topical anaesthesia of the mucous membranes of the nasal, oral, and laryngeal cavities in addition to off-label use as vasoconstrictive in the treatment of epistaxis before cauterization or packing	[33, 34]
Codeine (Fig. 1)	*Papaver somniferum*	Codeine is an alkaloid from opium or morphine used as a sedative, hypnotic, central analgesic, antinociceptive and is also used in insomnia and tuberculosis due to incessant coughing	[35]
Colchicine (Fig. 1)	*Colchicum autumnale*	Treatment of gout	[36]
Convallatoxin (Fig. 1)	*Convallaria majalis*	A cardiac glycosides used to treat atrial fibrillation and cardiac failure through inhibition of Na^+/K^+-ATPase	[37, 38]
Curcumin (Fig. 1)	*Curcuma longa*	Curcumin prevents carcinogenesis by affecting angiogenesis, cancer cell growth, in addition to the suppression of cancer cell metastasis and induction of cancer cell apoptosis	[39]
Deslanoside (Fig. 1)	*Digitalis lanata*	A cardiac glycoside used to treat supraventricular arrhythmias congestive heart failure and chronic atrial fibrillation. Moreover, studies showed its ability to inhibit the tumour growth of human prostate cancer cells	[40, 41]
Digoxin (Fig. 1)	*Digitalis purpurea*	A cardiac glycoside that has inotropic effects and is used to manage systolic dysfunction in congestive heart failure (CHF) patients and also work as atrioventricular nodal blocking agent to manage atrial tachydysrhythmias	[42]

Table 1 (continued)

Drug	Plant origin	Clinical uses	References
Emetine (Fig. 1)	*Cephaelis ipecacuanha*	An alkaloid used to treat amoebiasis	[43]
Ephedrine (Fig. 1)	*Ephedra sinica*	A sympathomimetic drug prescribed as a nasal decongestant. Furthermore, it used as antipyretic and diaphoretic effects	[44, 45]
Etoposide (Fig. 1)	*Podophyllum peltatum*	Podophyllotoxin used as chemotherapeutic drug against various cancers due to its anticancer activity	[46, 47]
Galantamine (Fig. 1)	Amaryllidaceae family (*Galanthus nivalis* and *Galanthus woronowii*)	An oral acetylcholinesterase inhibitor used for therapy of Alzheimer disease	[48, 49]
Glaucarubin (Fig. 2)	*Simarouba glauca*	An antimalarial and anticancer drug	[50]
Glaucine (Fig. 2)	*Glaucium flavum*	Isoquinoline alkaloid used as a cough suppressant	[51]
Glycyrrhizin (Fig. 2)	*Glycyrrhiza glabra*	It is used as a remedy for gastrointestinal problems, cough, bronchitis, arthritis and widely used to treat gastritis and peptic ulcers	[52]
Gossypol (Fig. 2)	*Gossypium species*	A lipid-soluble polyphenol that exhibits significant antineoplastic effects against various cancer types	[53]
Hesperidin (Fig. 2)	*Citrus species*	A bioflavonoid compound with antioxidant, antibacterial, antimicrobial, anti-inflammatory, and anticarcinogenic properties	[54]
Hyoscyamine (Fig. 2)	*Hyoscyamus niger*	An alkaloid used as mild antispasmodic, analgesic, sedative, and mydriatic	[55]
Irinotecan (Fig. 2)	*Camptotheca acuminata*	A topoisomerase I inhibitors used to treat various types of cancer	[56]
L-Dopa (Levodopa) (Fig. 2)	*Mucuna pruriens*	A drug used in the management of Parkinson's disease	[57]
Morphine (Fig. 2)	*Papaver somniferum*	A natural alkaloid with potent and analgesic effects used for severe pain, control of pain from angina pectoris, or acute myocardial infarction and other medical uses	[58, 59]
Ouabain (Fig. 2)	*Strophanthus gratus*	Cardenolide compound used for the treatment of congestive heart failure by inhibiting Na^+/K^+-ATPase. It also has a potential use in the treatment of cancer	[60, 61]
Paclitaxel (Fig. 2)	*Taxus brevifolia* Nutt	A broad-spectrum anticancer compound	[62]
Papain (Fig. 2)	*Carica papaya*	A cysteine protease known for its antibacterial activity, wound healing properties, inhibition of platelet, and inhibition of atherosclerosis	[63, 64]
Papaverine (Fig. 2)	*Papaver somniferum*	An alkaloid used as a vasodilator and direct-acting smooth muscle relaxant	[65]
Physostigmine (Fig. 2)	*Physostigma venenosum*	A reversible acetylcholine esterase inhibitor in both the periphery and central nervous system. It is used to treat glaucoma and anticholinergic toxicity	[66, 67]
Pilocarpine (Fig. 2)	*Pilocarpus jaborandi*	An alkaloid used to treat glaucoma and xerostomia	[68]
Pseudoephedrine (Fig. 2)	*Ephedra sinica*	A sympathomimetic used to treat the symptoms of paranasal sinuses and obstruction in the nasal cavity, in addition to vasomotor rhinitis, allergic rhinitis, and otitis media	[69]
Quinine (Fig. 2)	*Cinchona ledgeriana*	Prevention and therapy of malaria	[70]
Reserpine (Fig. 2)	*Rauvolfia serpentina*	An alkaloid extract used to treat hypertension	[71]
Scopolamine (Fig. 2)	*Hyoscyamus niger*	A natural alkaloid with potent anticholinergic effects that used for the treatment of nausea, vomiting, and motion sickness	[72]
Sennosides A, B (Fig. 3)	*Cassia species*	Anthraquinone glycosides used as Laxative by relaxing and loosening the bowels	[73]
Tetrahydrocannabinol (THC) (Fig. 3)	cannabis	A potent psychoactive compound used as an antiemetic anti-inflammatory and has the ability to reduce neuropathic and chronic pain	[74]
Theophylline (Fig. 3)	*Theobroma cacao*	Used as second-line treatment of asthma and chronic obstructive pulmonary disease (COPD)	[75, 76]

Table 1 (continued)

Drug	Plant origin	Clinical uses	References
Thymol (Fig. 3)	*Thymus vulgaris*	A phenolic monoterpene used mainly for the treatment of the upper respiratory system. It is used as expectorant, anti-inflammatory, antibacterial, antiseptic, and antiviral	[77]
Tubocurarine (Fig. 3)	*Chondodendron tomentosum*	A competitive blocker of nicotinic acetylcholine receptors used for the relaxation of skeletal muscles	[78, 79]
Yohimbine (Fig. 3)	*Pausinystalia yohimbe*	A monoterpenoid, indole alkaloid act by selective inhibition of presynaptic α2-adrenergic receptors (ARs) and used as a stimulant and aphrodisiac to improve erectile function	[80]

techniques, there is little information available regarding the composition of the majority of herbal medications. As a result, this page discusses the crucial role of medicinal plant extract in the battle against bacterial infections and the management of skin wounds and disorders such as atopic dermatitis (AD) and diabetic foot ulcers (DFUs). Additionally, extracellular matrix (ECM) and biopolymers derived from microorganisms, animals, and plants (cellulose, hyaluronic acid, collagen, alginate, and chitosan) all have bioactive qualities that make them useful in the treatment of wounds and the healing process.

Method

We evaluated the scientific literature collected from PubMed, CrossREF, and Google Scholar databases, considering all the articles published between 1975 and 2023. The keywords used were "herbal plants", "phytomedicine", "secondary metabolites", "synergistic", "antibacterial", and "wound healing". Article titles and abstracts were manually screened, and studies not related to the topic were excluded.

Main text

Antibacterial activities of medicinal plants

Globally high rates of morbidity and mortality are mostly caused by infectious diseases. Millions of people per year die as a result of the advent of bacterial strains that are resistant [81]. Antibiotic resistance in bacteria evolves through intrinsic or acquired resistance, by chromosomal mutation, or by horizontal gene transfer (HGT) [82, 83]. Several mechanism can lead to the development of antibiotic resistance such as alteration in cell membrane permeability either by reducing antibiotic penetration or increasing its elimination by efflux pumps; moreover, bacteria can deactivate the antibiotic itself or modify the antibiotic targets, in addition to other alternative pathways which were described in literature and are illustrated in Fig. 4 [83–88]. The most harmful microorganisms for human health have been recognized by the World Health Organization (WHO) and are categorized into three priority groups: critical pathogens (*Acinetobacter*, *Enterobacteriaceae*, *and Pseudomonas*), high-priority pathogens (*Campylobacter*, *Enterococcus faecium*, *Helicobacter pylori*, *Nisseria gonorrhoeae*, *Staphylococcus aureus*, *Salmonella* spp.), and medium-priority pathogens (*Streptococcus pneumoniae*, *Shigella* spp.) [83, 89–91]. Pathogenic plant bacteria can cause diseases on susceptible plant hosts which starts usually with low numbers of pathogen cells and then colonize and multiply to large amounts in living plant tissue. This results in the alteration of plant's developmental system which eventually leads to reduction of plant growth and yield. Disease severity depends on the host genetic constitute, environmental conditions, and the pathogen [92]. Herbal plants produce unlimited wide variety of secondary metabolites which are mostly aromatic and phenol derivatives that gives them the ability to safeguard plants against pathogens [9, 93, 94]. Plants use oxygen for their growth and development but in stress like pathogen attack; the usage of oxygen causes the production of reactive oxygen species (ROS) in the plant and results in photo-oxidative damage [95–97]. In stress conditions plants induce excessive biochemical changes to activate defence pathways such as changing cell wall composition, detoxification of several ROS species, induction of enzymatic and nonenzymatic components, and alteration of pathogen activates [98–101]. Numerous studies have demonstrated that various chemicals components of herbal plants possess antibacterial properties that can protect the human body against diseases without being damaging to cells [102]. Herbal or synthetic antimicrobial agents are both possible. The main negative effect of synthetic substances including antibiotics, metals, and metal oxide nanoparticles is the production of ROS, which is extremely hazardous and can lead to cancer [103]. On the other hand, herbal antimicrobial compounds including cinnamon, thyme, chamomile, eucalyptus, lemon balm, garlic, ginger, and others are free scavengers that can prevent ROS generation [102]. Antimicrobial phytochemicals can be divided into several categories such as phenolics and polyphenol (e.g. catechol and caffeic acids (Fig. 5)) [104]; terpenoids and essential oils (e.g. camphor, farnesol and artemisinin (Fig. 5)) [104, 105]; alkaloids (e.g. morphine (Fig. 5)) [104]; lectins and polypeptides

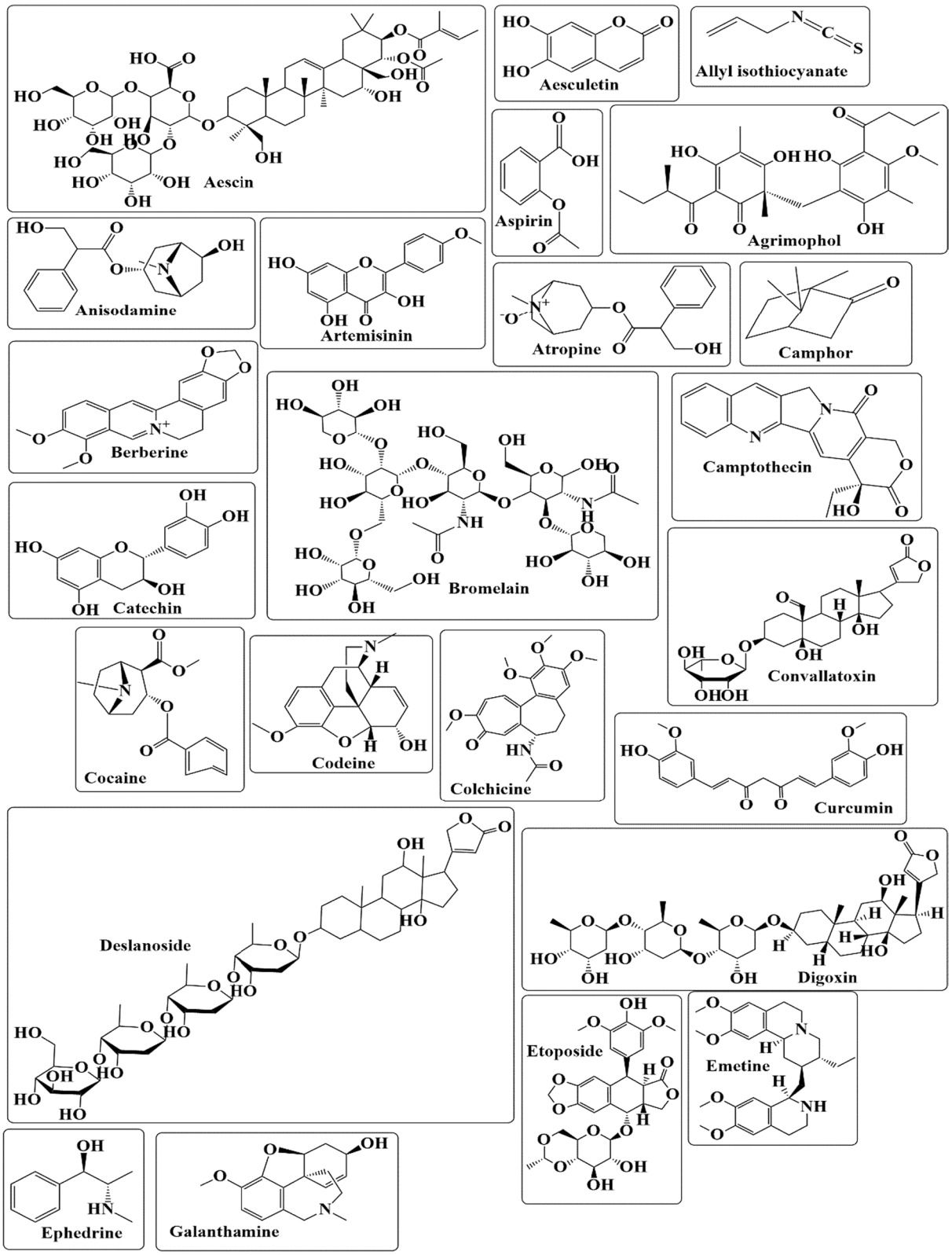


Fig. 1 Chemical structure of drugs derived from plant origin; Aescin, aesculetin, agrimophol, allyl isothiocyanate, anisodamine, artemisinin, aspirin, atropine, berberine, bromelain, camphor, camptothecin, catechin, cocaine, codeine, colchicine. Convallatoxin, curcumin, deslanoside, digoxin, emetine, ephedrine, etoposide, and Galantamine

(e.g. Thionins (Fig. 5)) [106–108]; polyacetylenes (e.g. 8*S*-heptadeca-2(*Z*),9(*Z*)-diene-4,6-diyne-1,8-diol (Fig. 5)) [109], and many others.

