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REVIEW ARTICLE

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Plant Secondary Metabolites as Antimicrobial Agents: Structural Diversity, Bioactivity and Modes of Action

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ABSTRACT

World Health Organization has defined medicinal plants as any plant which contains a substance that can be used for therapeutic purposes or which are precursors for semi-synthetic or synthetic new drug. Accessibility, cost effectiveness and potency are among the reasons why medicinal plants are drugs of choice for treatment of various diseases among the local populace. Medicinal plants are rich in phytochemicals which are also referred to as secondary metabolites. They are important source for the discovery and development of new medicinal products. There are various classes of secondary metabolites such as Phenolics, Alkaloid, Saponin, Tannin among others, which have been found to have high bioactivity as antioxidants, anti-depressants, anti-cancer, anti-viral, anti-parasitic, anti-fungal and antibacterial. Most research studies were centered on the use of the crude extracts for bioactivity determination rather than the phytochemicals, thus calling for urgent research attention in this regard and the modes of action of each specific secondary metabolite against human and microbial cells.

Keywords: Plant secondary metabolites, Phytochemicals, Antimicrobial activity, Phenolics.

INTRODUCTION

Medicinal plants in its array of diversity are the richest resources used in the treatment of various diseases in folkloric and modern medicine. They have been recognized as potential drug candidates because they possess drug like properties. The quest for research advancement into bioactive ingredients of different plant extracts promoted the isolation of secondary metabolites as a prospective basis of new antimicrobial agents (Prasad *et al.*, 2012; Shakya, 2016; Kushwaha and Kumar, 2017). The indiscriminate use of commercially available antimicrobial drugs in recent times has led to multiple resistances in human pathogenic microorganisms thus leading to the search for novel antimicrobial substances and screening of medicinal plants regularly for new antimicrobial agents (Prasad *et al.*, 2012).

Medicinal plants are known for their activity owing to the multitude of constituents present. These constituents are categorized into: (a) primary metabolites, which are essential for the survival and well-being of the organism, including biological molecules i.e., nucleic acids, fats, carbohydrates and proteins and (b) secondary metabolites, which are natural products i.e. those with nonessential functions and are exclusive to an organism acting as a defense mechanism against herbivores and against bacteria, fungi, parasites and viruses e.g. alkaloids, flavonoids, saponins, terpenoids, steroids, glycosides, tannins, volatile oils etc. (Dias *et al.*, 2012; Rungsung *et al.*, 2015; Wink, 2015; Shakya, 2016; Rehab and Amira, 2018, Sadaf *et al.*, 2018).

According to an estimate, more than 300,000 secondary metabolites exist in nature, which can either be used directly or as a lead for synthetic or semisynthetic derivatives in modern medicine (Gurnani *et al.*, 2014; Wink, 2015).

The production of secondary metabolites involves biological processes including photosynthesis, glycolysis and Krebs cycle. The outcome of these biological processes is the biosynthesis of "Shunt metabolites" or intermediates which proceed towards the production of secondary metabolites via alternate biosynthetic routes responsible for metabolite diversity in living organisms. The modification in biosynthetic routes of intermediates (such as shikimic acid, 1- deoxyxylulose-5-phosphate, acetyl coenzyme A and mevalonic acid) may be due to environmental changes, viral, chemical or radiation exposure (Rungsung *et al.*, 2015; Rehab and Amira, 2018, Sadaf *et al.*, 2018).

Secondary plant metabolites also referred to as Phytochemicals or Bioactive compounds are active ingredients which possess therapeutic properties that could be regarded as medicine or drug. Phytochemicals are therefore classified into several classes according to their chemical structures. The main categories of the secondary plant metabolites considered to be of therapeutic importance are discussed below as described by Compean and Ynalvez (2014), Rungsung *et al.* (2015), Shakya (2016), Kushwaha and Kumar (2017), Rehab and Amira (2018), Jain *et al.* (2019) and Othman *et al.* (2019). The secondary metabolites to be reviewed are: (i) Phenolics (ii) Alkaloids (iii) Saponins (iv) Terpenes (v) Quinones (vi) Phytosterols

Phenolics

Phenolics or polyphenols are known to constitute the largest group of ubiquitously distributed naturally occurring plant phytoconstituents with several phenolic rings and phenolic OH groups present in most drugs used in phytotherapy (Figure 1a). They are commonly found in herbs, vegetables, fruits, grains, tea coffee beans and red wine contributing significantly to the colour, taste and flavour of many herbs, foods and drinks. Phenolics beneficial biological activities includes antiviral, antibacterial, immune-stimulating, antiallergic, anti-hypertensive, anti-ischemic, anti arrhythmic, anti-thrombotic, hypocholesterolemic, anti lipoperoxidant, hepatoprotective (such as silybin), anti-inflammatory (such as quercetin), and anti-carcinogenic actions (Kumar and Pandey, 2013; Wink, 2015; Kushwaha and Kumar, 2017; Rehab and Amira, 2018) Others exert phytoestrogenic activity (such as genistein and daidzein), while others are insecticidal (naringenin). Many of the phenolic molecules are also effective antioxidants and free radical scavengers, especially flavonoids.

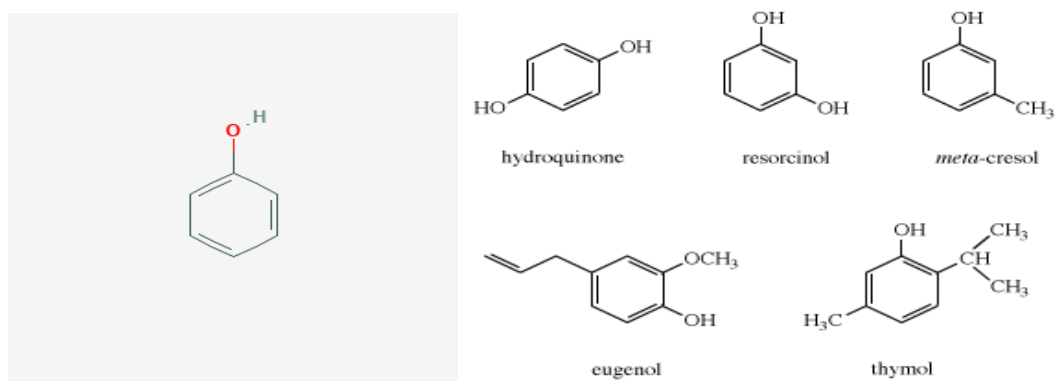


Figure 1a and b. Basic structure of Phenol and phenolic compounds based on functional group (Source: Álvarez-Martínez et al., 2021)

