Classification of Phytochemicals in Plants with Herbal Value

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Contents

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Abstract

In the past decade, there has been an increased concern about the effects of medicinal plants. Traditional medicinal herbs from diverse habitats and locations can be evaluated as novel treatment and prevention methods for injuries and diseases. Natural products, especially secondary metabolites in medicinal herbs, including those utilized in conventional and ethnic health care systems, provide prospective components for developing novel drug candidates. Phytochemicals have many potential roles as they can protect plants from enemies and act as antimicrobial, anti-inflammatory, antidiabetic, and chemopreventive agents. Their identification and classification are usually according to the chemical formula, such as flavonoids, terpenoids, alkaloids, saponins, phytosterols, carotenoids, essential oils, nonessential amino acids, and aromatic and aliphatic acids. Each group has characteristics, including anticancer, anthelmintic, and antigenotoxic. Additionally, they can offer direct/indirect protection against pathogens or hazardous conditions. Due to their potency and cost-effectiveness, phytochemicals have recently received considerable interest in this area. The impact of medicinal plant utilization is international and has been developing in many countries. Notably, as a potential source of alternative treatments, traditional medicine has attracted attention worldwide. This chapter will focus on classifying phytochemicals (primary and secondary metabolites), identifying some active secondary metabolites (such as flavonoids, alkaloids, terpenoids, phytosterols, and phenolic compounds), studying their potentiality in the treatment of some disorders, and the modern research advances in herbal medicine field.

Keywords

Phytochemicals · Herbal medicine · Flavonoids · Alkaloids · Cancer treatment · Antimicrobial properties · Artificial phytochemicals production

Abbreviations

5-FU	5-fluorouracil
ABTS	2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)
ACE	Angiotensin-converting enzyme
ATP	Adenosine triphosphate
COX	Cyclooxygenase
DPPH	α, α-diphenyl-β-picrylhydrazyl
ECa-09	Esophageal squamous carcinoma cell in the human
ESCC	Esophageal squamous cell carcinoma
HL-60	Promyelocytic leukemia cell line
HNSCC	Head and neck squamous cell carcinoma

IC_{50}	Half-maximal inhibitory concentration
JAK/STAT	The Janus kinase/signal transducers and activators of the transcription pathway
NF-B	Nuclear factor-B
Nrf-2	Nuclear factor-erythroid factor 2-related factor 2

1 Introduction

Phytochemicals (secondary metabolites) are the chemical substances synthesized by the plant through various chemical mechanisms. Most phytochemicals support plants' ability to compete with other plants and provide defense against diseases, herbivores, or abiotic challenges, such as high UV radiation doses. Usually, humans and animals can detect or smell and sometimes taste the secreted phytochemicals. Moreover, phytochemicals contain various chemical constituents, including alkaloids, flavonoids, saponins, steroids, terpenoids, and many other active groups. Plant metabolites can be classified depending on their physiological function in the plant system as follows: (1) Primary metabolites: They are biomolecules that directly affect the metabolism and the development of different species, and they are broadly distributed in plants, thus being appropriate for use as an edible human source. In addition, these primary components (carbohydrates, proteins, lipids, vitamins, and nucleic acid constituents) are produced through a complex system of metabolic processes to fulfill energy demands and serve as precursors for some physiological processes and biochemical synthesis of vital components (secondary metabolites) [1]. (2) Secondary metabolites are derived from the primary metabolites, in particular developmental stages of the plant. These sophisticated compounds have diverse purposes in the plant system (defense against enemies) and potential biological activity, such as medicinal components [2].

The identification and nomenclature of plant species and understanding their relationships to other species are fundamental for many researchers. Moreover, the botanical identification and taxonomic positions of studied plants, especially medicinal herbs, are crucial in the scientific investigation of their therapeutic usage or the foundation of crude pharmaceuticals. Numerous medicinal plants belonging to diverse plant families include Fabaceae, Apiaceae, Apocynaceae, Lamiaceae, Malvaceae, Mimosaceae, Papaveraceae, Phytolaccaceae, Asteraceae, Boraginaceae, Brassicaceae, Caryophyllaceae, Cesalpinaceae, and Cucurbitaceae [3].

Attributed to their significant biological activity, phytochemicals have been used for decades in traditional medicine, reflecting the critical therapeutic benefits of these chemical components [4]. Additionally, different tissues and organs of medicinal herbs may have unique therapeutic characteristics at distinct stages of development [5]. They are involved in valuable industries like pharmaceuticals, cosmetics, and fine chemicals [6].