Antibacterial phytochemicals

Phenolics and polyphenol Polyphenols are a wide class of chemical substances found in plants that have a variety of biological functions [110]. Flavonoids (such as luteolin (Fig. 5), quercetin (Fig. 5), catechin (Fig. 2), and epicatechin (Fig. 5)) and nonflavonoids (such as benzoic, cinnamic acids, tyrosol, and hydroxytyrosol (Fig. 5)) are two categories of polyphenols that can be simple, large, or complex compounds[111]. Phenolic compounds have been used in traditional medicine, and although their mode of action as antibacterial agents is still not completely understood, it does appear to be distinct from that of antibiotics, reducing the risk of cross-resistance and making them a promising agent against resistant pathogens [112–114]. Inhibiting the growth of *Helicobacter pylori* is one of the potential benefits of polyphenols, which are powerful antioxidant and anti-inflammatory compounds found in foods like broccoli, garlic, liquorice, cranberries, and curcumin [115, 116]. Due to antibiotic resistance and issues with patient compliance, *H. pylori* eradication rates with triple therapy, which includes clarithromycin, metronidazole, or amoxicillin in combination with a proton pump inhibitor, are lower than 50–70%. The bismuth-containing quadruple therapy, as well as sequential and hybrid regimens, is now advised for treating *H. pylori* infection. There is not currently a therapy with > 90% eradication rates, though [117–121]. To determine the impact of polyphenol components (garlic, liquorice, cranberry, curcumin, and broccoli) on the elimination of *H. pylori* infection, Wang et al. [122] conducted a meta-analysis study. The study discovered that polyphenol compounds may have a positive impact on the elimination of *H. pylori*, since the total elimination rate of the bacteria was higher in the polyphenol compounds group than in the control group. The research backs the adjuvant use of polyphenolic substances in the treatment of *H. pylori*. The polyphenol content of garlic makes it a potent alternative to conventional *H. pylori* treatment, according to in vitro studies [123–125]. Additionally, liquorice has anti-*H. pylori* properties [126]. Studies conducted in vitro revealed that *Glycyrrhiza glabra* and its aqueous extract have anti-*H. pylori* activity. Possible mechanisms of action include blocking dihydrofolate reductase, DNA gyrase, protein synthesis, and *H. pylori* adherence to human stomach tissue. Additionally, the components of cranberry juice prevent the adherence of a number of pathogenic infections, including the influenza virus, *E. coli*, and *H. pylori* [127–129]. According to in vitro research, *H. pylori* was prevented from proliferating and was caused to produce a coccoid form by the polyphenols in cranberry extract [130–132]. Turmeric root contains the poly-phenolic compound curcumin (diferuloylmethane) (Fig. 5) [133]. Curcumin administration significantly reduced inflammation in gastric mucosa infected with *H. pylori*, according to animal studies [134]. Additionally, in vivo administration of sulphoraphane-rich fresh broccoli (Fig. 5) sprouts to mouse models reduced *H. pylori* colonization and prevented lipid peroxidation in the stomach mucosa [135, 136]. Żurek et al. [137] investigated the biological potential of polyphenolic substances isolated from walnut (*Juglans regia* L.). The edible kernels of walnuts, which also include polyunsaturated fatty acids (PUFA), tocopherols, phytosterols, and vitamins in addition to a number of other bioactive chemicals, are a rich source of polyphenols [138–141]. In addition, other parts of walnuts such as leaves are valuable products as well and their content was assessed spectrophotometrically by UPLC-PDA-MS/MS method. Several phenolic compounds were identified and expressed as total phenolic (TPC), proanthocyanidin (TPA) (Fig. 5), and total flavonoid contents (TFC) with quercetin 3-*O*-glucoside (Fig. 5) and quercetin pentosides (Fig. 5) dominating. Aqueous walnut leaf extracts antibacterial and antifungal activities were tested against Gram-negative bacteria (*E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*), Gram-positive bacteria (*Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*), and fungus. (*C. albicans*). Result showed highest susceptibility (at 10 mg/ml concentration) against *K. pneumoniae*, and *S. pyogenes,* less bactericidal activity against gram-positive and without any antifungal effect. These findings may be explained by the fact that gram-negative bacteria's cell walls contain lipopolysaccharide (LPS), which creates a hydrophilic environment and shields it from hydrophobic molecules. The aqueous and ethanol extracts of walnut leaves may contain more hydrophilic compounds as a result, leading to higher inhibitory activity against gram-negative bacteria [137]. In similar context, Bouslamti et al. [142] tested antioxidant and antibacterial activity of *Solanum elaeagnifolium* leaf and fruit extracts against Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli* and *Proteus mirabilis*), and *Candida albicans*. HPLC and colorimetric methods were used to determine the chemical composition of *S. elaeagnifolium* fruits and leaf extracts which are quercetin (Fig. 5), luteolin (Fig. 5), gallic acid (Fig. 5), and naringenin (Fig. 5). Result showed that the extracts generated good antioxidant activity and potent antifungal activity. Nonetheless, further studies are needed to assess potential adverse effects. Meadowsweet plant (*Filipendula ulmaria* (L.) Maxim.) has been also used in traditional medicine due to its wide range of pharmacological

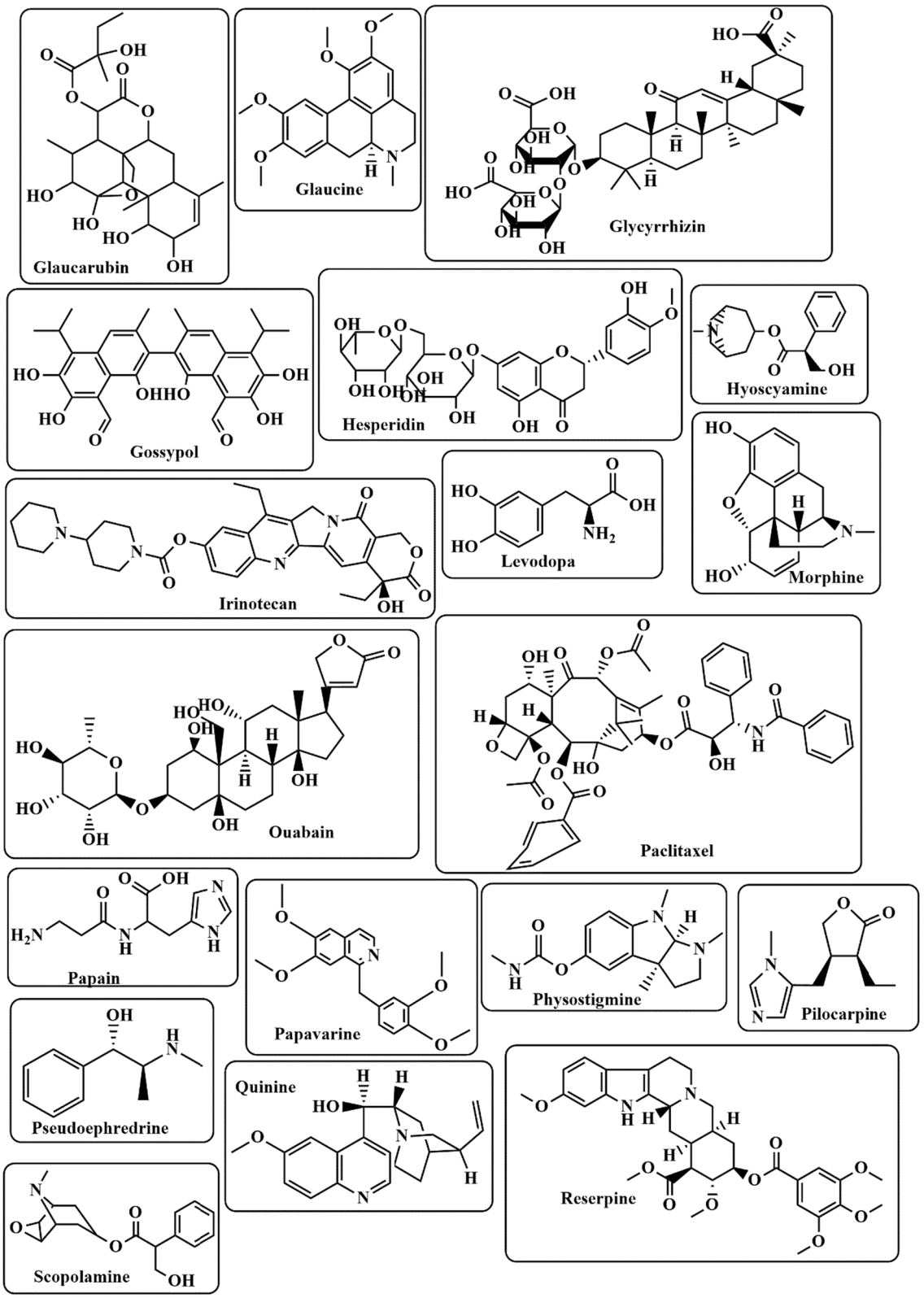


Fig. 2 Chemical structure of drugs derived from plant origin cont., glaucarubin, glaucine, glycyrrhizin, gossypol, hesperidin, hyoscyamine, irinotecan, L-Dopa (Levodopa), morphine, ouabain, paclitaxel, papain, papaverine, physostigmine, pilocarpine, pseudoephedrine, quinine, reserpine, and scopolamine

effects [143, 144]. For the biological activity of meadowsweet, phenolic secondary metabolites are thought to be responsible, including phenolic acids and their derivatives (such as gallic acid and salicylic acid in Fig. 5), flavonoids and flavonoid glycosides (such as kaempferol and astragalin in Fig. 5), and tannins (such as tellimagrandin I, II, and rugosin D) [145, 146]. Meadowsweet extracts from different organs and parts (leaves, flowers, fruits, and roots) have been studied for their antioxidant and antibacterial properties by Savina et al. [147] Gram-negative bacteria *P. aeruginosa* and Gram-positive bacteria *B. subtilis* were used to investigate the antibacterial activity of flower and fruit extracts. All portions of the meadowsweet plant had a high overall phenol level, whereas the flowers had a high flavonoid concentration. The primary flavonoids in meadowsweet include luteolin, kaempferol derivatives, and spiraeoside (Fig. 5), which all have potent antibacterial properties. Meadowsweet plants were also found to have significant amounts of salicylic acid and its derivatives, which are thought to have anti-inflammatory effects. Furthermore, it was shown that meadowsweet roots had greater total catechin and proanthocyanidin contents than other sections, while the fruits had higher total tannin contents, particularly tellimagrandins I and II and rugosin D. All of the components had anti-inflammatory and antibacterial effects.

Terpenoids and essential oils (EOs) More than 17,500 plant species can produce essential oils (EOs), which are volatile secondary metabolites with a particular flavour or scent [148]. The cytoplasm and plastid of plant cells produce EOs compounds, which are then stored in intricate secretory structures including glands and secretory cavities before being present as liquid drops in the flowers, leaves, stems, fruits, bark, and roots of plants. In addition to many other substances like fatty acids, oxides, and derivatives of sulphur, the primary constituents of EOs include terpenes, terpenoids, and phenylpropanoids [149, 150]. EOs are produced through mechanical cold pressing of plants, steam distillation, dry distillation, hydrodistillation, and more recent techniques including microwaves and supercritical fluid extraction. Depending on the method used, different chemical compositions of EO were obtained [150–152]. Due to their biological characteristics, including their antibacterial qualities, EOs have been utilized as perfumes, food spices, and in folk medicine [153]. Terpenes, which make up the majority of essential oils (EOs), are generated from the isoprenoid pathway and are made up of isoprene units (C5). On the basis of this, terpenes are classified as monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), triterpenes (C30), and carotenoids (C40). Terpenes have a variety of chemical properties, including alcohol (terpineol, menthol, carveol, linalool, and citronellol; Fig. 6), aldehyde (citral and citronellal; Fig. 6), ketone (carvone; Fig. 6 and camphor;

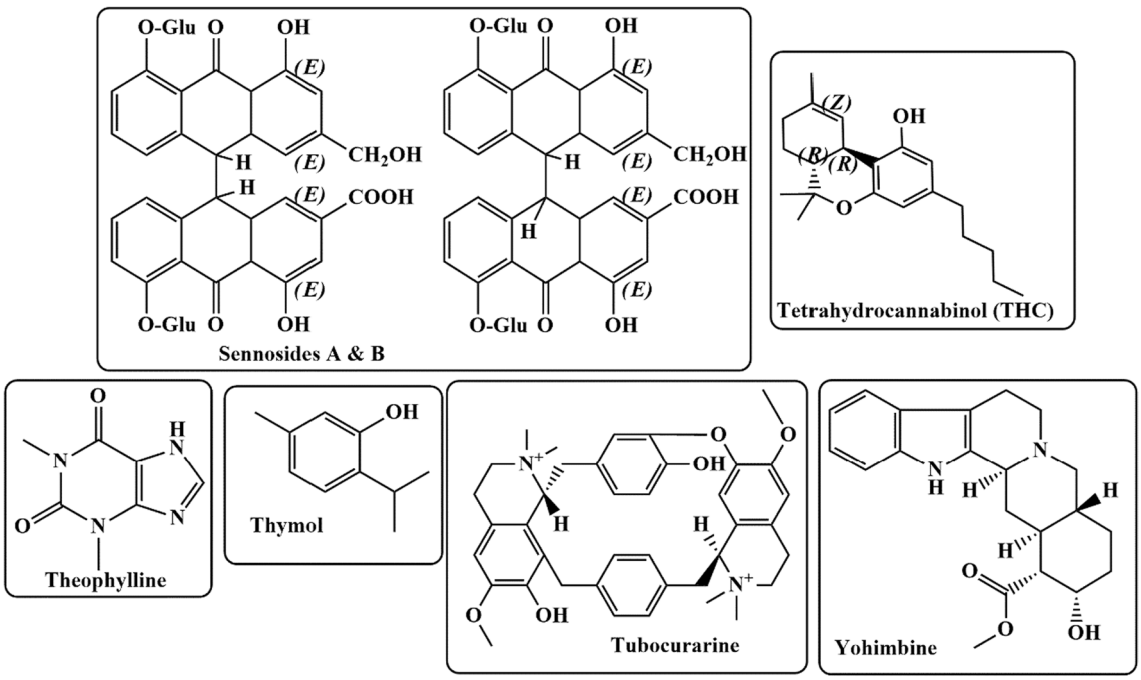


Fig. 3 Chemical structure of drugs derived from plants cont. sennosides A, B, tetrahydrocannabinol (THC), theophylline, thymol, tubocurarine, and yohimbine

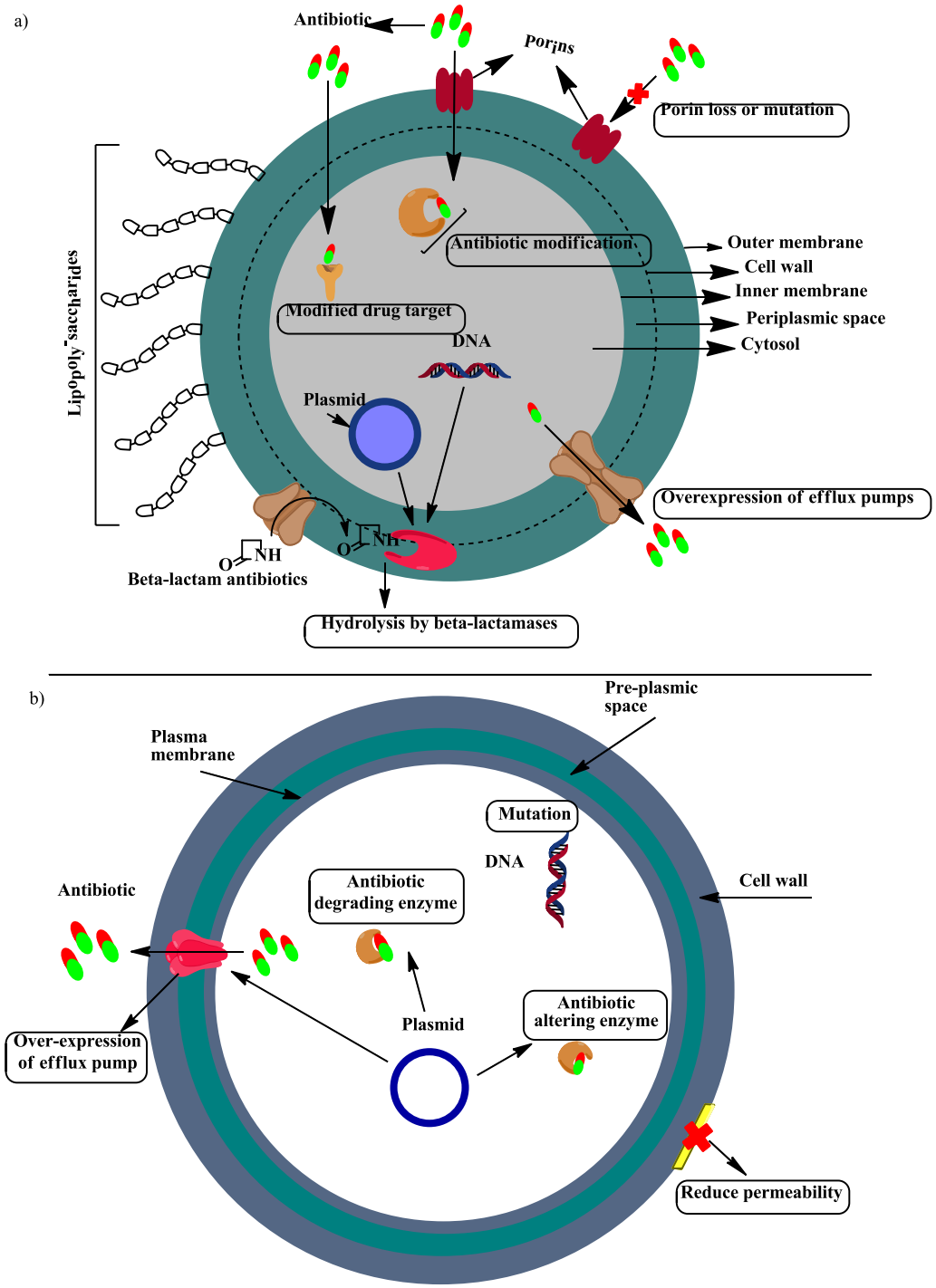


Fig. 4 Structure of **a** gram-negative bacteria and its mechanism of resistance and **b** gram-positive bacteria and its resistance mechanism