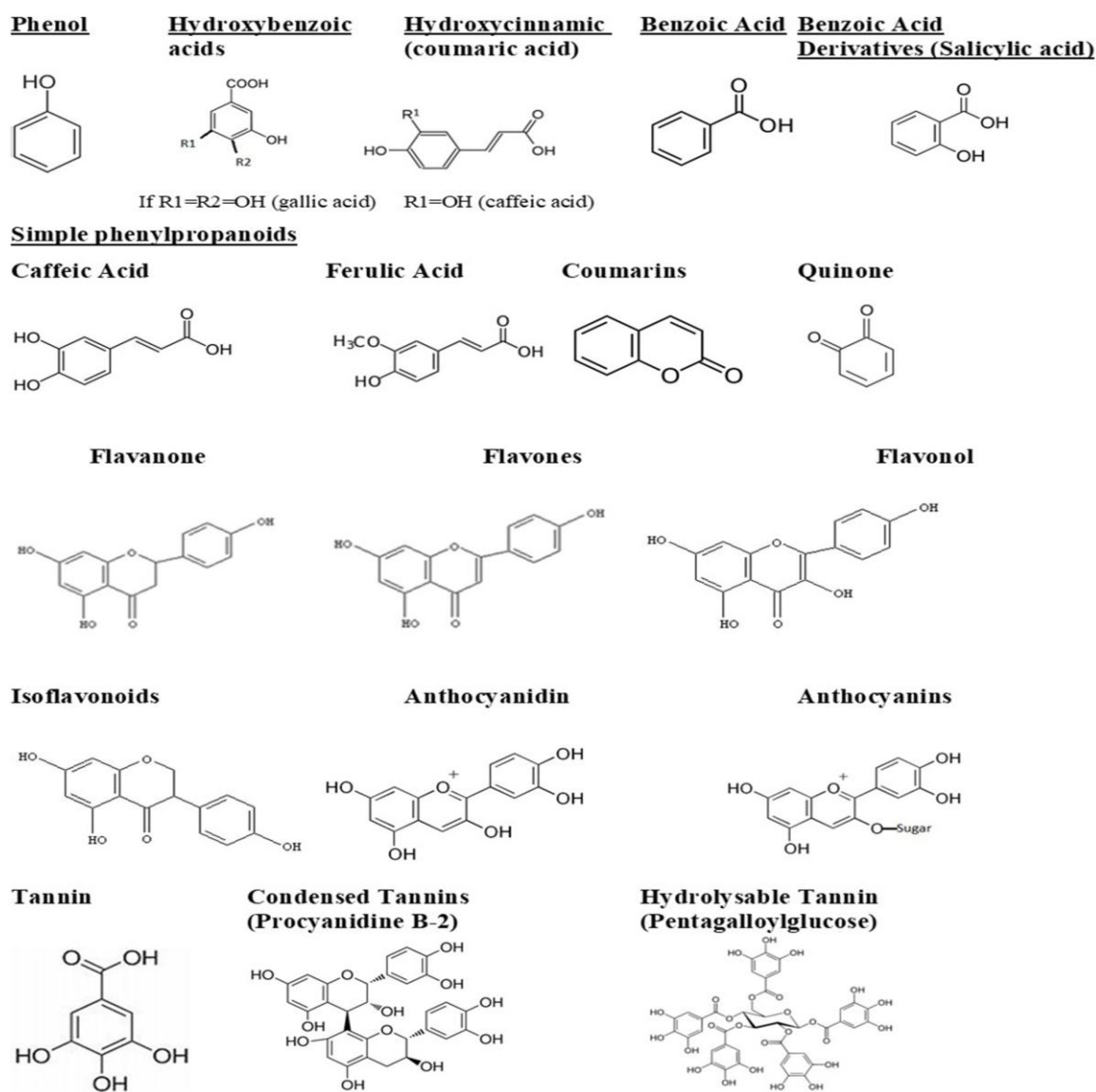


Figure 1b. Basic structure of Phenol and phenolic compounds based on functional group (Source: Othman et al., 2019).

The antioxidant capacity of phenolic compounds is also attributed to their metal ions chelating activity which is involved in free radical production as the structures have been found to strongly interact with proteins owing to the hydrophobic benzenoid rings and the hydrogen-bonding nature of the phenolic hydroxyl groups. The antioxidant properties of the phenolics enhance enzyme inhibition involved in radical generation of cytochrome P450 isoforms, lipoxygenases, cyclooxygenase and xanthine oxidase (Kushwaha and Kumar, 2017). Phenolics are capable of acting in redox-sensitive signaling cascades to inhibit DNA damage, which may be beneficial to preventing UV-induced oxygen free radical generation and lipid peroxidation. Phenolics modulate transcriptional factors such as AP-1 (activator protein-1), thus controlling the expression of various genes implicated in inflammation processes, cell differentiation, and proliferation. Phenolics may prevent oxidative stress induced mitochondrial transition pore complex opening by decreasing production of Bax and Bad protein (Mandel and Youdim, 2004). Phenolics are also involved in activation of several protein kinases, phase II antioxidant detoxifying enzymes and modulation of several cell survival/cell-cycle genes (Kushwaha and Kumar, 2017). Kushwaha and Kumar (2017) and Jain *et al.*, (2019) classify phenolics according to their structure or biosynthetic origin. Some phenolics classified based on their structures include (the first three will be discussed here):

- (i) Simple phenolics
- (ii) Tannins
- (iii) Flavonoids
- (iv) Coumarins
- (v) Chromones and xanthenes
- (vi) Stilbenes
- (vii) Lignans

Simple phenolics

Phenolic acids are known to be ubiquitous among plants however, free phenols are rare. Gallic acid (Figure 1b and 2), parent compound of the gallotannins is known for its astringent properties demonstrating in vitro antibacterial, antiviral, antifungal, anti-inflammatory, anti-tumor, anti-anaphylactic, anti-mutagenic, choleric and bronchodilatory activities. It also inhibits insulin degradation and promotes smooth muscle relaxation. The phenolic compounds in this group vary according to their functional group, which may be hydroxyl (eugenol - a phenolic phenylpropane), aldehydic (vanillin - a phenolic aldehyde), or carboxylic group (salicylic, ferulic and caffeic acids) (Figure 1a and b).

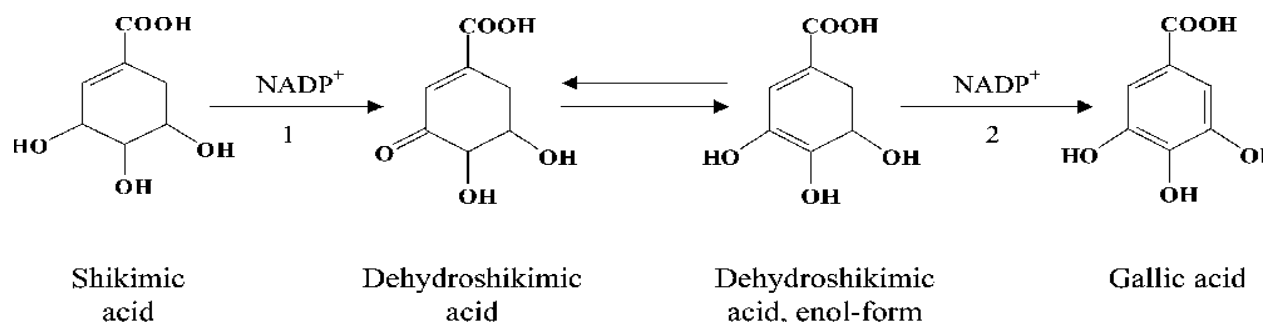


Figure 2. Illustration on Gallic acid formation (Woo et al., 2023).