Fig. 5), phenol (thymol; Fig. 3; and carvacrol; Fig. 6); ether (eucalyptol; Fig. 6), and hydrocarbon (pinene, and limonene; Fig. 6) groups [154, 155]. An antibacterial, antifungal, antioxidant, anti-inflammatory, analgesic, antimutagenic, and wound-healing compound, thymol is a phenolic monoterpene. Due to its strong antibacterial characteristics, it also enhances digestion, lessens respiratory issues, and is used in dentistry to treat infections of the oral cavity [156]. *Majorana syriaca*, sometimes known as thyme, is a widespread east Mediterranean aromatic

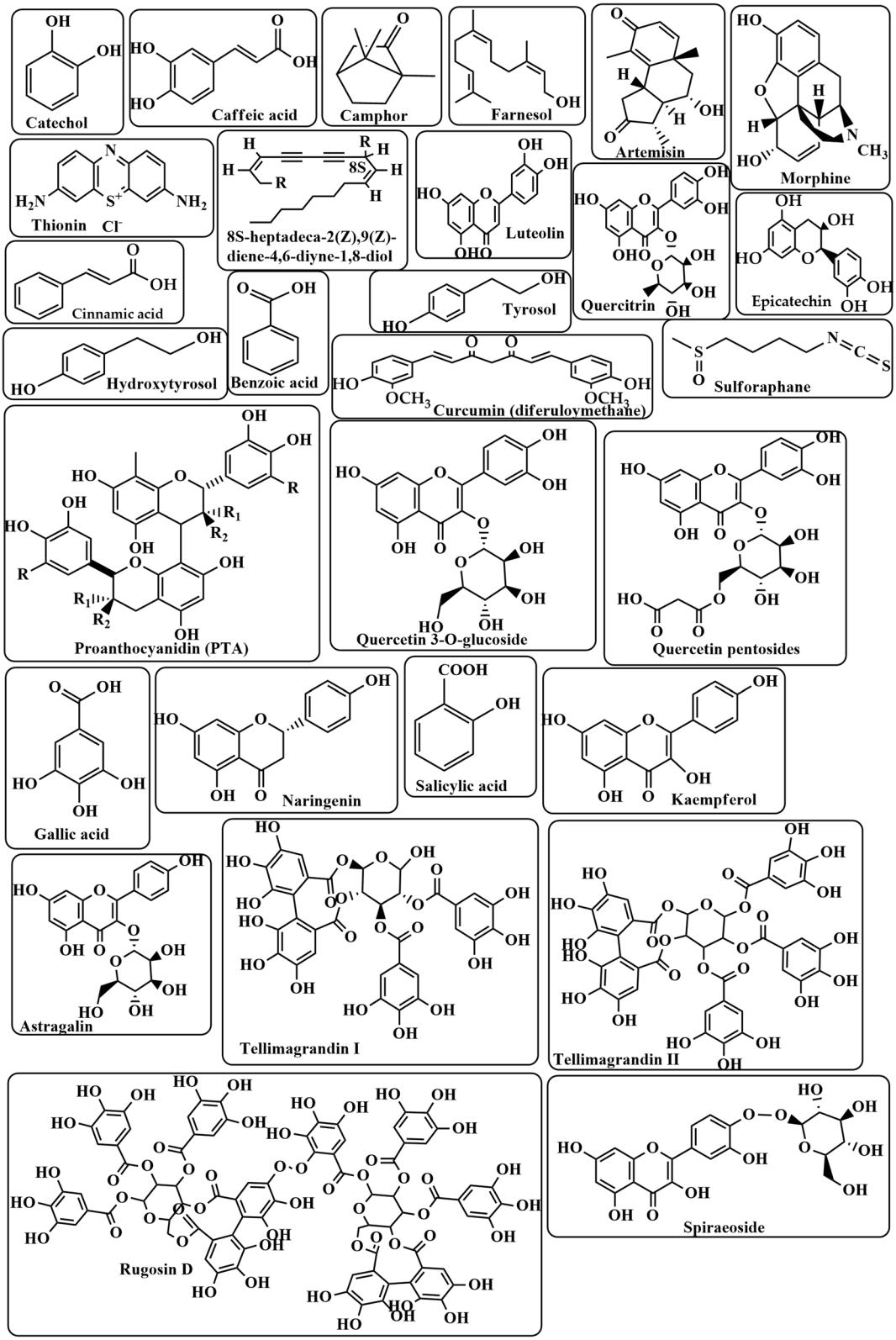


Fig. 5 Chemical structure of antimicrobial phytochemicals including catechol, caffeic acids, camphor, farnesol, artemisinin, morphine, thionins, 8*S*-heptadeca-2(*Z*),9(*Z*)-diene-4,6-diyne-1,8-diol, luteolin, quercetin, epicatechin, benzoic, cinnamic acids, tyrosol, hydroxytyrosol, sulphoraphane, proanthocyanidin (TPA), quercetin 3-*O*-glucoside, quercetin pentosides, gallic acid, naringenin, salicylic acid, kaempferol, astragalin, tellimagrandin I, II, rugosin D, and spiraeoside

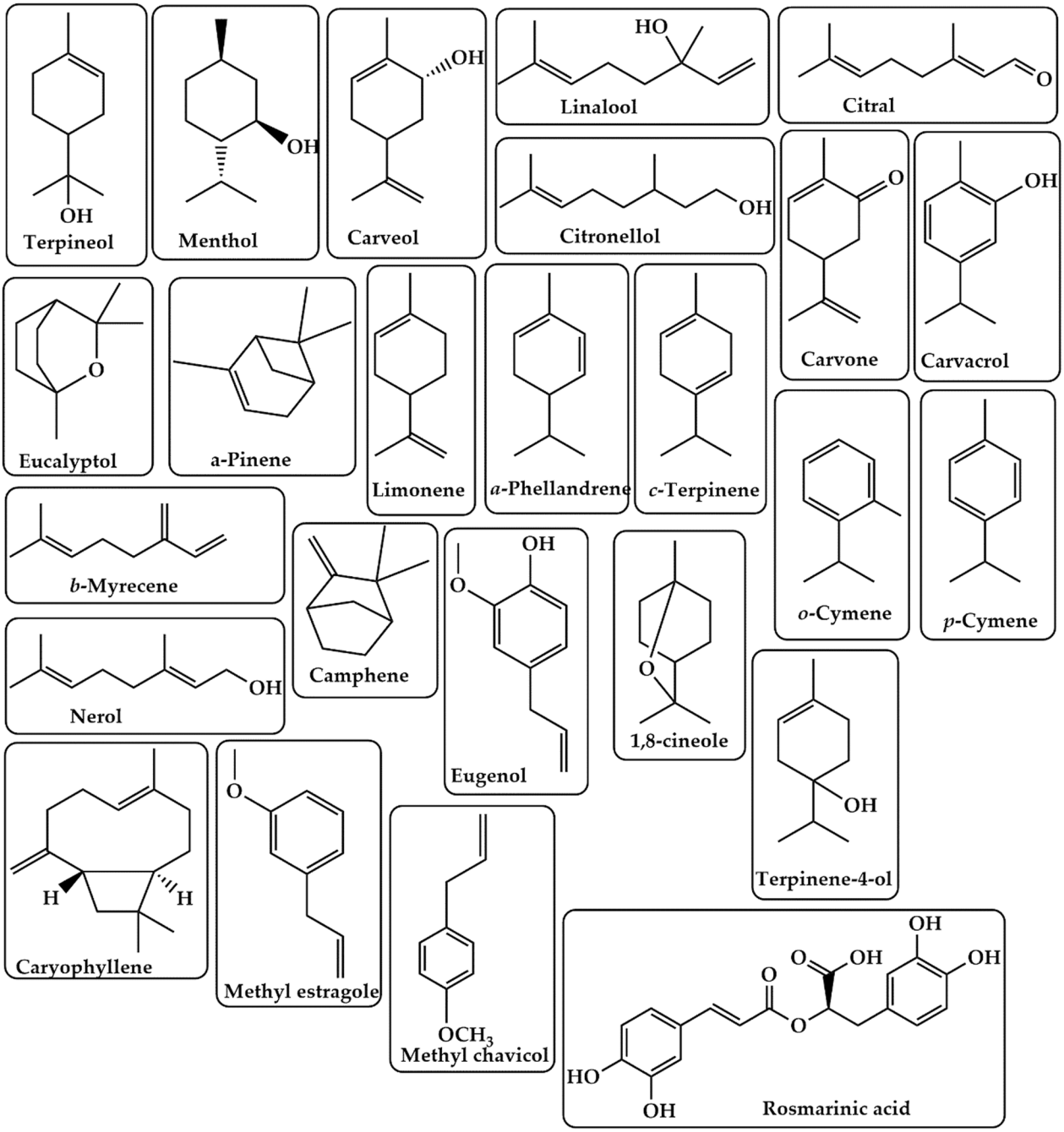


Fig. 6 Chemical structure of essential oils (EOs) and terpenoids including terpineol, menthol, carveol, linalool, citronellol, citral, carvone, carvacrol, eucalyptol, a-pinene,limonene, a-phellandrene, c-terpinene, o-cymene, p-cymene, b-myrcene , camphene, eugenol, 1,8-cineole, terpinen-4-ol, nerol, caryophyllene, methyl estragole, methyl cinnamate, methyl chavicol, and rosmarinic acid

species with a high content of essential oils that give the plants their distinct flavour and perfume as well as antibacterial and antifungal properties. Due to its high volatile oil content, *M. syriaca* is used in traditional medicine to cure the flu, colds, and cough. The primary essential oil in thyme is thymol, which is used in mouthwashes as an antibacterial. Additionally, thyme extracts are added to cough syrups to treat coughs and other respiratory issues like bronchial issues. Thyme essential oils' high phenol concentration is what gives them their potent antibacterial properties, allowing for usage as a potent disinfectant, in oral medicinal preparations, and as a flavouring ingre-

dient in numerous food products [157–161]. Abu-Lafi et al. [162] used static headspace-gas chromatography/mass spectrometry (SD-GCMS) analysis to determine essential oils in thyme leaves and identified 29 monoterpenes (oxygenated and hydrocarbons) such as thymol, carvacrol, *a*-phellandrene, *a*-pinene, *c*-terpinene, *o*-cymene, *p*-cymene, and *b*-myrcene (Fig. 6). The primary components of oxygenated monoterpenes in thyme leaves were the phenolic substances thymol and its geometric isomer carvacrol. The investigation also revealed the presence of thymoquinone, which is known to play a protective function against oxidative damage brought on by chemicals that produce free radicals, such as carbon tetrachloride. Free terpenes present in EOs were investigated for their antibacterial activity by Guimares AC et al. [154]. Results showed that hydrocarbons such terpinene, camphene, R-(-)-limonene, and (+)-α-pinene have inferior antibacterial action to oxygenated terpenes like phenolics (Fig. 6), which is consistent with the findings of earlier studies [163–167]. Eugenol and terpineol showed rapid and excellent bactericidal action against *Salmonella enterica* and *S. aureus* strains, respectively. Moreover, carveol, citronellol, and geraniol exhibited rapid bactericidal effect against *E. coli*. Therefore, hydroxyl groups in phenolic and alcohol compounds resulted in higher antimicrobial activity than hydrocarbons [154]. The antibacterial properties of EOs from *Cinnamomum cassia* bark and *Eucalyptus globulus* leaves are well established. These EOs' main secondary metabolites, 1,8-cineole (Fig. 6) and *trans*-cinnamaldehyde (Fig. 6), are what provide these compounds their therapeutic properties. However, ethnobotanical physicians prefer the use of entire EOs over purified components to treat bacterial infections [168–170]. Therefore, a set of 6 g-positive and -negative bacteria were used by Nguyen HTT et al. [171] to evaluate the antibacterial activity of plant EOs to their separated main components. According to the findings, entire oils of eucalyptus and cinnamon with low concentrations of 1,8-cineole (61.2%) and *trans*-cinnamaldehyde (89.1%) have more favorable effects than the active components that have been refined to less than 99%. Additionally, CC crude extract had greater and stronger effects on both gram-positive and gram-negative bacteria compared to EG. The study's findings support the use of complete essential oils for bacterial infections in traditional medicine since they offer advantages over isolated constituents that might not have the same effects when used as medications. To combat foodborne infections, EOs can also stop bacterial growth [172]. Another study by Trinh et al. [173] looked at the antibacterial properties of *trans*-cinnamaldehyde, the major component of Cinnamomum cassia essential oil, in relation to the *Listeria innocua* strain. The accumulation of *trans*-cinnamaldehyde in the hydrophobic core of the cytoplasmic membrane of *L. innocua*, which results in membrane disruption, was found to be the cause of the antibacterial action of *trans*-cinnamaldehyde as well as other minor *C. cassia* essential oil. Although there was no evidence of large hole creation or cell lysis, viable but nonculturable (VBNC) cells did start to appear. To use *C. cassia* EO and *trans*-cinnamaldehyde rationally in food preservation, a better understanding of their modes of action is required. Kolozsváriné Nagy J et al. [174] tested EOs of cinnamon, eucalyptus, thyme, clove, tea tree, rosemary, lemon grass, lemon balm, and citronella grass against *Xanthomonas arboricola* pv. *pruni* (*Xap*) which is responsible for water-soaked spots on the surface of leaves, and fruits that may lead to severe infections and complete destruction of the plant. High-performance thin-layer chromatography (HPTLC)-*Xap* combined with solid-phase microextraction-gas chromatography/mass spectrometry (SPME-GC/MS) was used to identify active EOs' components. All EOs inhibited bacterium isolates with superiority to cinnamon with MIC values of 31.25 µg/mL and 62.5 µg/mL, while the tea tree EO was the least effective with the highest MIC values. Compounds that are identified to have antibacterial activity by HPTLC zones are *trans*-cinnamaldehyde in cinnamon, thymol in thyme, eugenol in clove, terpinen-4-ol (Fig. 6) in tea tree, borneol in rosemary (Fig. 6), citral in lemon grass and lemon balm, and citronellal and nerol in citronella grass (Fig. 6). Biofilms produced by bacteria are one of the reasons for the resistance of bacteria and can act as reservoirs for spoilage bacteria in food such as *Shewanella putrefaciens* which is the chief spoilage bacteria in fish [175, 176]. Therefore, Xie et al. [177] studied antibacterial effectiveness of *Ocimum gratissimum* L. essential oil (OGEO) in vitro against *Shewanella putrefaciens* to be used as natural preservative. The main active ingredients of OGEO are eugenol and caryophyllene (Fig. 6) which have antibacterial activity according to previous studies. The study demonstrated that OGEO had a positive inhibitory effect on the growth of *S. putrefaciens* and act by disrupting the formation of biofilms and cell membranes of the bacteria with minimum inhibitory concentration and minimum bactericidal concentration of 0.1%. inhibiting *S. putrefaciens* by EOs provide a new method of inhibiting the spoilage of food. *Ocimum basilicum* (Great basil or Saint-Joseph's wort) from *Lamiaceae* family contains many bioactive secondary metabolites such as polyphenols, flavonoids, and terpenes. Main EOs included in the plan are linalool, methyl estragole, methyl cinnamate, and methyl chavicol (Fig. 6) [178–181]. *Ocimum basilicum* has many pharmacological activities and has been used in traditional medicine as antioxidant, anticancer, antiviral, antiaging, and antimicrobial properties [182–184]. Studies showed that the bio-

logical activity of O. *basilicum* is related to cinnamic acid (Fig. 5) derivative of the polyphenoid rosmarinic acid (Fig. 6) [185]. Eid et al. [186] studied *O. basilicum* seeds essential oil biological activity and showed that it had a broad-spectrum antibacterial activity. The oil suppressed the development of all tested microbial strains (minimum inhibitory concentrations (MICs) between 1 and 2.3 µg/mL) and fungus strain *C. albicans* (MICs of 1.3 µg/ml for fungus). Antibacterial activity may refer to the presence of phenolic components in the essential oil which trigger intracellular ATP and potassium ion leakage and lead to cell death. Yaldiz et al. [187] also investigated antibacterial, antiquorum sensing, and antibiofilm capabilities of the ethanol extract and essential oil derived from *O. basilicum*. Results revealed that in addition to having antifungal effects on *C. albicans*, basil essential oil also demonstrated antibacterial activity and antiquorum sensing activity against some Gram-positive and -negative bacterial species.

Alkaloids Alkaloids are a wide and diverse group of secondary metabolites found in 300 plant families and can be found as well in bacteria, fungi, and animals. Alkaloid name came from their basic nature and is characterized by the presence of a basic nitrogen atom in the form of a primary (RNH_2), secondary (R_2NH), or tertiary amine (R_3N). Alkaloids can be monomers or oligomers and can be classified into three major categories: true-alkaloids with N-atom in the heterocycle, proto-alkaloids without N-atom, and pseudo-alkaloids with a basic carbon skeleton [112, 188–192]. Heterocyclic alkaloids can be divided into 14 subgroups that include, pyrrolizidines, pyrrolidines, indoles, isoquinolines, quinolizidines, purines, piperidines, tropanes, and imidazoles [193]. A rich source of bioactive compounds is Marine invertebrates which developed a defence chemical system to protect themselves from predation. Marine sponges are a rich source of secondary metabolites which are responsible for their numerous biological activities such as anti-inflammatory,anticancer, antiviral, antibacterial, and anticoagulant activities [194–196]. The sponge *Luffariella variabilis* exhibit antibacterial activity against gram-positive bacteria due to the presence of sesterterpenes manoalide, secomanoalide,and *trans-* and *cis*-neomanoalide (Fig. 7) [197]. Moreover, the sponges *Poecillastra* sp. and *Jaspis* sp., contain psammaplin A (Fig. 7), a bromotyrosine-derived natural product, while the sponge *Siliquaria* sp. contain the motualevic acids (A–F) (Fig. 7) a halogenated glycyl-lipid conjugates which all inhibit gram positive-bacteria only and are inactive against gram-negative bacteria [198, 199]. Antibacterial and antibiofilm activity of another group called the pyrrole-imidazole alkaloids was studied and tested against gram-positive and -negative bacteria. Bromoageliferin (Fig. 7) is a member from pyrrole-imidazole alkaloids family isolated from marine sponges with other members such as oroidin and sceptrin (Fig. 7). Reports documented the inhibition of *Rhodospirillum salexigens* SCRC 113 biofilms formation a marine bacterium by oroidin and bromoageliferin which resulted in using them as templates to develop numerous analogues and study their antibiofilm activity [200–209]. Melander et al. [210] studied pyrrole-imidazole alkaloids (monomeric and dimeric alkaloids) ability to inhibit biofilm formation and suppress antibiotic resistance against gram-negative *Acinetobacter baumannii* and gram-positive methicillin-resistant *S. aureus* (MRSA). Result showed that monomeric alkaloid oroidin exhibited modest activity against both strains, while stevensine (monomeric oroidin analogue) (Fig. 7) was inactive. On the other hand, the dimeric alkaloids Sceptrin was slightly more active against *A. baumannii*, while dibromosceptrin (Fig. 7) and bromoageliferein were both more active against MRSA with bromoageliferin as the most potent compound. Result indicated that both monomeric and dimeric alkaloids can inhibit phenotypic and genotypic bacterial resistance mechanisms; therefore, a high-throughput screening is needed to identify marine natural compounds to be used as adjuvants with antibiotics to restore FDA-approved antibiotics efficacy and to find alternative approaches to combating MDR bacteria. Tuberculosis (TB) is a widespread infectious disease, and due to the increase of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains new antiTB agents are needed. Arai et al. [211] isolated several compounds from marine sponge of *Haliclona* sp. such as tetracyclic alkylpiperidine alkaloid, 22-hydroxyhaliclonacyclamine B, and haliclonacyclamine A and B alkaloids (Fig. 7) to be used as antidormant mycobacterial compounds. Result showed strong antimycobacterial activity under both aerobic and hypoxic condition against *Mycobacterium smegmatis* and *M. bovis Bacille de Calmette et Guérin* (BCG) from both haliclonacyclamine. Haliclonacyclamine B exhibited bactericidal activity against *M. bovis*(BCG), while hydroxyhaliclonacyclamine B showed weaker antimicrobial activities against *Mycobacterium bacilli* and reduced antimycobacterial activity which may be due to the presence of the 22-hydroxy group. Wijaya et al. [212] studied *Dicranostigma franchetianum* plant from Papaveraceae family and isolated a wide spectrum of isoquinoline alkaloids (IAs) such as berberine, chelerythrine, protopine, and sanguinarine (Fig. 7). Alkaloids were tested against *Mycobacterium tuberculosis* H37Ra and four other mycobacterial strains. Most isolated alkaloids exhibited weak or no antimycobacterial activity; however, benzophenanthridine (6-ethoxydihydrochelerythrine) and bisbenzophenanthridine (*bis*-(6-(5,6-dihydrochelerythrinyl))ether) alkaloid derivatives (Fig. 7) showed mod-

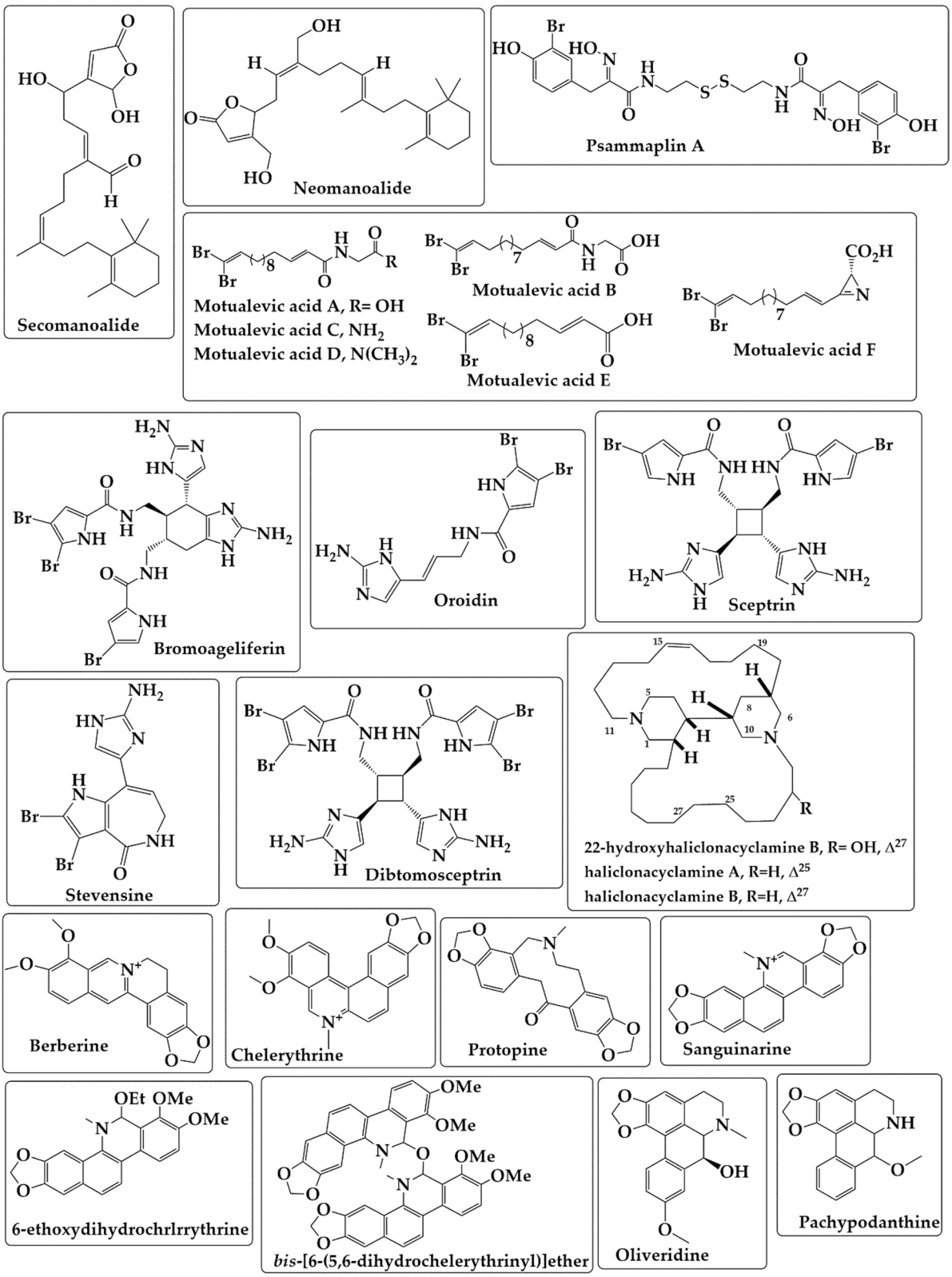


Fig. 7 Chemical structure of alkaloids compounds including secomanoalide, neomanoalide, psammaplin A, motualevic acids (**A**–**F**), bromoageliferin, oroidin, sceptrin, stevensine, dibromosceptrin, 22-hydroxyhaliclonacyclamine B, haliclonacyclamine A and B, berberine, chelerythrine, protopine, sanguinarine, 6-ethoxydihydrochelerythrine, *bis*-(6-(5,6-dihydrochelerythrinyl))ether, oliveridine, and pachypodanthine

erate antimycobacterial activity against all tested strains. Moreover, semisynthetic berberine derivatives resulted in a significant increase in antimycobacterial activity against all tested strains. Further studies are needed to develop more potent berberine derivatives with low cytotoxic profile. On the other hand, Dong et al. [213] conducted a bioassay-guided phytochemical study on the semi-mangrove plant *Myoporum bontioides* A. Gray, which belong to Myoporaceae family and tested its activity against methicillin-resistant *S. aureus* (MRSA). New sesquiterpene alkaloids and furanosesquiterpenes were isolated from the plant, and result showed that sesquiterpene alkaloids displayed potent anti-MRSA activity. Alkaloids also can be used in food system to prevent or treat foodborne diseases such as oliveridine and pachypodanthine (Fig. 7) an aporphinoid alkaloids. Marco Di et al. [214] tested these alkaloids against *Yersinia enterocolitica* an important foodborne pathogen that cause a gastrointestinal disease in humans called yersiniosis. Result showed that both oliveridine and pachypodanthine inhibited the growth of *Y. enterocolitica* with superiority for oliveridine with lower MIC values which open an opportunity to develop potential antimicrobial agents to prevent or treat foodborne diseases.

Lectins and polypeptides Naturally antimicrobial proteins and peptides can be found in humans, animals, plants, and microorganisms. Plants include proteins called lectins that attach to certain carbohydrates on the surfaces of microbes, aiding in the defensive mechanisms against pathogens. Plant lectins are classified according to their affinity for monosaccharides and complex glycans, but they do not interact with endogenous cellular glycans. Instead, they have a strong affinity for the sugars on bacteria, fungi, and other organisms, which suggests that they serve as a plant defence molecule [215–218]. Lectins have different types including C-type lectins (e.g. endocytic lectins), S-type lectins (e.g. galectins), L-type lectins, P-type lectins, M-type lectins, Jacalin-related lectin (JRL),siglecs, *Oscillatoria agardhii* agglutinin homolog (OAAH), Cyanovirin-N homologs (CVNHs), *Galanthus nivalis* agglutinin-like (GNA-like) lectins, and others [219]. Lectins have been used in medicine as immunomodulators against tumour cells and microbial infections. Moreover, lectins showed to be able to disrupt quorum sensing (QS) signal transduction and interfere with nonessential functions for cell viability [220, 221]. Lectins purified from *Moringa oleifera* leaf (SLL-1, SLL-2, and SLL-3) showed variable antibacterial potency against *E. coli*, *Shigella dysenteriae,* and *S. aureus*, while water-soluble lectin purified from *Moringa oleifera* seeds significantly reduced *S. aureus* but not *E. coli* [222, 223]. On the other hand, mannose-glucose-binding lectin isolated from *Calliandra surinamensis* leaf did not kill *S. aureus* nor *Staphylococcus saprophyticus* but reduced their growth and their biofilm formation with no activity against *E. coli* [224]. In addition, a rich source of lectins is Marine species that include green algae (22%), red algae (61%), and cyanobacteria (17%) [225]. Few literature studies discussed the potential usefulness of algal or cyanobacterial lectins as antibacterial agents [226–228]. Purified lectins isolated from two red algal species, *Eucheuma serra* (ESA) and *Galaxaura marginate* (GMA), showed strong inhibitory action against marine gram-negative *Vibrio vulnificus*, while no action recorded for other two Vibrio species, *V. peagius* and *V. neresis* according to Liao et al. [229] study. Selectivity in the inhibition is referred to the differences in bacterial surface carbohydrates. Furthermore, Hung et al. [230] isolated lectins from *Eucheuma denitculatum* (EDA) red algae which also exhibited activity selectivity against *V. alginolyticus*, but not against *V. parahaemolyticus* or *V. harveyi* due to the binding of lectins to high-mannose N-glycans. Moreover, Holanda et al. [231] isolated lectins from *Solieria filiformis* red alga and tested its activity against gram-negative and -positive bacteria. Result showed that lectins inhibited the growth of the gram-negative species; *Salmonella typhi, Serratia marcescens, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter aerogenes*, and *Proteus sp.*, while it stimulated the growth of the gram-positive species *Bacillus cereus*. No activity was noticed against *S. aureus, B. subtilis, E. coli*, and *Salmonella typhimurium*. The interaction between the *S. filiformis* lectin and the gram-negative bacteria's cell surface receptors, which encouraged changes in the flow of nutrients, may be the cause of the activity against gram-negative bacteria. These findings raised the possibility of using marine lectins as organic substitutes for antibiotics in the treatment of gram-negative pathogens [232]. As mediators of innate immunity in all living things, antimicrobial peptides (AMPs) or host defence peptides are also recognized to play a significant role in biological processes. Because AMPs are cationic and amphipathic, they can more easily pass through microbial cytoplasmic membranes and cause cell lysis. The usage of AMPs is constrained for a variety of reasons, including their undesirable cell toxicity, restricted availability, high cost during synthesis, sensitivity to protease degradation, and others [233, 234]. Compared to other species, plants have more AMPs, which typically have 20–50 amino acid residues and are abundant in glycine, cysteine, and positively charged residues [234, 235]. Plant AMPs are divided into thionins, defensins, α-hairpinins, nonspecific lipid transfer proteins (nsLTPs), hevein- and knottin-like peptides based on their 3D structure and cysteine signature [236]. A study of cysteine-rich peptides (CRPs) revealed that they all had a structural component in common called

the γ-core that is responsible for their antibacterial activity. This structural element has an antiparallel β-hairpin conformation [237]. Thionins are poisonous to yeast, fungus, and bacteria. Antifungal activity was defined as the development of pores or a specific contact with a particular lipid domain as a result of direct protein-membrane interactions between positively charged thionin and the negatively charged phospholipids in fungal membranes [238, 239]. The antibacterial, antifungal, proteinase, and insect amylase inhibitory properties of plant defensins also classify them as γ-thionins [240, 241]. Although the exact mechanism of action of defensins is yet unknown, and not all plant defensins work in the same way, they almost certainly use glucosylceramides as receptors for fungal cell membrane entry. Ion outflow and membrane rupture are caused by defensins' positive charges repelling one another into the cell membrane [242]. Similar behaviour has been seen with nsLTPs, which interfere with the biological membrane permeability and integrity of pathogens [243]. Gram-positive bacteria (*Bacillus megaterium* and *Sarcina lutea*) and a number of fungi were able to halt the formation of powerful nsLTPs that were isolated from onion seeds [244, 245]. Sunflower (*Helianthus annuus*) seed-derived nsLTP also demonstrated antifungal activity [246]. The α-hairpinins are a different small family of AMPs that includes peptides with a wide range of biological activities, including antifungal and antibacterial activity [247]. The rubber tree (*Hevea brasiliensis*) (which produces latex that is similar to hevein) gave its name to the family of AMPs that resembles hevein. Hevein-like peptides are extremely stable, cysteine-rich substances that withstand heat and protease activity. They are active against a variety of phytopathogens, including bacteria and fungus, due to their capacity to interact with pathogens' cell wall chitin, which is missing in plants [248]. Tk-AMP-$K2_{10-23}$, a knottin-like peptide isolated from *T. kiharae* seeds, was also discovered to have antibacterial action. According to the results of flow cytometry, there were less *Cr. neoformans* cells, which suggest that the peptide caused cell lysis by interfering with the integrity of the membrane [249–251]. More research and focus are required on peptides that are particularly effective against specific infections in order to create new antimicrobial agents.