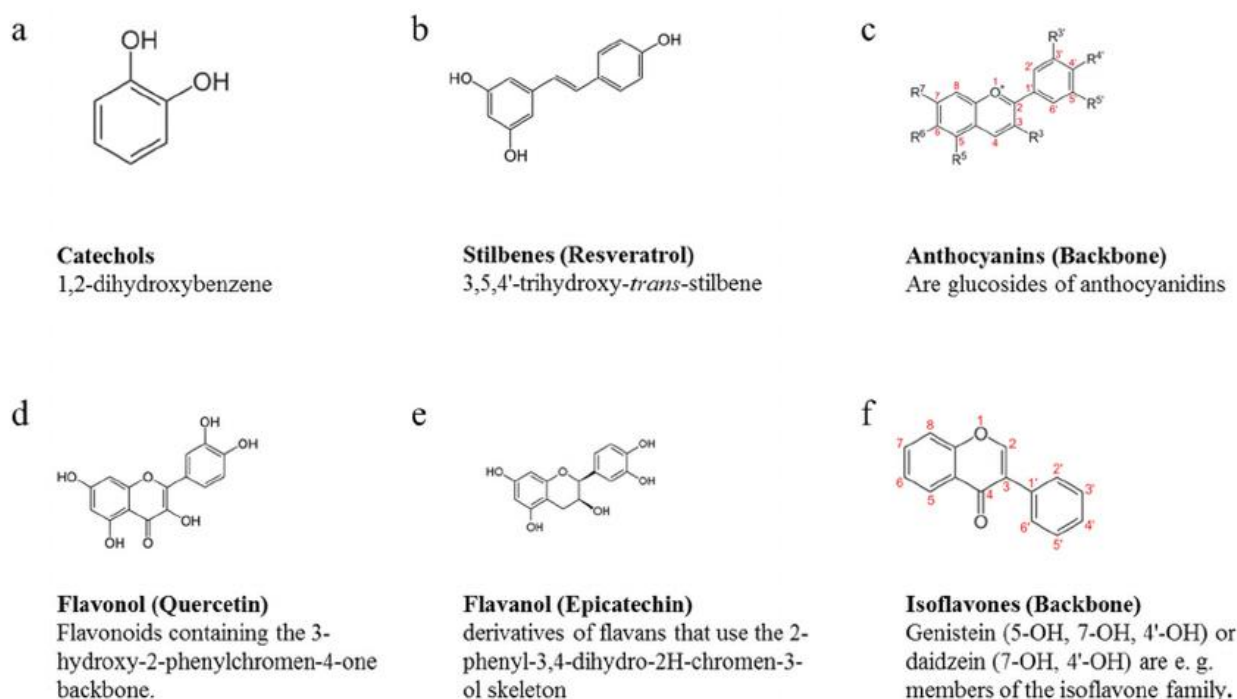


Figure 3. Examples of simple phenolics (Woo et al., 2023).

Hydroquinone, a member of the simple phenols is most widely distributed, occurring in a number of plants as the glycoside arbutin. Glycoside formation is common, and the widely distributed glycoside coniferin and other derivatives of phenolic cinnamic alcohols are precursors of lignin. The pharmacological properties of these phytoconstituents are exemplified in arbutin as the urinary tract antimicrobial agent and salicylates, an anti-inflammatory agent.

Tannins

Tannins are large polyphenolic compounds containing sufficient hydroxyls and other suitable groups (such as carboxyls). These groups can form strong complexes with proteins and other macromolecule. These compounds have been used for decades to convert raw animal hides into leather. In this process, tannin molecules crosslink the protein and make it more resistant to bacterial and fungal attack.

Two major types of tannins exist: (i) hydrolyzable tannins (figure 4a) and (ii) condensed tannins (figure 4b).

(i) Hydrolyzable tannins formed from several molecules of phenolic acids such as gallic and hexahydroxydiphenic acids, are unified by ester linkages to a central glucose molecule. Two main types of hydrolysable tannins exist, which are gallotannins and ellagitannins, composed of gallic acid and/or ellagic acid units respectively (i.e. polymers of ellagic acid, or of gallic and ellagic acids with glucose).

(ii) Condensed tannins, or proanthocyanidins, are compounds whose structures are based on oligomeric flavonoid precursors and vary in the type of linkages between flavonoid units; hydroxylation patterns; stereochemistry of carbons 2, 3 and 4 of the pyran rings and the presence of additional substituents.

Proanthocyanidins are important active principles of the red latex containing species. It aids in lowering plasma cholesterol levels, inhibit LDL oxidation, and activate endothelial nitric oxide synthase to prevent platelet adhesion and aggregation that allow formation of blood clot. Scavenging of free radicals, trace metals chelation and binding of proteins with suppression of their enzymatic activity are exerted by their antioxidant activity.

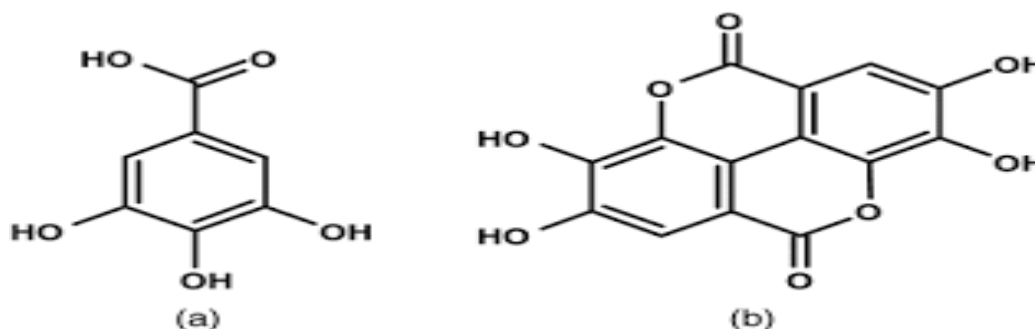


Figure 4. Basic structures of (a) Hydrolyzable Tannins (b) Condensed Tannins (Source: Researchgate.net and Kushwaha and Kumar, 2017))

Flavonoids

Flavonoids are natural substances containing the largest group of naturally occurring phenols (polyphenolic compounds) in photosynthesizing cells. About 500 of the over 4000 flavonoid compounds known occur in free state and are mainly present in fruits, vegetables, grains, and bark, roots, stems, flowers, propolis, honey, tea, and wine. The primary flavonoid structural skeleton is the flavan nucleus, which include a chroman ring bearing an aromatic ring in position 2, 3 or 4 consisting of 15 carbon atoms grouped in three rings (C6-C3-C6), which are labeled A, B, and C (Figure 5.2).

Flavonoids may be divided into various classes according to the oxidation and pattern of substitution level of the central ring (ring C), which are flavones, flavanones, isoflavones, flavonols, flavanonols, flavan-3-ols and anthocyanidins), while individual compounds within a class differ in the pattern of substitution of the A and B rings. The flavones and their close relations are often yellow (Latin *flavus*, yellow) and are widely distributed in nature, more common in the higher plants and in young tissues, occurring in the cell sap as glycosylated derivatives. Flavonoids are active water-soluble antioxidants and free radical scavengers, preventing oxidative cell damage and have strong anti-cancer activity. They are known for its anti-allergic, anti-inflammatory, anti-thrombotic and vasoprotective properties, inhibition of tumor promotion and as a protective for the gastric mucosa. The very important and powerful flavonoids, flavones and catechins, are for protecting the body against reactive oxygen species (ROS). Anti-inflammatory and anti-thrombogenic properties of flavonoids are due to their inhibitory effect on arachidonic acid metabolism (initiation point for inflammation). Flavonoids also chelate metal ion resulting in the removal of causal factor for the development of free radicals. The binding sites for trace metals to flavonoids in different rings of their structure are shown in figure 5.1.