Polyacetylenes A wide variety of biomasses, including plants (particularly species of the Apiaceae family and carrot), marine organisms, fungi, insects, and people, include polyacetylenes, which are naturally occurring molecules characterized by the presence of two or more carbon–carbon triple bonds. There are just a few papers on the antibacterial potential of polyacetylenes, which are renowned for their anti-inflammatory and anticancer properties [252, 253]. A large number of natural polyacetylenes have been isolated such as 8*S*-heptadeca-2(*Z*),9(*Z*)-diene-4,6-diyne-1,8-diol (Fig. 5) from *Bupleurum salicifolium Soland* (Umbelliferae). This polyacetylene showed antibiotic activity against gram-positive bacteria *S. aureus* and *Bacillus subtilis* with no activity against gram-negative bacteria (*E. coli, Salmonella sp., Pseuknas aeuriginosa*) and the yeast *Candida albicans* [109]. Falcarinol-type polyynes (Fig. 8) showed to have antifungal activity that protects carrots from fungi as *Botrytis cinerea Pers*, while panaxydol and panaxytriol (Fig. 8) from *Panax ginseng* found to have cytotoxic effect against numerous cancer cell lines [254–256]. *Exocarpos latifolius Kuntze* stems were used to extract exocarpic acid derivatives (Fig. 8); some derivatives exhibited antimycobacterial activity against *M. tuberculosis*, while others exhibited no activity [253, 257]. Amadaldehyde, a C63 polyacetylenic aldehyde that was isolated from mango ginger (the rhizomes of *Curcuma amada* Roxb.), was shown to have antibacterial and antioxidant activity against microorganisms in addition to cytotoxicity and platelet aggregation inhibitory effect [258]. Several polyynes such as epoxide-ketone are found in one of the most important oriental medicinal plants *P. ginseng C.A. Meyer*. These compounds exhibited antimicrobial activity against several bacteria such as *Bacillus subtilis, S. aureus, Cryptococcus neoformans*, and *Aspergillus fumigatus* which conclude that *P. ginseng* releases antimicrobial polyacetylenes into the surrounding soil from roots to defend the plant[259]. Moreover, triyne carboxylic acid compound (octadeca-9,11,13-triynoic acid) (Fig. 8) isolated from the roots of *Polyalthia cerasoides* (Roxb.), showed antimalarial and antimycobacterial activity against *Plasmodium falciparum* and *M. tuberculosis*, respectively. Furthermore, 13,14-dihydrooropheic acid (Fig. 8) from the extract of *Mitrephora celebica* Scheff, and debilisones A–F (Fig. 8) from the Thai herbal plan *Polyalthia debilis* (Pierre) exhibited antibacterial activity against *Mycobacterium smegmatis* and *M. tuberculosis*, respectively [260–262].

Medicinal plants with antimicrobial activities

St. John's wort (SJW) (Hypericum perforatum) There are 500 species in the *Hypericum* (Hypericaceae) family, and they are all found worldwide. The most prevalent species is *Hypericum perforatum*, also known as St. John's wort (SJW), which is one of the most well-known and widely used herbs in the world. The herb has been widely used for therapeutic purposes across the globe [263, 264] and has been included into traditional medicine. The aerial parts or flowering tops make up the crude form of SJW medicine, which is employed in multi-ingredient formulations or as a monopreparation (either as is or as an extract) [265]. The upper stem leaves and flowering tops of *H. per-*

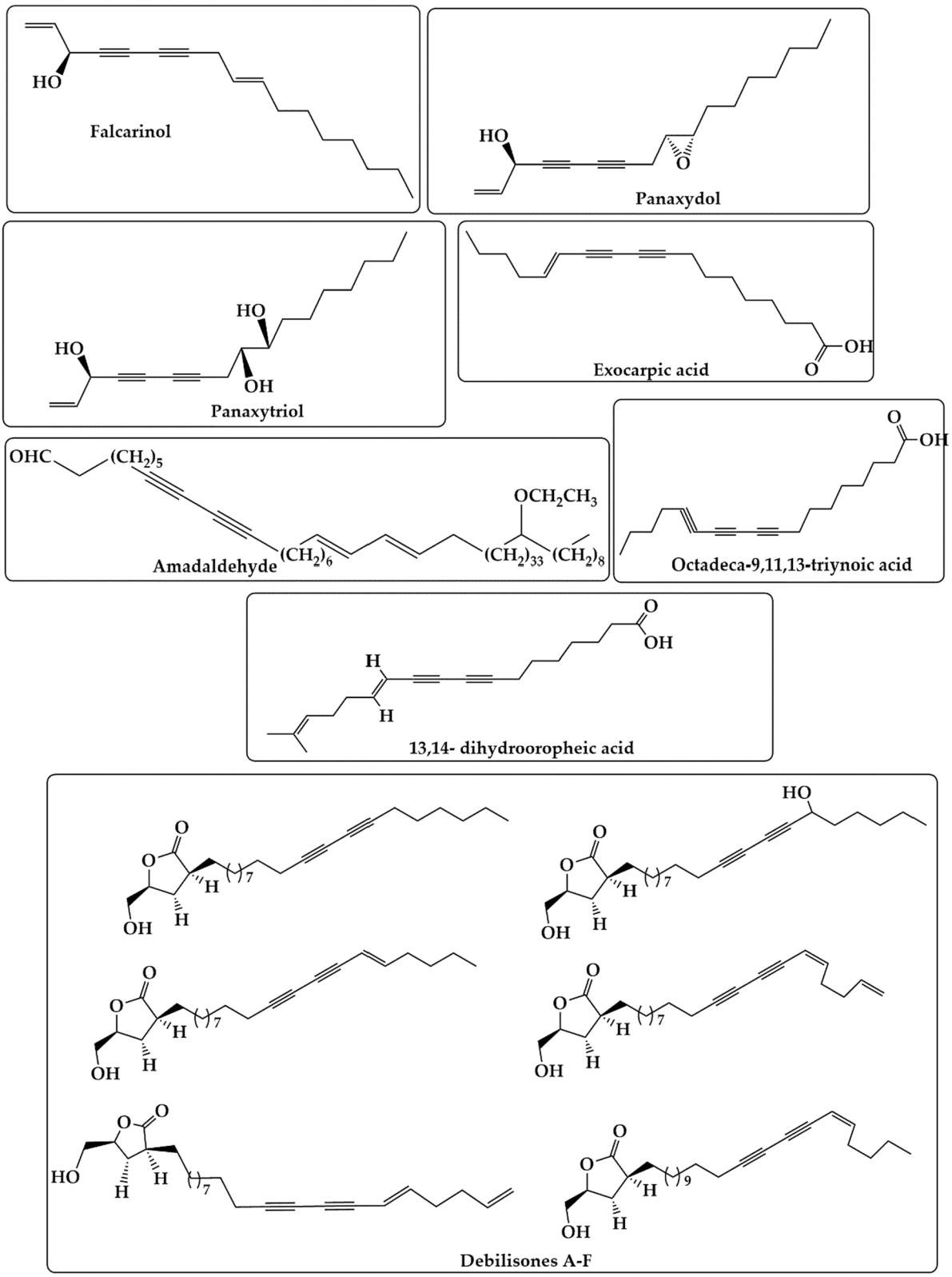


Fig. 8 Chemical structure of polyacetylenes compounds including falcarinol, panaxydol, panaxytriol, amadaldehyde, octadeca-9,11,13-triynoic acid, 13,14- dihydrooropheic acid, debilisones (**A**–**F**)

foratum are used in dietary supplements to treat mild to severe depression [266]. The flowering tops are typically prepared and used for its hypnotic and tonic properties or to speed wound healing. Due to varying extraction techniques, individual plant extracts do not include the entire group of phytoconstituents but only some of them, which causes a number of issues that affect the usage of *H. perforatum* in pharmaceutical formulations. Additionally, some of the active ingredients may experience problems with stability with exposure to time or light[267]. Due to the plant's synthesis of bioactive secondary metabolites like naphthodianthrones, flavonoids, bioflavonoids, phloroglucinols, xanthones, proanthocyanidins, acid phenols, and essential oils [263, 268, 269], it has been the subject of phytochemical studies.

Antibacterial activity of SJW Sherif et al. [270] investigated the antibacterial activity of the *Hypericum perforatum* plant. The plant extract and its fractions were evaluated by Liquid Chromatography Electrospray Ionization Tandem Mass Spectrometric (LC–ESI–MS/MS) and tested against MRSA, *Enterococcus faecalis, E. coli,* and *K. pneumonia* MDR isolates. The results demonstrated that different extract from *H. perforatum* had a promising antibacterial activity against tested pathogens, particularly MDR-*K. pneumoniae*, with inhibition zones ranging from 17.9 to 27.9 mm and strong antioxidant effects, as opposed to sub-fractions extract, which demonstrated lesser inhibition zones and higher MIC values. Bacterial cell membranes are affected by extract of *H. perforatum*, which causes cell shrinkage and deformation that results in cell lysing. Additionally, the extract promoted cell elongation and thickness, which is similar to the actions of penicillin and the antibiotic cefotaxime, according to published research [271–274]. These findings indicate that these herbal extracts can be used to treat resistant bacteria, but further research is required to clarify why the total extract showed the most potent antibacterial activity over the subfraction? Is it an additive effect of specific compounds that act together with different mechanism to inhibit resistance bacteria or something else?. Using *H. perforatum* flower extracts, Okmen et al. [275] investigated the antibacterial activity of the bacteria that cause mastitis, a complicated condition characterized by inflammation of the parenchyma of the mammary glands and bacterial alterations in milk. Along with coagulase-negative *staphylococci* (CNS), *Staphylococcus, Streptococcus*, and *coliform* bacteria are the pathogens that cause the disease [276]. Although this condition is frequently treated with antibiotics, new antibiotics are still needed to combat germs because of the emergence of antibiotic resistance. The study's findings indicated that *H. perforatum* flower methanol extracts exhibit bactericidal action against gram-positive and gram-negative bacteria (*S. aureus, Proteus vulgaris, P. aeruginosa,* and *E. coli*), with the highest inhibition zone against Coagulase-negative *Staphylococci*. The plant extract also demonstrated antimutagenic qualities. However, additional tests are needed to know the extract constitutes and the bioactive compounds responsible for the biological activities. Polyphenolic substances with pharmacological characteristics are called xanthones. Strong free radical scavengers, xanthones have been shown to have activity against a variety of bacteria, including vancomycin-resistant *enterococci*, methicillin- and multidrug-resistant *S. aureus*, and M. tuberculosis [277–283]. When *H. perforatum* was exposed to *Colletotrichum gloeosporioides* cell wall extracts, xanthone (Fig. 9) buildup was seen as a defence mechanism [284]. After elicitation with *Agrobacteriumtumefaciens*, Franklin et al. [285] demonstrated that the antioxidant and antibacterial properties in *H. perforatum* cells had dramatically increased. The up-regulation of xanthone metabolism, particularly paxanthone (Fig. 9), which increased 12-fold within 24 h, was the cause of the enhanced activity. After 12 h of co-cultivation, the viability of *A. tumefaciens* was reported to have dramatically decreased. As a result of the buildup of xanthones, *H. perforatum* cell antibacterial activity rose ten times. Numerous infectious illnesses are brought on by *S. aureus*. Due to its development of resistance against practically all standard of care (SOC) antibiotics, Methicillin-resistant S. aureus (MRSA) has, regrettably, become a significant problem. Therefore, it is urgently necessary to create new tactics to combat MRSA [286–288]. Wang et al. [289] investigated the effect of hypericin (HYP) from *H. perforatum* on the susceptibility of β-lactam antibiotics (cefazolin, oxacillin, and nafcillin) and their synergistic effect with oxacillin in a murine bacteremia model. Result showed that HYP significantly reduced the minimum inhibitory concentrations (MICs) of β-lactam antibiotics and SarA (RNA-binding protein)

(See figure on next page.)

Fig. 9 Chemical structure of bioactive compounds found in St. John's wort (SJW), rosemary, ginger which include, xanthone, paxanthone, hypericin, carnosol carnosic acid, p-cymene-7-ol, suberoylanilide hydroxamic acid, rosmanol, epirosmanol, isorosmanol, rosmaridiphenol, pyrogallol, ellagic acid, benzoic acid, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), α-curcumene, α-farnesene, β-bisabolene, β-sesquiphellandrene, zingiberene, gingerol, paradol, shogaol, gingerenone-A, zingerone, 6-dehydrogingerdione, 10-gingerol, 12-gingerol, *trans*-anethole, and m-phenylphenol

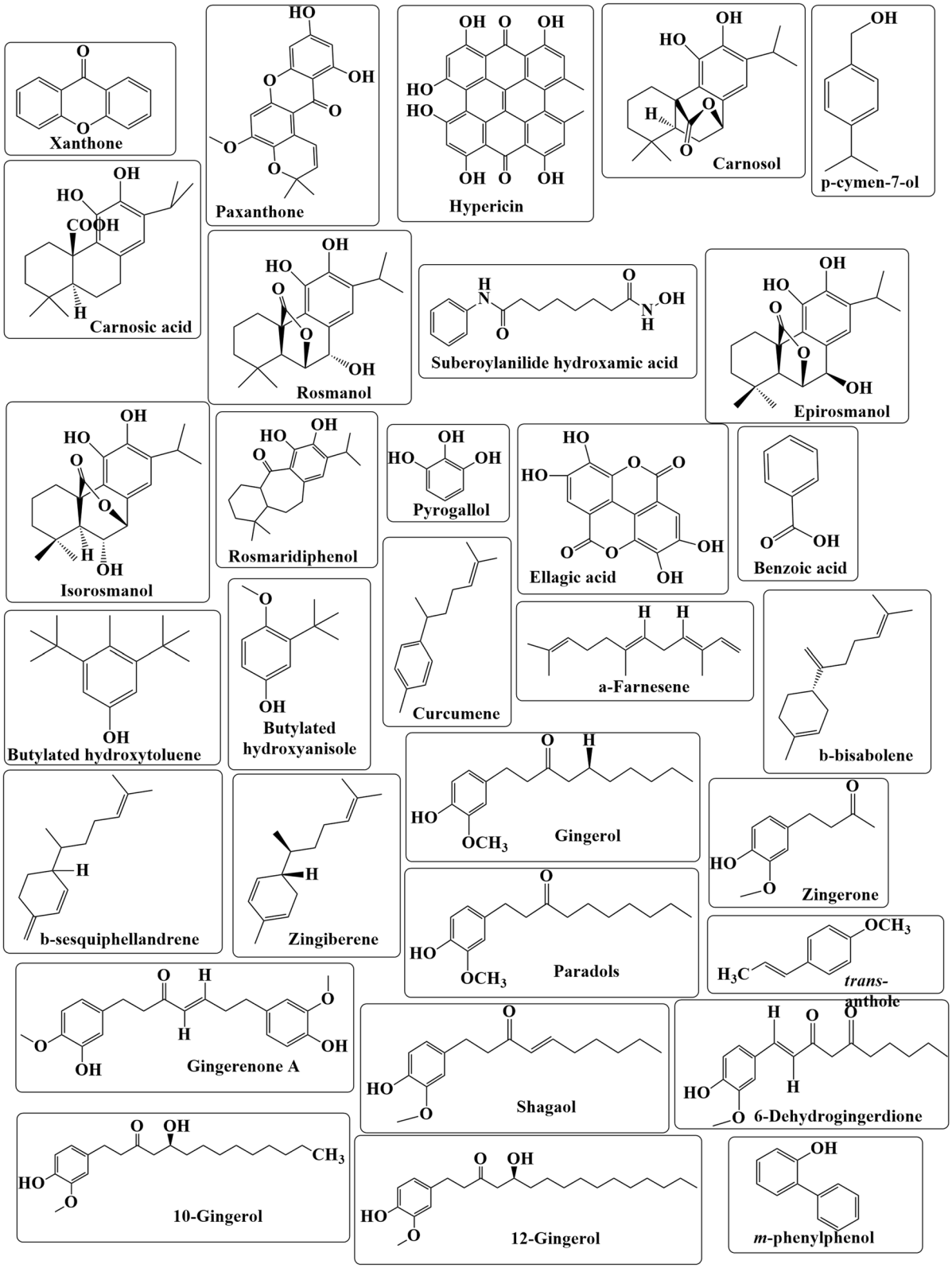


Fig. 9 (See legend on previous page.)

which is a key regulator that bind on target promoters to control *S. aureus* virulence factors. Moreover, HYP enhanced the efficacy of oxacillin in MRSA bacteremia model; therefore, these results might be due to the synergistic effect of HYP with oxacillin.

Rosemary (Rosmarinus officinalis, L.)

In addition to its use in food preservation to stop oxidation and microbial contamination, *Rosmarinus officinalis*, L., a member of the *Lamiaceae* family that originated in the Mediterranean, is renowned for its antioxidant, hepatoprotective, antiangiogenic, and potential treatment for Alzheimer's disease properties [290–292]. Numerous polyphenolic substances, including rosmarinic acid (Fig. 6), hesperidin (Fig. 2), carnosol, and carnosic acid, are found in rosemary (Fig. 9). According to various studies [293–295], rosemary essential oil contains 1,8-cineole, camphor, and -pinene p-cymene-7-ol in addition to borneol (Fig. 9). Fresh or dried leaves, flowers, fruits, roots, stems, seeds, and bark can all be used to make plant extracts, while dried samples were shown to contain higher quantities of flavonoids. Air, microwave, oven, and freeze drying are all acceptable drying techniques [296–298].

Antibacterial activity of rosemary *Rosmarinus officinalis* was found to have antibacterial properties in many research. In their research on the antibacterial properties of several natural extracts, including rosemary, Fernández-López et al. [299] examined how long the shelf life of veal meatballs could be stored for. The results showed that all of the studied microorganisms were susceptible to rosemary extracts (oil extract, water miscible extract, oil, and water-miscible extract), with oil extract having the strongest inhibitory impact. The most vulnerable bacteria were *Brochothrix* spp., which might be a reference to the antibacterial action of nonpolar phenolic compounds against gram-positive bacteria. Govaris et al. [300], Gomez-Estaca et al. [301], and both Camo et al. [302] and Quattara et al. [303] reported that rosemary EOs prevented food-spoileding bacteria from growing. *Rosmarinus officinalis* and *Ocimum basilicum* essential oils have been shown to have antibacterial action against multidrug-resistant clinical isolates of *E. coli* by Sienkiewicz et al. [293]. Since both EOs were effective against every clinical strain of *E. coli*, it can be inferred that they can be used to treat and prevent the emergence of resistance strains. Probuseenivasan et al. [304] and Mihajilov-Kristev et al. [305] found similar results, confirming rosemary essential oil's potent antibacterial action against *E. coli*. Carnosol, carnosic acid, rosmarinic acid, rosmanol, epirosmanol, isorosmanol, and rosmaridiphenol (Fig. 9) interact with the cell membrane and alter the production of nutrients, genetic material, and fatty acids to produce rosemary's inhibitory effects. Additionally, they affect electron transport, result in cellular component leakage, interact with proteins in the membrane, and cause a loss of membrane functionality [306, 307]. To increase the effectiveness of antibiotics against multi-drug-resistant bacteria like MRSA, Ekambaram SP et al. [308] looked into the antibacterial activity and synergistic effect of rosmarinic acid (dimer of caffeic acid) with conventional antibiotics. The agar well diffusion method was used to assess the antibacterial activity of rosmarinic acid against microorganisms. In comparison to using an antibiotic alone, the results demonstrated that rosmarinic acid had a synergistic impact with the medications ofloxacin, amoxicillin, and vancomycin against *S. aureus*. However, only the vancomycin and rosmarinic acid combination was effective against MRSA. The activity of rosmarinic acid on surface proteins known as microbial surface components recognizing adhesive matrix molecules (MSCRAMM's) present in *S. aureus* and MRSA was suggested to be the mechanism of action. Pomegranate, rosemary, and antibiotic were combined in a study by Abu El-Wafa et al. [309]. *P. aeruginosa* isolates with significant biofilm producers and antibiotic resistance were examined for the synergistic effects of the combination. Pomegranate and rosemary plant extracts were the most successful at inhibiting biofilm by lowering swimming and twitching motility, which in turn decreased bacterial cells adhering to surfaces and quorum-sensing (QS) signals. The presence of polyphenol molecules such catechol, pyrogallol (Fig. 9), gallic, ellagic, rosmarinic acid, and benzoic acid may be referred to as these activities. There are, however, limited reports of plant extracts' antibacterial and antibiofilm activity [114, 310–312]. As a result, combining plant extracts with antibiotics may be able to prevent and get rid of microbial biofilms. Pomegranate and rosemary plant extracts combined with piperacillin, ceftazidime, imipenem, gentamycin, or levofloxacin had synergistic effects against a *P. aeruginosa* isolate and dramatically reduced biofilm mass after 24 h compared to the use of the plant extracts separately or together. To investigate the effects of medicinal plants and commercial antibiotics against bacterial pathogens, additional in vitro and in vivo investigations are required. In vitro tests using butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA), two antioxidant food additives, and rosemary methanol extract were also conducted by Romano et al. [313] to examine the antioxidant and antibacterial properties of the extract (Fig. 9). The outcomes demonstrated that rosemary extracts (rosmarinic acid, carnosic acid, and carnosol) increased the antioxidant activity of BHT and BHA as well as the antibacterial activity of BHA.

Ginger (Zingiber officinale)

Zingiber officinale, a member of the Zingiberaceae family, has been used as a spice and a herbal remedy since ancient times [314]. Due to the presence of numerous bioactive components like terpene (e.g. α-curcumene, α-farnesene, β-bisabolene, β-sesquiphellandrene, and zingiberene) (Fig. 9), and phenolic compounds (e.g. gingerols, paradols, shogaols, gingerenone-A (Fig. 9), quercetin (Fig. 5), zingerone, and 6-dehydrogingerdione (Fig. 9)) [315–319], the ginger root is the most significant component that is used to cure a variety of illnesses including nausea, emesis, headaches, and colds. The majority of biological actions, including those that are antioxidant, anticancer, anti-inflammatory, and antibacterial, are caused by phenolic compounds [319–322]. Additionally, a number of studies [323–328] demonstrated that ginger can prevent and treat a wide range of illnesses, including neurodegenerative diseases, diabetes mellitus, obesity, cardiovascular diseases, respiratory problems, and nausea and emesis brought on by chemotherapy.

Antibacterial activity of ginger Ginger essential oil is derived from the roots and has potential uses in a variety of industries, including pharmaceuticals, cosmetics, and food. *Shewanella putrefaciens* is a Gram-negative spoilage bacterium that can be found in aquatic products. *Zhang* et al. [329] studied the antibacterial activity of ginger essential oil against this bacterium. Result showed that ginger EO (Zingiberene, zingerone and α-curcumene) displayed significant antibacterial activity with MIC and MBC values of 2.0 and 4.0 µL/mL, respectively, against *S. putrefaciens* by disturbing cell membrane integrity. Additionally, ginger essential oil (EO) has the power to alter biofilm metabolism and kill it, supporting its usage as a natural food preservative. By Wang et al. [330], who extracted ginger essential oil using supercritical CO2 and steam distillation techniques, ginger was also demonstrated to be excellent for food preservation. The primary components were identified by GC–MS as zingiberene and α-curcumene, and their antibacterial efficacy was evaluated mostly against the pathogens that cause food deterioration, *E. coli* and *S. aureus*. Through bacterial cell membrane damage that resulting in protein and nucleic acid leaks, ginger EOs demonstrated remarkable bactericidal efficacy. This decreases bacterial metabolic activity, which ultimately leads to bacterial cell death. The expression of several genes encoding important enzymes, the tricarboxylic acid cycle, DNA metabolism, and proteins involved in cell membranes is all inhibited by ginger EOs. Similar mechanisms of action were also observed by Zhang et al. [331] who found that ginger extract damaged the *Ralstonia solanacearum* cell membrane's permeability and integrity, leading to the leakage of several cell components, including nucleic acids, proteins, and others, as well as changes in the bacteria's shape. Additionally, Atai et al. [332] showed that ethanol ginger extract can be utilized to treat oral candidiasis and suppress the growth of *Candida albicans*. In the same context, Park et al. [333] assessed the ginger's ability to suppress mouth microorganisms linked to periodontitis. Result revealed that ginger extracts including 10-gingerol and 12-gingerol (Fig. 9) exhibited antibacterial activities against anaerobic Gram-negative bacteria, *Porphyromonas endodontalis, Porphyromonas gingivalis*, and *Prevotella intermedia* which causes periodontal diseases. Chairgulprasert et al. [334] extracted ginger EOs by steam distillation of fresh rhizomes and identified its chemical constituents by GC–MS which found the presence of *trans*-anethole, *m*-phenylphenol, (Fig. 9) estragol, and camphor in the extract. Results showed that petroleum ether and dichloromethane extracts in addition to the EOS were able to inhibit different bacterial pathogens such as *E. coli, S. aureus, Bacillus substilis,* and *Sarcina* sp.; on the other hand, no activity was recorded against *P. aeruginosa.* Research investigations are focusing on the effectiveness of combining medicinal herbs with antibiotics for enhanced antibacterial action. Using antibiotics (Ceftazidime), Sagar PK et al. [335] assessed the antibacterial activity of crude methanol extracts of medicinal plants like eucalyptus, clove, and ginger against *P. aeruginosa*. Isolates. With ceftazidime, all plant extracts had a synergistic impact on *P. aeruginosa*. When ginger and eucalyptus extracts were mixed, their separate MICs were not reduced; however, when ginger and clove extracts were combined, a maximum twofold reduction in MIC was discovered. When ginger extract was used with aminoglycosides to treat vancomycin-resistant *enterococci* (VRE), MIC values were also lowered. By increasing membrane permeability and improving the influx of aminoglycosides into enterococcal cells, 10-gingerol has been shown by Nagoshi et al. [336] to be able to lower MICs of many aminoglycosides, including arbekacin, bacitracin, and polymyxin B. The effectiveness of 6-gingerol alone and in combination with amphotericin B against Leishmania in vivo murine models was evaluated by Alireza Keyhani et al. [337]. In addition to its capacity to create an apoptotic index, raise the expression of Th1-related cytokines, and decrease transcription factor levels, the combination demonstrated a strong antioxidant and extreme leishmanicidal activity. When combined with fluconazole, methanol ginger extract demonstrated antifungal activity against drug-resistant *vulvovaginal candidiasis* (VVC) in a mouse model, according to Khan et al. [338]. As compared to fluconazole or ginger extract used alone, which did not entirely cure VVC, in vitro results revealed better activity for the combination of fluconazole

and ginger extract against *C. albicans*. Azole-resistant candidiasis may therefore be treated by administering this combination.

Cactus (Opuntia ficus-indica)

Opuntia ficus-indica (*L.*), sometimes known as the nopal cactus, is a tropical and subtropical plant found in South Africa, Mexico, Latin America, and Mediterranean nations [339]. All cactus portions contain high levels of polyphenols, which have anti-inflammatory and antioxidant qualities. The most significant source of polyphenols and flavonoids, including gallic acid, is found in flower parts. These compounds have cytotoxic and antioxidant properties that lessen DNA damage [340–342]. Cactus fruit, also known as cactus pear, also contains fibres, ascorbic acid, vitamin E, amino acids, and carotenoids, all of which have hypoglycemic and hypolipidemic effects [342–344]. Due to the abundance of fatty acids, it contains, including oleic acid, palmitic acid, linolenic acid, and linoleic acid (Fig. 10); cactus cladodes can have a hypocholesterolemic impact [345, 346]. Therefore, *Opuntia ficus indica* have been used in traditional medicine due to the abundance natural compounds and derivatives for treating burns, oedema, wounds obesity, and hyperlipidemia, in addition to its antiviral, anti-inflammatory, and hypoglycemic properties[347].

Antibacterial activity of Cactus The extensive use of cactus pears flowers in traditional medicine is a result of their abundance in natural bioactive substances. Protein, fibre, and minerals make up the chemical makeup of cactus hexane extracts, as demonstrated by Ennouri et al. [348]. In the plant extract, octadecadienoic acid and palmitic acid (Fig. 10) were the primary components and potassium was the leading mineral. Antibacterial activity against *E. coli* and *S. aureus* was highly effective which suggest using cactus as a food preservative. There are few studies available on the antibacterial activities of *O. ficus-indica*. The plant has proven to be effective in wound healing and skin conditions such as healing laser-induced skin burns. Khémiri et al. [349] demonstrated that cactus was able to inhibit cutaneous infections by showing antimicrobial effect against *Enterobacter cloacae,* antifungal activity against *Penicillium, Aspergillus, and Fusarium* (opportunistic cutaneous moulds), and antiyeast effect against *Candida sake* and *Candida parapsilosis*. Therefore, cactus-extracted oil is a good healing agent due to its antibacterial effect and the ability to reduce reepithelialization phase. Future investigations are needed to identify the active compounds in the oil extract and its mechanism of action involved in the healing process. Ammar et al. [350] also evaluated cactus flowers extracts (mucilaginous and methanol) antioxidant and antibacterial activities for enhancing wound healing in excision wound model in rats. A beneficial effect was noticed on cutaneous repair which assessed by acceleration in wound contraction and remodelling phases. Both extract showed antibacterial activities against tested gram-negative and gram-positive bacterial strain, *E. coli, S. aureus, Bacillus subtilis,* and *Listeria monocytogenes*, while no antibacterial activity was noticed against *P.aeruginosa.* The result supports the use of *O. ficus-indica* as therapeutic agent for dermal wound healing, but more research is needed to know the exact mechanism of action. Alqurashi et al. [351] explored biological activities of oil from *Opuntia ficus-indica* seed and showed that it possesses an inhibitory action against *Saccharomyces cervisiae* while no activity against *Aspergillus niger.* On the other hand, Elkady et al. [352] isolated endophytic *Aspergillus niger* fungus from cactus fruit peels and tested the effect of endophytic ethyl acetate extract and its isolated compounds (dihydroauroglaucin, isotetrahydroauroglaucin, and cristatumin B) (Fig. 10) on resistant bacterial strains. Result showed excellent activity against Gram-negative and gram-positive resistant bacteria. Another study done by Elkady et al. [353] tested methanol extract of cactus against pneumonial pathogens (*Streptococcus pneumoniae, Klebsiella pneumoniae, P. aeruginosa, Legionella pneumophila, Moraxella catarrhalis, and Stenotrophomonas maltophilia*). The isorhamentin3-O-glucoside and isorhamnetin (Fig. 10) compounds show moderate antibacterial activity against all tested microorganisms, while quercetin5,4'-dimethyl ether, which was isolated from the cactus ethyl acetate fraction, demonstrated the most antibacterial activity. According to these findings, *O. ficus-indica* and the components that were extracted from it can work as new all-natural antibacterial agents for the treatment of infectious disorders. Further studies in vivo are needed to confirm the antibacterial activity of the extracts. Sánchez et al. [353] studied antibacterial and antibiofilm activity of several methanolic plant extracts against nosocomial microorganisms. Methanolic plant extracts were tested against specific clinical bacterial isolates by using well diffusion method, and results showed that Prosopis *laevigata* extract was active against all the clinical isolates with highest inhibition diameter against *S. aureus* strain compared to *Gutierrezia microcephala* and *O. ficus-indica* that showed lesser inhibition diameter and no activity for Nothoscordum *bivalve* extract. *E. coli* was less susceptible, while *K. pneumoniae* and E. *faecalis* were more resistant to the extracts except for P. *laevigata* and *O. ficus-indica.* The major reduction on the specific biofilm formation index (SBF) in dose-dependent manner and on cytotoxic activity (using brine shrimp lethality test) was caused by *O. ficus-indica.* Unfortunately, there are no available studies and data on the synergistic effect of *O. ficus-indica* with antibiotics which highlights

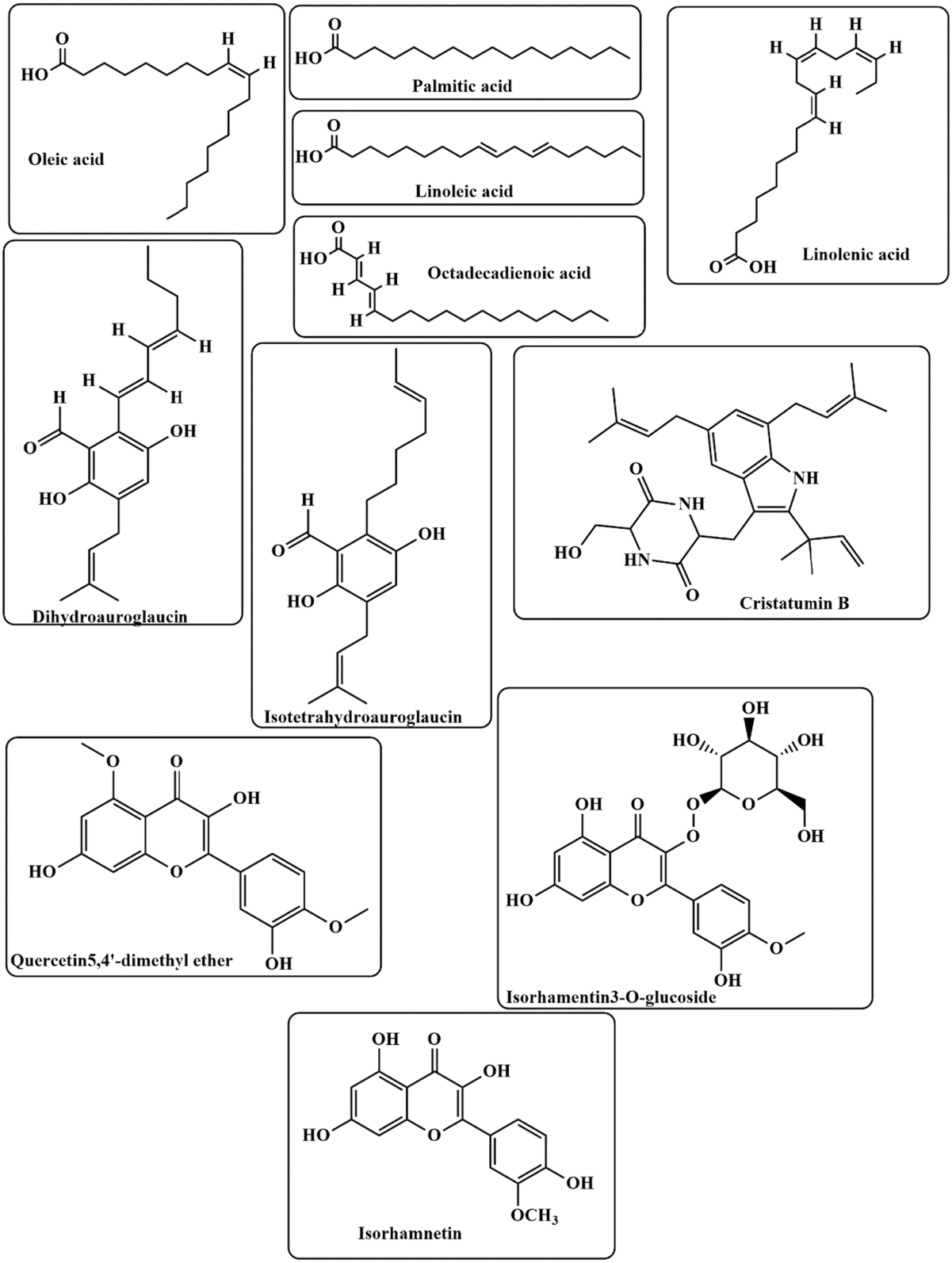


Fig. 10 Chemical structure of bioactive compounds from nopal cactus including oleic acid, palmitic acid, linolenic acid, linoleic acid, octadecadienoic acid, dihydroauroglaucin, isotetrahydroauroglaucin, cristatumin B, quercetin5,4′-dimethyl ether, isorhamentin3-O-glucoside, isorhamnetin

the need for researcher to focus on studying synergistic or additive effect of herbal plants, especially *O. ficus-indica* with antibiotic to discover new treatments.