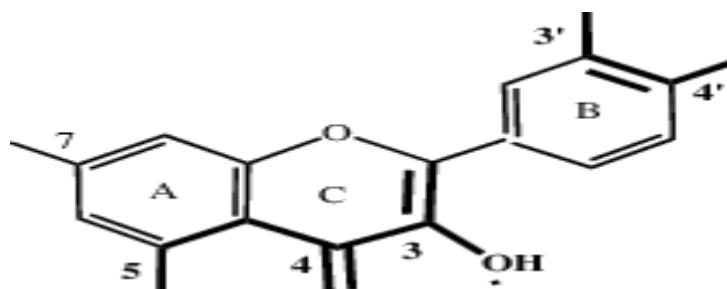


Figure 5.1. Binding sites for trace metals (Source: Kushwaha and Kumar, 2017)

Reduction in complement activation, decreasing the adhesion of inflammatory cells to the endothelium and in general resulting in a reduced inflammatory response and reduction in the release of peroxidase can be achieved by flavonoids. This reduction prevents the origination of ROS by neutrophils. It has been reported that flavonoids could improve blood circulation and lower blood pressure. The biochemical effect of flavonoids is on some enzymes inhibition such as aldose reductase, xanthine oxidase, phosphodiesterase, ATPase, lipoxygenase, cyclooxygenase, etc. they also have a regulatory role on different hormones like estrogens, androgens, and thyroid hormone.

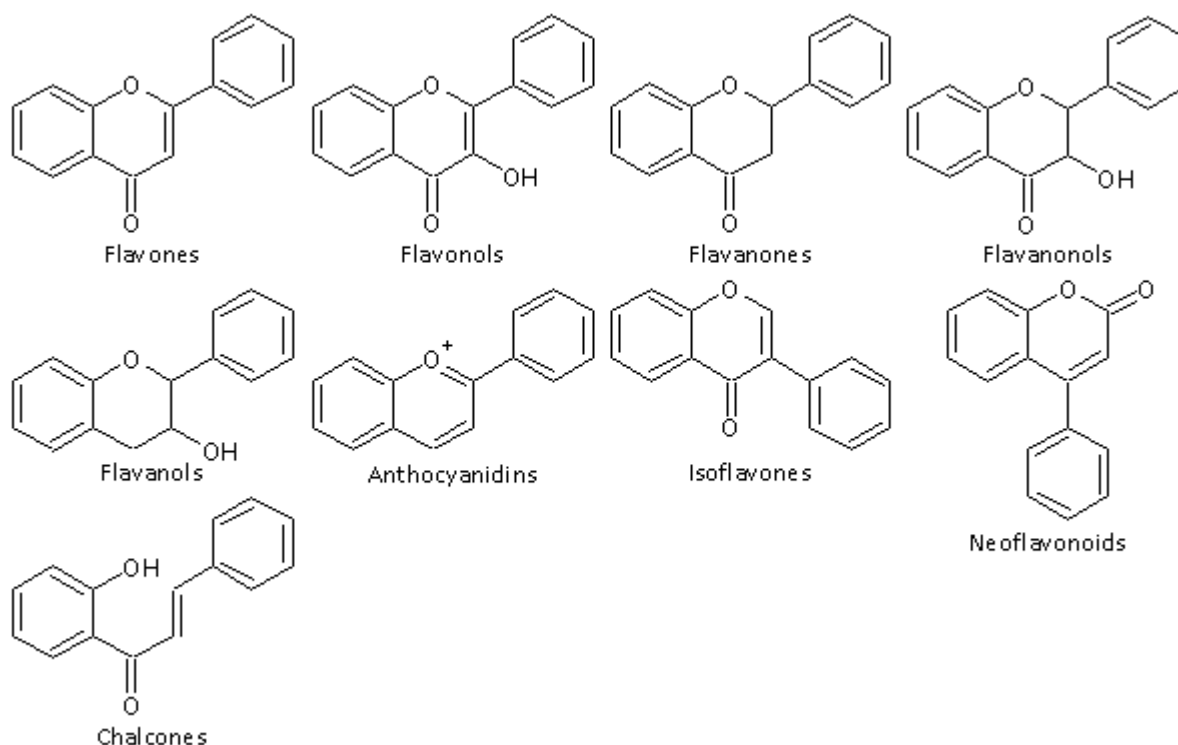


Figure 5.1. Examples of flavonoids (Source: Álvarez-Martínez et al., 2021)

Alkaloids

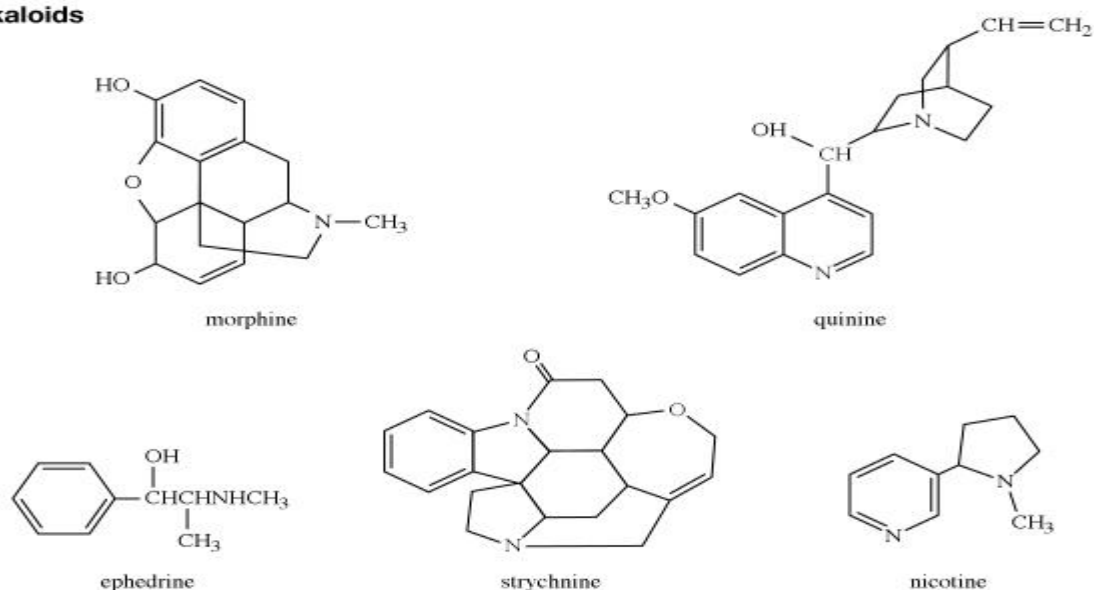
Alkaloids are heterocyclic organic ring compounds with at least one nitrogen atom. Alkaloids can be divided according to their basic chemical structure into different types. The following are basic types of alkaloids: acridones, aromatics, carbolines, ephedras, ergots, imidazoles, indoles, bisindoles, indolizidines, manzamines, oxindoles, quinolines, quinoxolines, phenylisoquinolines, phenylethylamines, piperidines, purines, pyrrolidines, pyrrolizidines, pyrroloindoles, pyridines and simple tetrahydroisoquinolines.

Plants containing alkaloids have been used by man for 3000 years as medicines (as purgative, antitussive and sedatives in snakebite, fever, and insanity), teas and potions. Alkaloids are not common in lower plants. Lysergic acid derivatives and sulfur-containing alkaloids, e.g., the gliotoxins, are detected in fungi. Alkaloids demonstrate a diverse array of pharmacological actions including analgesia, local anesthesia, cardiac stimulation, respiratory stimulation and relaxation, vasoconstriction, muscle relaxation and toxicity, as well as antineoplastic, hypertensive and hypotensive properties.