Medicinal plants and wound healing

The epidermis, dermis, and hypodermis are the three layers of the skin, one of the biggest organs in the body. Additionally, it serves as the initial line of defence against aggressors like infections, chemicals, and physical contact. Due to the function of the epidermis, which blocks the entry or exit of water- or water-soluble substances, and the hypodermis, which blocks heat loss due to the poor thermal conductivity of fat, it also has the capacity to prevent water loss and preserve temperature [354–357]. In order to maintain skin hemostasis during inflammation, immune cells and nonimmune cells form a structure known as skin-associated lymphoid tissue (SALT). Additionally, the skin's microbiome, which includes bacteria, fungi, and viruses, is crucial for immune response, concluding that the skin serves as more than just a physical barrier [354, 358, 359]. Over the years, natural product ingredients such polyphenols, fatty acids, probiotics, polysaccharides, and others have demonstrated their efficacy as immune system modulators. The secret to controlling or curing skin inflammatory problems may lie in using natural products [360–362]. Skin can react to infectious agents through innate and adaptive immune processes, just as other tissues like mucosal surfaces. To isolate the damaged area, stop bleeding, and initiate the coagulation cascade, a clot must first form in order for the wound healing process to begin. Then comes the inflammatory phase, where immune cells begin to infiltrate and high levels of pro-inflammatory mediators are discovered to stop pathogen entry and more serious problems. The next stage is the proliferative phase, which is characterized by a significant growth of skin-resident cells including fibroblasts and high levels of angiogenesis. The remodelling phase, which may last for more than a year after the injury, is the longest and involves the skin regaining its natural structure. Any issue throughout these stages may hamper wound healing, which may then result in infections, excruciating pain, and occasionally neurological damage [363–366]. Several factors can cause impaired wound healing such as local factors that influence the characteristics of the wound like oxygenation and infections and systemic factors in which overall health or disease state affects the ability to heal like hormones and diabetes [367–370]. Impaired wound healing can result from a variety of factors, including local ones that alter the characteristics of the wound, such oxygenation and infections, as well as systemic ones, like hormones and diabetes, that have an impact on overall health or disease states and the capacity to heal. Numerous abnormalities, including fibrosis, scarring, and nonhealing wounds like persistent ulcers, can result from aberrant wound repair [371, 372]. New compounds with antioxidant, anti-inflammatory, and anticarcinogenic properties are being researched to prevent skin damage. Natural substances have been employed as antitumoural, analgesic, anti-inflammatory, and antioxidant agents [373, 374]. Table 2 lists the top plants for healing wounds.

Biopolymers

Pathogenic microorganisms (bacteria, viruses, and unicellular and multicellular eukaryotes) can cause several series diseases which are a public health concern [440]. Different pathogens accumulate in acute and chronic wounds such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, and others which can affect wound healing process and increase life-threatening problems [441, 442]. Because they are naturally occurring biomolecules derived from bacteria, animals, and plants, biopolymers play a significant role in wound care. These bioactive features include antimicrobial, cell proliferative, angiogenic, and immune-modulatory polymers. These qualities, along with their biodegradability, renewability, and decreased antigenicity, rendered them more advantageous for the healing process than synthetic materials, which have problems with biocompatibility because of their harmful effects [443–445]. Natural biomaterials like cellulose, hyaluronic acid, collagen, alginate, and chitosan (Table 3) are frequently used in the wound care industry. With the advancement of technology, the characteristics of biopolymers can be improved to meet a variety of wound care needs, including tissue repair, scar-less healing, and integrity restoration of lost tissue [446, 447]. By preventing microbes from directly interacting with the bacterial cell wall, producing ROS to increase oxidative stress, and inducing the leaking of macromolecules like DNA and proteins from microorganisms, antimicrobial biomaterials can aid in the healing of wounds [442, 448].

Extracellular vehicles (EVs)

Extracellular matrix (ECM), growth factors, and hormones are just a few of the biomaterials and composites that have recently undergone modifications to improve cell survival, motility, and proliferation. One of the most promising methods for wound healing is extracellular vehicles (EVs). EVs are released by a variety of cells and are crucial for the phases of wound healing (hemostasis, inflammation, proliferation, and remodelling) as well as intercellular communication that promotes regeneration. Additionally, by labelling EVs with certain surface proteins, they can be created to carry particular cargo and employed for targeted delivery [469–473]. Exosomes,

Table 2 Most used medicinal plants in treating skin disorders

Plant name	Active compounds	Therapeutic uses	References
Achillea millefolium L	Flavonoids, monoterpenes, and sesquiterpenes	Skin inflammatory and wound healing	[375–379]
Aloe vera	Acemannan (Fig. 11)	Wound healing	[380, 381]
Bletilla striata	Triterpenoids and polysaccharides	Drug delivery, wound dressing, and wound healing	[382, 383]
Blumea balsamifera	L-Borneol (Fig. 11)	Dermatitis, eczema, skin bruises, and skin injury	[384, 385]
Boswellia sacra	Boswellic acids (Fig. 11)	Improvement of blood circulation, pain treatment, and rheumatoid arthritis	[386–389]
Caesalpinia sappan	Brazilin and Sappanchalcone (Fig. 11)	Improvement of blood circulation, pain treatment, and oedema	[390, 391]
Calendula officinalis	Esculetin, and Quercetin-3-O-glucoside (Fig. 11)	Burns, dermatitis, and wound healing	[392–394]
Celosia argentea	Celosin I and Celosin II (Fig. 11)	Skin sores and ulcers	[395, 396]
Centella asiatica	Asiaticoside and Madecassoside (Fig. 11)	Wounds healing	[397–399]
Cinnamomum cassia	Cinnamaldehyde (Fig. 5)	Analgesia and improvement of blood circulation	[399, 400]
Commiphora myrrha	Furanoeudesma-1,3-diene and Terpene (Fig. 12)	Gastrointestinal diseases, wounds, and pain	[401–404]
Curcuma longa	Curcuminoids (Fig. 12)	Digestive diseases, liver disorders, menstrual difficulties, pain disorders, sprains, and wounds	[405, 406]
Entada phaseoloides	Tannin (Fig. 12)	Aging, atherosclerosis, cancer, diabetes, and neurodegenerative disorders	[407, 408]
Ganoderma lucidum	Ganoderma lucidum polysaccharide	Cancer, diabetes, hepatitis, leukaemia, and ulcer	[409–413]
Ligusticum striatum	Phthalide lactones, and alkaloids	Antiatherosclerotic, antioxidant, neuroprotective, and vasorelaxant	[414–418]
Panax ginseng	Ginsenosides (Fig. 12)	Laser burn, excision wounds models in mice, cell migration, and wound healing assays	[419–424]
Polygonum cuspidatum	Emodin, polydatin, and resveratrol (Fig. 12)	Hepatitis, hyperlipidemia. Jaundice, scald, skin burns, and suppurative dermatitis	[425–428]
Rheum officinale	Emodin (Fig. 12)	Chronic kidney disease, hepatitis, and wounds healing	[429–431]
Sanguisorba officinalis	Polysaccharides, tannins, triterpenoid glycosides, and triterpenoids	Burns, chronic intestinal infections, haemorrhoids, menorrhagia, and scalds	[432–434]
Sophora flavescens	Kushenol, and sophoraflavanone B (Fig. 12)	Asthma, burns, dysentery, eczema, fever, hematochezia, inflammatory Jaundice, oliguria, and vulvar swelling	[435]
Wedelia trilobata	Kaurenoic acid (Fig. 12) and Luteolin (Fig. 5)	Arthritic painful joints, rheumatism, and stubborn wounds	[436, 437]
Zanthoxylum bungeanum	Afzelin, hyperoside quercitrin, and rutin (Fig. 12)	Skin wrinkles	[438, 439]

which are created during endosomal sorting, microvesicles, which directly arise from plasma membranes, and apoptotic bodies, which are created following cell death, can all be classified as subpopulations of EVs [474–476]. The regulation of hemostasis and each stage of wound healing are considerably aided by EV. The most prevalent EVs in blood circulation are platelet-derived EVs (PEVs) [476–478]. The activated form of integrin IIb-3 mediates the role of PEVs from thrombin-stimulated platelets in the development of fibrin clots [479]. This form of integrin αIIbβ3 has a high affinity for fibrinogen. PEVs were also discovered to bind tissue factor (TF) and factor XII, as well as to stimulate the generation of thrombin, but only in the presence of factor VII and xii, indicating that they mediate both intrinsic and extrinsic coagulation pathways [480]. Neutrophil-derived EVs (NDEVs) have been shown to have pro- or anti-inflammatory effects by boosting the production of ROS and IL-8 [481]. EVs are also involved in inflammation. Additionally, EVs take part in the remodelling phase (starting fibroplast differentiation) and the proliferation phase (EVs from wound edge keratinocytes, or KCs-EVs) [482]. EVs can be made from plants, stem cells, or engineering [482, 483]. Membranous vesicles formed from plants are similar to mammalian exosomes but have different chemical compositions and include fewer proteins and no cholesterol in the lipid layer. EVs made from plants are less harmful, safer, and expensive. Wheat, broccoli, ginger,

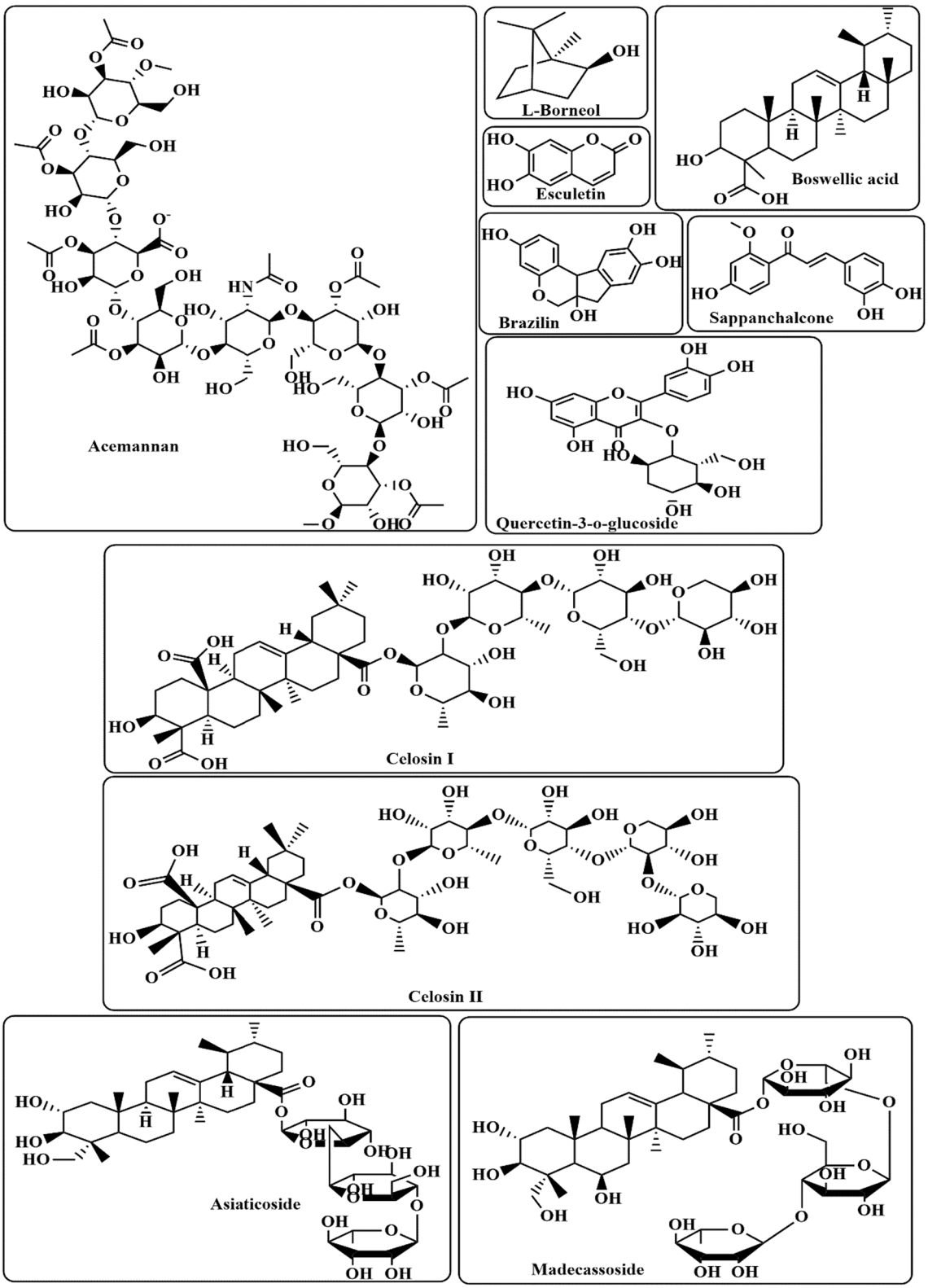


Fig. 11 Chemical structure of active compounds found in medicinal plants used to treat skin disorders including, acemannan, L-Borneol, boswellic acids, brazilin, sappanchalcone, esculetin, quercetin-3-O-glucoside, celosin I, celosin II, asiaticoside, and madecassoside

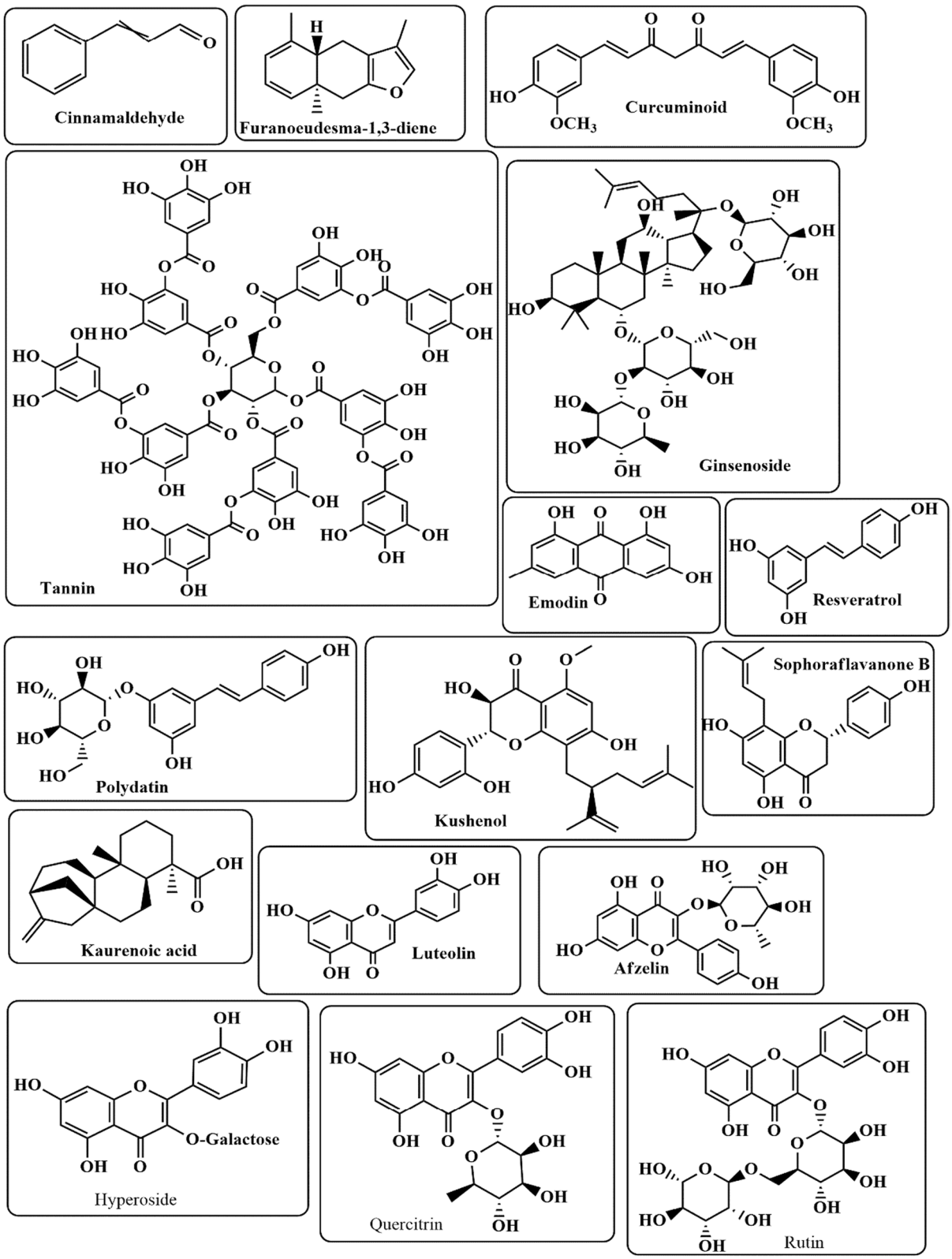


Fig. 12 Chemical structure of active compounds found in medicinal plants used to treat skin diseases cont. including cinnamaldehyde, furanoeudesma-1,3-diene, tannin, ginsenoside, emodin, polydatin, resveratrol, kushenol, sophoraflavanone B, kaurenoic acid, afzelin, hyperoside, and rutin

Table 3 Natural biopolymers used in wound healing process

Biopolymer	Source	Biological role	References
Collagen	Cattle and porcine slaughterhouse wastes	Skin tissue engineering, nerve regeneration, vitreous replacement, coating of bioprostheses, and others	[449–452]
Cellulose	Plant's cell wall (e.g. *Hibiscus Cannabinus*) and in several bacteria (e.g. *Gluconacetobacter, Agrobacterium*, and *Sarcina*)	Artificial skin substitute and as regeneration of tissue for wound healing purposes	[453, 454]
Alginate	Brown algae	Biomedical, cosmetics, pharmaceutical, food industries	[455–459]
Hyaluronic acid	Synovial fluid, articular cartilage, and mammalian bone marrow	Bone regeneration, tissue engineering, drug delivery, tumour cell targeting, skin aging treatment, reduced wrinkles, skin firmness, skin hydration, wound healing, and others	[459–462]
Chitosan	Partially deacetylation of chitin	Wound healing, tissue engineering, cartilage regeneration, gene delivery, drug delivery, bioadhesive, and others	[459, 463]
κ-carrageenan	Red seaweeds (Rhodophyceae)	Anti-inflammatory, antithrombotic, cytoprotective, antiviral, antitumour, antioxidant, antipathogenic, drugs delivery, wound dressing, and wound repair	[464, 465]
Silk fibroin	Silkworms, spiders, and other insects	wound healing, skin restoration, cellular adhesion, wound contraction, re-epithelialization, angiogenesis, collagen production, stimulation of cell migration, and inactivation of the apoptotic pathway	[466–468]

grapefruit, grape, lemon, and EVs were also discovered in the xylem and phloem of woody plants, according to recent investigations [484, 485]. Several plant have been known in pharmacognosy and phytochemistry to own antibleeding and hemostatic properties such as *Rubia cordifolia*,*Alchornea cordifelia*, *Aspilia africana*, *Baphia nitida*, *Ageratum conyzoides*, *Chromolaena odorata, Jathropha curcas*, *Landolphia owariensis, Dalbergia sissoo*, *Aloe spesiosa*, *Beta vulgaris*, *Humulus lupulus*, *Salix alba*, and others [486–488]. Different studies demonstrated the effect of plant-derived EVs on wound healing; Perut et al. [489] isolated and purified plant-derived exosome-like nanovesicles (EPDENs) from strawberry juice of *Fragaria* x *ananassa* which is characterized of high anthocyanins, folic acid, flavonols, vitamin C, and short RNAs and miRNAs contents. The uptake of *Fragaria*-derived EPDENs by mesenchymal stromal cells (MSC) did not affect cell viability and prevented oxidative stress which may be due to the presence of vitamin C. Additionally, exosome-like nanovesicles isolated from Citrus limon L. (EXO-CLs) were investigated and examined in vitro on MSC by Baldini et al. [490]. The findings indicated that EXO-CLs contained short RNA sequences (20–30 bp), vitamin C, and citrate. EXO-CLs were taken up by MSC and had a significant antioxidant activity, according to in vitro tests. Ju et al. team also found that grape exosome-like nanoparticles (GELNs) have a protective effect against dextran sulphate sodium-induced colitis and facilitate intestinal tissue remodelling [491]. Similar outcomes were also observed with ginger-derived EVs, which promoted intestinal wound healing and are presently being investigated in clinical trials for inflammatory bowel disease and colon cancer [320, 482, 484]. Other plant-derived EVs, such as those from grapefruit and wheatgrass, improved wound healing by boosting cell viability and motility [485, 492]. The formation of hypertrophic scars and keloid lesions has also been demonstrated to be decreased by herbal extracts and active herbal compounds, including onion extract, epigallocatechin gallate from green tea, resveratrol obtained from peanuts, and others [493]. To retain EVs at the wound site and encourage longer, more effective results, they can be applied topically or encapsulated into scaffolds like hydrogels. Natural polymers like chitosan, alginate, and collagen are examples of hydrogels. Synthetic polymers like polyethene glycol, polyglycolic acid, and polyurethane are also possible [494–497]. A promising method to introduce EVs into the wound site with extended release involves encapsulating them in hydrogels [498]. To create naturally produced EVs for wound healing, further research on particular plant species is required.

Treatment of skin disorders

Diabetic foot ulcers (DFUs) Patients with uncontrolled diabetes mellitus frequently develop diabetic foot ulcers (DFUs), which can be brought on by poor glycemic management, peripheral vascular disease, neuropathy, or inadequate foot care [499]. According to the International Diabetes Foundation [500], there are 40–60 million persons worldwide with DFUs. DFUs can be treated using several methods, including as gene therapy, stem cells, skin substitutes, and antibiotics. Due to the high cost of local debridement (removal of nonviable wound tissue) and negative pressure therapy, antibiotic resistance as

a result of prolonged use, the ineffectiveness of growth factors to inhibit bacterial growth, and the existence of stem cell and gene therapies in the experimental stage, nonsurgical treatments for DFUs must be quick and inexpensive [501]. Due to their anti-inflammatory qualities, several herbal extracts have been utilized as traditional treatments to treat wounds. Liu et al. [501] designed an experiment to explore the effects of five herbal extracts on wound healing, *Bauhinia purpurea* (inhibit inflammation, and act as analgesic and antipyretic) [502], *Paeoniae rubrae* (ameliorating inflammation by inhibiting glycogen synthase kinase 3β (GSK3β)) [503], *Angelica dahurica* (accelerate wound healing by regulating inflammation) [504], *Acorus calamus* L (promote collagen maturation) [505], and *Radix Angelicae biseratae* (inhibit inflammation and regulate immune system in osteoarthritis) [506]. In order to determine the mechanisms of action for wound healing, the mixture of herbal plants was identified by Ultra-High-Performance Liquid Chromatography (UHPLC) and Quadrupole Exactive-Mass Spectrometer (QE-MS) and tested in vivo on a rat model with diabetic ulcer wound utilizing transcriptomics and proteomics. The mixture speeds up the healing of wounds by encouraging angiogenesis and the growth of M2 macrophages, according to the results. Specific miRNAs and proteins were found to be crucial for controlling wound healing by transcriptomics and proteomics. Consequently, the herbal combination may offer a potential method to quicken the healing of diabetic wounds [501].

Atopic dermatitis (AD) Atopic dermatitis (AD), a chronic and relapsing inflammatory skin condition that affects children and is characterized by itchy, eczematous skin lesions, is another skin condition [507, 508]. Intense itching results in skin damage that compromises tissue repair and allows microorganisms to infiltrate the skin [509, 510]. The absence of precise disease processes is a challenge for the development of successful AD therapeutics. Flavonoids, a type of secondary metabolite found in plants, exhibit a variety of antiallergic properties, including antioxidant, anti-inflammatory, antiangiogenic, antibacterial, and antiviral effects [511, 512]. In foods ingested as part of a daily diet, quercetin (Fig. 5) is an illustration of a flavonoid [513]. Quercetin inhibits the release of histamine, proinflammatory cytokines, and interleukin (IL)-4 and -13, among other antiallergic characteristics. Despite this, there have only been a few research on quercetin's effects on AD [514, 515]. Therefore, Beken et al. [516] studied the effect of quercetin on AD model of human keratinocyte and treated it with IL- 4, -13, and tumour necrosis factor-α (TNF-α) to mimic AD in vitro. Result showed that quercetin accelerated wound healing by reducing AD-inducing agents IL-1β, IL-6, IL-8, thymic stromal lymphopoietin, phosphorylation of extracellular signal-regulated kinase 1/2/mitogen-activated protein kinase (ERK1/2 MAPK), and nuclear factor-kappa B (NF-κB), while it upregulated the expression of IL-10, and antioxidant enzymes; glutathione peroxidase (GPx), superoxide dismutase-1 (SOD1), SOD2, and catalase (CAT), in addition to mRNA expression of Twist and Snail. Therefore, quercetin may act as a potential therapy for AD symptoms.

Conclusions and future recommendations

Extensive and inappropriate uses of antibiotics resulted in the development of antimicrobial resistance and the rise of bacterial strains that were resistant to multiple drugs (MDR) and multiple drugs extensively (XDR), which made the most powerful medications useless. Antimicrobial resistance is very concerning and urgent issue, and scientists are aware that the shelf life of antibiotics is finite. Natural product research is receiving a lot of interest internationally. Today, millions of people around the world turn to phytomedicine as one of their top options for the treatment of chronic illnesses. Medicinal plant extracts are crucial in the fight against infectious diseases that pose a threat to public health globally. Alkaloids, phenolics, polyphenols, terpenoids, essential oils, lectins, polypeptides, and polyacetylenes are a few examples of antimicrobial phytochemicals that can be utilized as adjuvants or substitutes against bacterial infections. Medicinal plants including St. John's wort (*Hypericum perforatum*), Rosemary (*Rosmarinus officinalis*), Ginger (*Zingiber officinale*), and nopal cactus (*Opuntia ficus-indica* (*L.*)) are attracting the interest of researchers due to their high phytochemical contents. Additionally, probiotics, polysaccharides, polyphenols, fatty acids, and other bioactive substances can modulate the immune system and treat inflammatory skin diseases such atopic dermatitis (AD) and diabetic foot ulcers (DFUs). Natural anticarcinogenic, anti-inflammatory, and antioxidant substances can be employed to stop skin deterioration. Biopolymers derived from microorganisms, animals, and plants (cellulose, hyaluronic acid, collagen, alginate, and chitosan) and extracellular matrix (ECM) have bioactive properties that make them promising approaches for wound healing. These properties include antimicrobial, immune-modulatory, cell proliferative, and angiogenic effects.

It is essential to create innovative plans and tactics to deal with the issue of rising AMR. Medicinal plants contain unlimited source of bioactive compounds which has been used in the treatment of many diseases, especially against bacterial infections. Despite that fact, natural compounds have not yet been thoroughly investigated and many are still unexplored. Therefore, researchers

should make efforts to isolate and identify new bioactive compounds from plant source to face antibacterial resistance and find new effective treatments. Researchers should focus on using appropriate extraction methods to isolate compounds from bioactive extracts, study the mechanism of action, test the compounds in vivo in animal models, and apply structural modification to improve pharmacodynamics and pharmacokinetics. Moreover, further studies should be done on the synergistic or additive interactions between plant compounds itself and with antibiotics to enhance the action of medications.

Abbreviations

AMPs	Antimicrobial peptides
AD	Atopic dermatitis
BHT	Butylated hydroxytoluene
BHA	Butylated hydroxyanisole
CAT	Catalase
COPD	Chronic obstructive pulmonary disease
CNS	Coagulase-negative staphylococci
CHF	Congestive heart failure
CVNHs	Cyanovirin-N homologs
COX-2	Cyclooxygenase-2
CXCL	Chemokine
CRPs	Cysteine-rich peptides
DFUs	Diabetic foot ulcers
DCM	Dichloromethane
EAE	Enzyme-assisted extraction
SFE	Supercritical fluid extraction
EOs	Essential oils
EDA	Eucheuma denitculatum
ESA	Eucheuma serra
EXO-CLs	Exosome-like nanovesicles isolated from *Citrus limon* L.
ECM	Extracellular matrix
ERK1/2 MAPK	Extracellular signal-regulated kinase 1/2/mitogen-activated protein kinase
EVs	Extracellular vehicles
GNA-like	Galanthus nivalis agglutinin-like
GMA	Galaxaura marginate
GC	Gas chromatography
GPx	Glutathione peroxidase
GSK3β	Glycogen synthase kinase 3β
GELNs	Grape exosome-like nanoparticles
SD-GCMS	Headspace-gas chromatography/mass spectrometry
HTS	High-throughput screening
HPLC	High-performance liquid chromatography
HPTLC	High-performance thin-layer chromatography
HA	Hyaluronic acid
HPF	Hyperforin
Hyp	Hypericin
IR	Infrared spectroscopy
IFN-γ	Interferon
IL	Interleukin
IAs	Isoquinoline alkaloids
JRL	Jacalin-related lectin
LC–ESI–MS/MS	Liquid Chromatography Electrospray Ionization Tandem Mass Spectrometric
LPS	Lipopolysaccharide
MS	Mass spectrometry
MSC	Mesenchymal stromal cells
MeOH	Methanol
MRSA	Methicillin-resistant *S. aureus*
MSCRAMM's	Microbial surface components recognizing adhesive matrix molecules
MICs	Minimum inhibitory concentrations
MDR/XDR	Multi- and extensively drug-resistant
NDEVs	Neutrophil-derived EVs
NLRP3	NOD-like receptor 3
NF-κB	Nuclear factor-kappa B
NMR	Nuclear magnetic resonance spectroscopy
OGEO	*Ocimum gratissimum* L. essential oil
OAAH	Oscillatoria agardhii agglutinin homolog
OA	Osteoarthritis
PC	Paper chromatography
PEVs	Platelet-derived EVs
TPA	Proanthocyanidin
PGE2	Prostaglandin E2
QE-MS	Quadrupole exactive-mass spectrometer
QS	Quorum sensing
ROS	Reactive oxygen species
STAT	Signal transducer and activator of transcription
SALT	Skin-associated lymphoid tissue
SPME-GC/MS	Solid-phase microextraction-gas chromatography/mass spectrometry
SJW	St. John's wort
SOC	Standard of care
SAHA	Suberoylanilide hydroxamic acid
S-CO2	Supercritical carbon dioxide
SF	Supercritical fluid
SOD1	Superoxide dismutase-1
THC	Tetrahydrocannabinol
TLC	Thin-layer chromatography
TF	Tissue factor
TLR4	Toll-like receptor 4
TFC	Total flavonoid contents
TPC	Total phenolic
TCM	Traditional Chinese medicine
TB	Tuberculosis
TNF-α	Tumour necrosis factor-α
UHPLC	Ultra-high-performance liquid chromatography
UAE	Ultrasound-assisted extraction
UV	Ultraviolet spectroscopy
VRE	Vancomycin-resistant enterococci
VBNC	Viable but nonculturable cells
VVC	Vulvovaginal candidiasis
WHO	World Health Organization
ARs	α2-Adrenergic receptors

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