The activity of alkaloids against herbivores, cytotoxic activity, the molecular targets of alkaloids, mutagenic or carcinogenic activity, antibacterial, antifungal, antiviral and allelopathic properties have previously been described. Many alkaloids are toxic to other organisms causing death if consumed. Nicotine and anabasine are used as insecticides.

Alkaloids are a group of naturally occurring chemical compounds and are widely distributed, with about 12000 - 16000 alkaloids known, which comprises the largest single class of secondary plant metabolites. They are known to have pharmacological effects and are used in medication, as recreational drugs, and in entheogenic rituals. Alkaloids have been maximized as pharmaceuticals, stimulants, narcotics, dyes, spices and poisons owing to their potent biological activity.

Alkaloids



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Figure 6. Examples of alkaloids (Source: Woo et al., 2023)

Terpenoids

Terpenes are important natural plant products of secondary metabolites. The isoprene unit is a five-carbon molecule which can arrange itself in various paths. Terpenes are characterized by bonding an isoprene unit with a second isoprene. The single isoprene unit delineates the most basic class of terpenes, which is referred to as the hemiterpenes (C₅), two isoprene units as monoterpenes (C₁₀), three isoprene units as sesquiterpenes (C₁₅), diterpenes (C₂₀), sesterterpenes (C₂₅), triterpenes (C₃₀), and polyterpenes (>C₃₀). The structures of monoterpenes can be either cyclic, linear, regular or irregular. Studies have

shown that some derivatives of monoterpenes include alcohols, esters, phenols, ketones and aldehydes. Terpenes undergo two biosynthetic pathways: (1) Mevalonic-acid pathway, which mostly produces sesquiterpenes, sterols and ubiquinones, (2) Methyl-erythritol phosphate pathway, which the majority of the compounds synthesized are hemiterpenes, monoterpenes and diterpenes. Terpenes are the most structurally diverse plant natural products. Based on their numbers and diversity, terpenes offer much potency in an array of industrial and medicinal applications. Example of terpene derivatives is terpenoids.

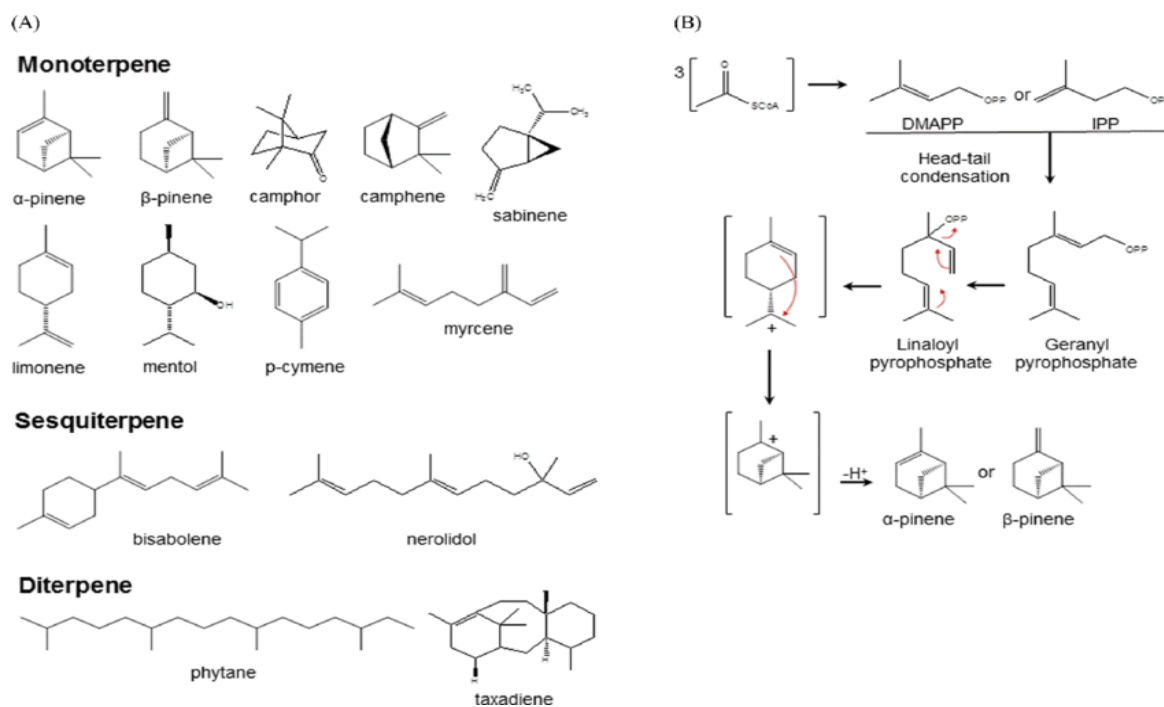


Figure 7. Structural examples of Terpenes (Source: Uttam et al., 2025)

Saponins

Saponins are natural compounds possessing polycyclic aglycone moiety containing either a steroid (steroidal saponins) or triterpenoid (triterpenoidal saponins) attached to a carbohydrate unit (a monosaccharide or oligosaccharide chain). Saponins are large group of glycosides in higher plants. The aglycone portion of the saponin compound is referred to as *genin* or *sapogenin*. These sugar units are either composed of pentoses, hexoses, or uronic acids. They are soap-like forming foam in aqueous solutions and have the ability to lower surface tension. They cause hemolysis of blood erythrocytes in vitro.

Saponins are ubiquitous among plants and have been found to be present in more than 500 plants from at least 90 different families. These substances have been isolated from all parts of plants: leaves, stems, roots, bulbs, flowers and fruits, though they tend to be concentrated in the roots of many species such as *Digitalis purpurea* (foxglove), *Dioscorea villosa* (wild yam), and *Panax ginseng* (Korean ginseng).

Saponins are main ingredient of many plant drugs and folk medicines, and have demonstrated various pharmacological properties. Some saponins have antitumor, piscicidal, molluscicidal, spermicidal, sedative, expectorant and analgesic properties. Various literatures have reported antimicrobial, antifungal, antiviral, anti-ulcerogenic, wound

healing and hepatoprotective activity. Glycyrrhizin from *glycyrrhizae radix* (from *Glycyrrhiza glabra*, Fabaceae) is useful as expectorant and antitussive agent. It is also used to treat chronic hepatitis and cirrhosis.

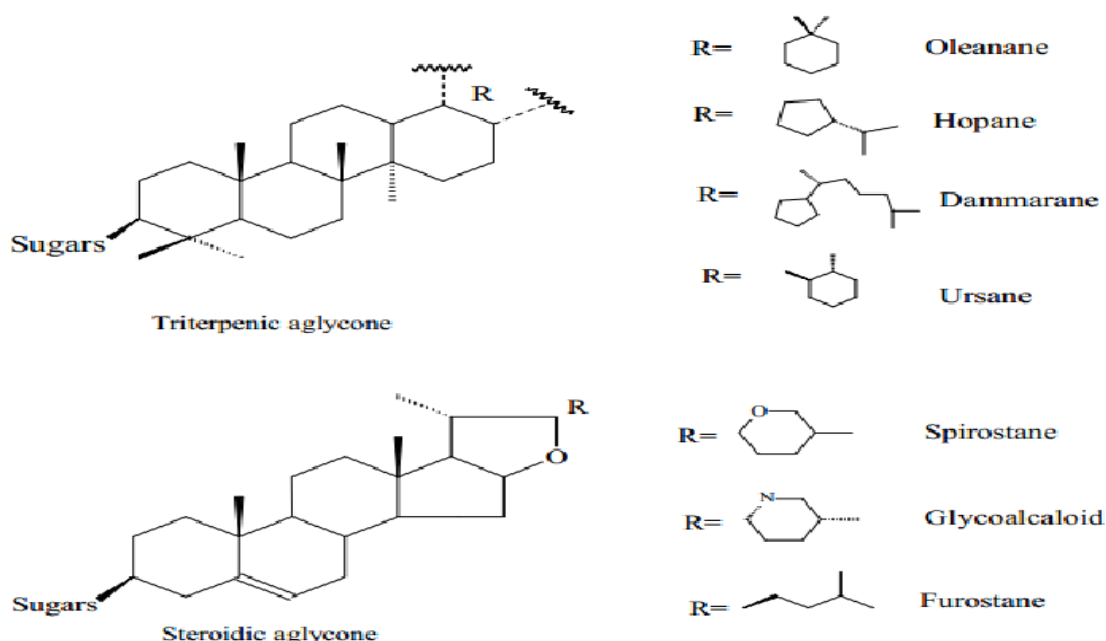


Figure 8. Example of triterpenoidal and steroid aglycone saponin
(Source: Uttam et al., 2025).

QUINONES

Quinones are compounds that contain aromatic rings with two ketone substitutions. About 400 naturally occurring quinones, which are found in all plant organs, have been identified. Naphthoquinones, a class of quinones are one of the largest groups of secondary metabolites with diverse biological activities. Quinones are synthesized via several pathways: (1) Ortho-succinyl benzoic acid pathway for lawsone and juglone, (2) Para-hydroxybenzoic acid-mevalonic acid pathway for shikonin and (3) Acetic acid-mevalonic acid pathway for plumbagin.

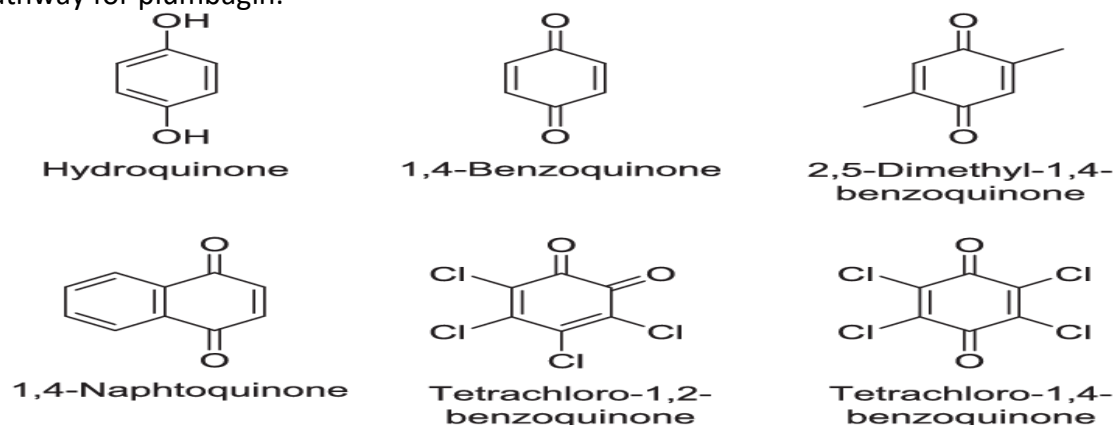


Figure 9: Structures of Quinones (Source: Chen et al., 2024)

PHYTOSTEROLS

Phytosterols are known to be frequently present in higher plants are the building materials for the biosynthesis of plant steroids. Plant sterols are industrially important chemical sources for steroid compounds, insecticides, antioxidant and anticancer drugs. Sterols are made up of a number of major groups of steroids characterized by having a hydroxyl group at C-3, normally in the beta configuration and branching side chains from eight or more carbon atoms at C-17. They have both structural roles, as membrane constituents, and a key place in the biosynthetic sequences which lead to the steroidal species. It was evident from various studies that phytosterols possess antioxidant activity, anti-inflammatory activity, and anti-cancer activity and most often isolated sterols from higher plants are β -sitosterol, β -stigmasterol, lanosterol and campesterol.

Table 1 Classification of Phytochemicals.

s/n	Phytochemicals	Chemical Structure	Examples
1	Alkaloids	Nitrogen atom in heterocyclic rings	Morphine, caffeine, Berberin, codeine (Shakya, 2016)
2	Glycosides	Derived from carbohydrates and noncarbohydrates molecules	Amygdalin, gentiopicrin, and rographolide, polygalin, Cinnamyl acetate (Shakya, 2016)
3	Polyphenoles (Flavonoids, Phenolics Tannins)	Aromatic aliphatic ring containing phenols	Quercetin, resveratrol kaempferol and quercitrin, caffeic acid, flavones, rutin, naringin, hesperidin and chlorogenic, tannic acid, gallic acid and ellagic acid (Shakya, 2016)
4	Saponins	Sugar attached to triterpene or steroid aglycone	Diosgenin and hecogenin (Shakya, 2016)
5	Terpenes (Carotenoids, steroids)	Long unsaturated aliphatic chains (isoprene units)	Artemisinin, α -carotene, β -carotene, lycopene, lutein and zeaxanthin (Shakya, 2016)
6	Anthraquinones	Derivatives of phenolic and glycosidic compounds	Rhein, salinos poramide and luteolin (Shakya, 2016)

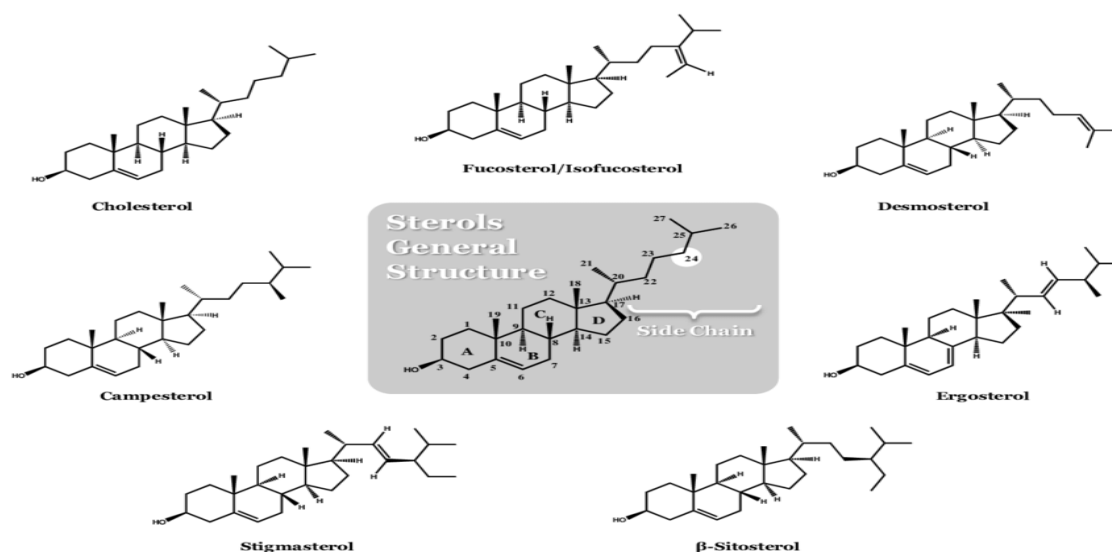


Figure 10. Structures of Phytosterols (Chen et al., 2024).

Antibiotics (synthetic and semi-synthetic) have been developed and undergoing modification in the treatment of infectious diseases. Infectious disease control has been very effective since the discovery and development of antimicrobial drugs. Some of the pathogens are rapidly becoming resistant to many of the antibiotics increasing morbidity, mortality and increased health care cost (Chen et al., 2024).

Throughout man's history many infectious diseases have been treated with herbs as antibiotic resistance has become a global concern. The emergence of multidrug-resistant pathogens has threatened the clinical efficacy of many existing antibiotics. Antimicrobial activity of various herbs and spices in plant leaves, flowers, stem, roots, and fruits and their phytochemicals has been investigated by various researchers using different solvent systems.

Papaverine, a benzyloquinoline alkaloid, has shown to have an inhibitory effect on several viruses and indoquinoline alkaloids from *Cryptolepis sanguinolenta* displayed activity against some Gram-negative bacteria and yeast. Quinine, an alkaloid, has been used in folkloric medicine as an antimalarial against plasmodium parasite. Many alkaloids are also toxic to other organisms (Jain et al., 2019).

Monoterpenes with phenolic hydroxyl groups or with an aldehyde function can bind to proteins exhibiting remarked antiseptic properties and have been found to be active against many bacteria and fungi (Wink, 2015). Sesquiterpene lactones found in several plants have been used in traditional medicine such as *Achillea*, *Arnica*, *Matricaria*, and *Parthenium* owing to their antibacterial, antifungal and antiparasitic properties (Wink, 2015). Several medicinal plants, rich in iridoid glucosides, a subclass of monoterpenes, have been used in treating infections, including *Harpagophytum procumbens*, *Plantago spec.*, *Scrophularia nodosa*, *Warburgia salutaris* (Wink, 2015).

Essential oils are known to be bioactive mixture of complex compounds synthesized as secondary metabolites by various plant parts. The lipophilic nature of essential oils makes them permeable to cellular membrane. The report of Paiva et al. (2010) showed that *Lippia rugosa* oil contains geraniol, nerol and geranial as their main components which were able to inhibit *Aspergillus flavus* growth. *Moringa oleifera* essential oil was found to possess

antifungal activity on dermatophytes, *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum* and *Microsporum canis*. *Salvia pisidica* and *Achillea ligustica* essential oils was reported to have antibacterial activity against Gram positive bacteria. Analysis on the essential oil of *Salvia tomentosa* contains β -pinene (39.7%), α -pinene (10.9%) and camphor (9.7%), and was found to be highly active showing minimal inhibitory concentration, which ranged from 0.54 mg/mL against *Clostridium perfringens* to 72.00 mg/mL against *Moraxella catarrhalis*, *Enterobacter aerogenes* and *Klebsiella pneumonia* while *Escherichia coli*, *Proteus mirabilis* and *Pseudomonas aeruginosa* were resistant to the essential oil.

Phenolic compounds (flavone, quercetin and naringenin) were effective as antimicrobial inhibiting the growth of *Aspergillus niger*, *Bacillus subtilis*, *Candida albicans*, *Escherichia coli*, *Micrococcus luteus*, *Pseudomonas aeruginosa*, *Saccharomyces cerevisiae*, *Staphylococcus aureus* and *Staphylococcus epidermidis* while gallic acid only inhibited *P. aeruginosa*. However, rutin and catechin showed no antimicrobial effect on the tested microorganisms (Paiva *et al.*, 2010).

Different types of secondary metabolites in organic solvent extracts were identified as the bioactive agents with antimicrobial properties (Table 2). The tannins methyl gallate and gallic acid from *Galla rhois* inhibit *Actinomyces viscosus*, *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus salivarius*, *Streptococcus mutans* and *Streptococcus sobrinus* (associated with cariogenic infection) and *Porphyromonas gingivalis* (periodontopathic) and the *in vitro* formation of biofilms by *Streptococcus mutans* (Paiva *et al.*, 2010).

Paiva *et al.* (2010) reported the antifungal activities of diterpene (labda-7,13E-dien-2 β ,15-diol) and coumaric acids (3-prenyl-*p*-coumaric acid and 3,5-diprenyl-*p*-coumaric acid) obtained from dichloromethane extract of *Baccharis grisebachii* against *Epidermophyton floccosum*, *Microsporum canis*, *Microsporum gypseum*, *Trichophyton mentagrophytes* and *Trichophyton rubrum*. Also, gallic acid, a tannin was detected as the bioactive component of ethanolic extracts of *Caesalpinia mimosoides* having antifungal activity against *M. gypseum* and *T. rubrum*. Methanolic extract of *Myracrodruon urundeuva* contains cinamic derivatives, flavonoids, gallic acid, luteolin, and tannins possess antifungal activity against *Fusarium* spp (*Fusarium lateritium* and *Fusarium oxysporum*).

MODE OF ACTION OF PLANT SECONDARY METABOLITES

Plant secondary metabolites have mechanisms of antimicrobial action which are yet to be fully understood. According to Briskin (2000) and Paiva *et al.* (2010), it was observed that no single bioactive compound is solely responsible for the mode of action as compared to synthetic antibiotics but may be as a result of synergistic or additive combination of interacting metabolites acting at single or multiple target sites associated with a physiological process (Briskin, 2000; Paiva *et al.*, 2010). Flavonoids, probably inhibit cytoplasmic membrane function, DNA gyrase and β -hydroxyacyl-acyl carrier protein dehydratase activities; Changes in the cellular morphology in the formation of filamentous cells is typified by the activity of isoflavone genistein, which also inhibit the synthesis of DNA and RNA of *Vibrio harveyi*. Terpenes is suggested to promote the disruption of membrane, coumarins cause decrease in cellular respiration while tannins act on membranes of microorganism as well as bind to polysaccharides or enzymes promoting inactivation. (Paiva *et al.*, 2010).

Table 2. Antimicrobial activity of secondary metabolites from medicinal plants.

Microorganism	Compound	Plant	Reference
<i>Bacillus cereus</i> , <i>Bacillus subtilis</i> , <i>Micrococcus kristinae</i> , <i>Staphylococcus aureus</i> , <i>Aspergillus flavus</i> , <i>Cladosporium sphaerospermum</i>	3,5,7-Trihydroxyflavone (galangin)	<i>Helichrysum aureonitens</i>	Paiva et al. (2010)
<i>B. cereus</i> , <i>S. aureus</i> , <i>Staphylococcus epidermis</i> , <i>Candida albicans</i> , <i>Cryptococcus neoformans</i>	Benzoquinone and benzopyran	<i>Gunnera perpensa</i>	Paiva et al. (2010)
<i>B. cereus</i> , <i>B. subtilis</i> , <i>Enterococcus faecalis</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>S. aureus</i> , <i>C. albicans</i> , <i>C. neoformans</i>	Helihumulone	<i>Helichrysum cymosum</i>	Paiva et al. (2010)
<i>B. cereus</i> , <i>S. aureus</i>	Carnosol and 7-O-methylepirosmanol	<i>Salvia chamelaeagnea</i>	Paiva et al. (2010)
<i>B. subtilis</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>S. aureus</i>	Anolignan B	<i>Terminalia sericea</i>	Paiva et al. (2010)
<i>B. subtilis</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>S. aureus</i>	Sesquiterpenoid	<i>Warburgia salutaris</i>	Paiva et al. (2010)
<i>B. subtilis</i> , <i>E. faecalis</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>Aspergillus niger</i>	Flavonoids	<i>Combretum erythrophyllum</i>	Paiva et al. (2010)
<i>E. coli</i> , <i>S. aureus</i> , <i>C. albicans</i>	Flavonoids	<i>Erythrina burttii</i>	Paiva et al. (2010)
<i>E. coli</i> , <i>Salmonella typhimurium</i> , <i>Staphylococcus epidermis</i> , <i>S. aureus</i> , <i>C. albicans</i> , <i>Saccharomyces cerevisiae</i>	Flavonoids	<i>Broussnetia papyrifera</i> , <i>Echinosophora koreensis</i> , <i>Morus alba</i> , <i>Morus mongolica</i> and <i>Sophora</i>	Paiva et al. (2010)

		<i>flavescens</i>	
<i>E. coli</i> , <i>S. aureus</i>	Terpenoids	<i>Spirostachys africana</i>	Paiva et al. (2010); Wink (2015)
<i>E. coli</i> , <i>K. pneumoniae</i> , <i>S. aureus</i>	Vernolide and vernodalol	<i>Vernonia colorata</i>	Paiva et al. (2010)
<i>Epidermophyton floccosum</i> , <i>Microsporum canis</i> , <i>Microsporum gypseum</i> , <i>Trichophyton mentagrophytes</i> , <i>Trichophyton rubrum</i> , <i>S. aureus</i>	Diterpene and coumaric acids	<i>Baccharis grisebachii</i>	Paiva et al. (2010); Wink (2015)
<i>Actinomyces viscosus</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus acidophilus</i> , <i>Lactobacillus salivarius</i> , <i>Porphyromonas gingivalis</i> , <i>Streptococcus mutans</i> , <i>Streptococcus sobrinus</i>	Methyl gallate and gallic acid	<i>Galla rhois</i>	Paiva et al. (2010)
<i>C. albicans</i>	Alkaloids	<i>Aniba panurensis</i>	Paiva et al. (2010)
<i>S. aureus</i>	Naphtoquinones	<i>Tabebuia avellanedae</i>	Paiva et al. (2010)
<i>A. niger</i> , <i>Botrytis cinerea</i>	Saponin	<i>Astragalus verrucosus</i>	Paiva et al. (2010); Wink (2015)
<i>S. aureus</i> , <i>B. cereus</i> , <i>Clostridium perfringens</i> , <i>E. faecalis</i> , <i>Micrococcus luteus</i> , <i>Aeromonas hydrophila</i> , <i>Enterobacter sakazakii</i> , <i>K. pneumoniae</i> , <i>E. coli</i> , <i>Enterobacter cloacae</i> , <i>P. aeruginosa</i> , <i>Vibrio vulnificus</i> , <i>Pseudomonas luteola</i> , <i>Chryseobacterium indologenes</i> , <i>C. albicans</i> , <i>A. niger</i> , <i>Penicillium sp.</i>	Glucosinolates	<i>Aurinia sinuata</i>	Paiva et al. (2010)

<i>Mycobacterium tuberculosis</i>	Quassinoids	<i>Ailanthus altissima</i>	Paiva et al. (2010)
<i>M. tuberculosis</i>	Xanthones	<i>Canscora decussata</i>	Paiva et al. (2010)
<i>Mycobacterium smegmatis</i> , <i>Mycobacterium intracellulare</i> , <i>Mycobacterium chelonae</i> , <i>Mycobacterium xenopi</i>	Ferruginol	<i>Juniperus excelsa</i>	Paiva et al. (2010)
<i>Mycobacterium avium</i> , <i>M. tuberculosis</i>	Gingerols	<i>Zingiber officinale</i>	Paiva et al. (2010)

Table 3. Bioactive use of selected secondary metabolites applied as isolated compounds in medicine (Wink, 2015). Key: alkaloid (A), terpenoids (T).

Plant Species	Substance (Class)	Mode of Action	Properties/Applications
<i>Aconitum napellus</i>	aconitine (A)	activates Na ⁺ channels	analgesic
<i>Atropa belladonna</i>	L-hyoscyamine (A)	antagonist of mAChR	parasympathomimetic
<i>Camptotheca acuminata</i>	camptothecin (A)	inhibitor of DNA topoisomerase	tumour therapy
<i>Cannabis sativa</i>	tetrahydrocannabinol (T)	activates THC receptor	analgesic
<i>Catharanthus roseus</i>	dimeric Vinca alkaloids (A)	inhibit microtubule assembly	tumor therapy
<i>Chondrodendron tomentosum</i>	tubocurarine (A)	inhibits nAChR	muscle relaxant
<i>Cinchona pubescens</i>	quinidine (A)	inhibits Na ⁺ channels	antiarrhythmic
<i>Coffea arabica</i>	caffeine (A)	inhibits phosphodiesterase and adenosine receptors	Stimulant
<i>Colchicum autumnale</i>	colchicine (A)	inhibits microtubule assembly	gout treatment

Overview of Mechanism of Action of Polyphenols

The mode of action of the antimicrobial activity of polyphenols as reported by Othman *et al.* (2019) involve enzyme inhibition by the oxidized compounds through reactions with proteins, SH- groups or nonspecific interactions. Studies revealed that highly oxidized phenols (those with more OHs) have more inhibitory activity than those that are less oxidized. It was also reported that flavonoids with more hydroxyl groups had a greater antimicrobial activity while those ones lacking hydroxyl groups on their b-rings were more

active in membrane disruption in microbial targets. Conversely, some phenolics such as quinones act as a source of stable free radicals and bind irreversibly with proteins leading to its loss of function. Other targets are including enzyme inactivation, binding to adhesions molecules on the microbial cell surface, binding to cell wall proteins, and substrate interaction, thus rendering them unavailable to the microorganism, and forming complexes with metal ions (Chen et al., 2024).

Mechanisms of Action of Alkaloids

Alkaloids being structurally diverse compounds (such as quinolones, metronidazole) act through enzyme inhibition (Othman *et al.*, 2019). Different mechanisms of action exist between different alkaloids which include:

- (i) Affecting cell division
- (ii) Respiratory inhibition and enzyme inhibition in bacteria.
- (iii). Bacterial membrane disruption.
- (iv). Affecting virulence genes.

CONCLUSION

Secondary metabolites are a fascinating compendium of bioactive compounds with broad activities towards human cells and microorganisms. They are novel therapeutic lead compounds with minimal side effects and the process of discovery and development of secondary metabolites has been monotonous. However, with recent advancements in genomics, proteomics, metabolomics, and transcriptomics, several phytochemicals have been screened for their bioactivity which could possibly contribute immensely to future drug development and use in clinical medicine. It is very imperative for an extensive study on the modes of action of the various secondary metabolites against microbes and toxicological studies on animal and human subjects. It was also observed that most studies on the therapeutic effect of secondary metabolites are centered on the crude extracts after phytochemical determination rather than determining the activity of the secondary metabolites. This area of research calls for urgent attention.

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