In this chapter, the classification of some phytochemicals, including main active groups (terpenoids, flavonoids, alkaloids, phytosterols, and phenolic components) are highlighted and their general biosynthesis pathway, their vital activity in the

treatment of some diseases, artificial production of secondary metabolites, and some recent advances in their research are presented.

2 Classification of Phytochemicals

The secondary metabolites are very specialized and can be prevalent in several plant species. The complicated combinations of plant secondary metabolites provide distinctive chemical characteristics among the plant classes, which is an essential classification tool for taxonomists [7]. A summary of some active compounds of different medicinal plant species and their potential treatment effects are presented in Table 1.

2.1 Flavonoids

Flavonoids belong to the polyphenol family of plant secondary metabolites, with more than 6,000 structures, widely distributed in various parts of the plant due to the multiple potential benefits provided by the experts that have received significant attention [56]. Like most metabolites described, flavonoids are essential for adapting plants to their environment, helping to cope with biotic and abiotic stresses, and having critical pharmacological activities. The biosynthesis of flavonoids was studied by using many plant species, including *Arabidopsis thaliana*, *Petunia hybrida*, and *Zea mays*. The synthesis of flavonoids begins with the phenylalanine pathway; multiple enzymes are involved, which makes flavonoids one of the rich families in the plant kingdom [57–59]. The basic structure of most flavonoids contains two phenyl rings (A and B), connected by a heterocyclic pyrene ring with an oxygen atom (C-ring) with the general formula of C6-C3-C6 (Fig. 1). Usually, flavonoids are water-soluble metabolites and classified following the position of ring B into isoflavone and other types, while according to the degree of saturation of the central heterocyclic C-ring can be subdivided into seven categories, including flavanone, flavone, flavanonol, flavanol, flavonol, anthocyanidins, and chalcones (Fig. 2) [60].

The most significant flavonoids are quercetin, quercitrin, and kaempferol, which are expressed in about 70% of all plant species. Several flavonoids play a vital role in anticancer and improving cardiovascular health. For example, hesperidin (Hsp) is a vital flavonoid with high anticancer activity. Also, quercetin is an antioxidant flavonoid, improving blood vessel health and reducing cardiovascular disease risk [61, 62].

2.1.1 Isoflavone

The distribution of isoflavone in plants is limited. It is mainly existed in soybean and legumes and known as phytoestrogens. It has a unique structure to other flavonoids; the position of the B ring for isoflavone is in the third place of the C ring, while the B ring is in the second place of the C ring for other flavonoids. Isoflavone has potential

Table 1 Overview of some bioactive secondary metabolites in herbal medicine

Scientific name	Family of the plant	Active chemical compound	Medical importance	Reference
Cajanus cajan	Fabaceae	Hydroalcoholic, cyanidin-3-monoglucoside, longistylin C	Antioxidant, anti-inflammatory activities, anticancer	[8, 9]
Coriandrum sativum	Apiaceae	Linalool, γ-terpinene, and α-pinene	Hepatoprotective	[10]
Calotropis procera	Apocynaceae	Group of cardiac glycosides (calotropin, calactin, and calotoxin)	Anti-ATPase, antidiarrheal, anticonvulsant, and antiviral	[11–13]
Psychotria nervosa Sw.	Rubiaceae	Emetine (emetine dihydrochloride) and cephaeline	Anti-dengue virus infection	[14–17]
Hippeastrum puniceum (Lam.) Kuntz	Amaryllidaceae	isoquinoline alkaloids (9-O-demethyllycoramine, 9-demethyl-2α-hydroxyhomolycorine, lycorine and tazettine)	Antioxidant, antifungal, antiparasitic, and acetylcholinesterase inhibitory activity	[18]
Hymenocallis caribaea (L.) Herb	Amaryllidaceae	Narciclasine and prancristatin	Antineoplastic compounds	[15, 19, 20]
Thespesia populnea (L.) Sol. ex Corrêa	Malvaceae	Thespesenone and dehydrooxoperezinone-6-methyl ether	Antihepatotoxic compounds	[21–23]
Lagerstroemia speciose (L.) Pers.	Lythraceae	Corosolic acid and ellagitannins	Diabetes treatment, antihyperlipidemic, and antioxidant activities	[24]
Persea americana Mill.	Lauraceae	Peptone, b-galactoside, and glycosylated abscisic acid	Hypertension, stomachache, bronchitis, diarrhea, and diabetes	[25]
Cocos nucifera L.	Arecaceae	Folate (vitamin B_9)	Reduce the risk of breast cancer and anemia during pregnancy	[26, 27]
Acorus calamus L.	Acoraceae	β-asarone, eugenol, asaronaldehyde, and acorin	Antidiabetic, anti-obesity, antihypertensive, anti-inflammatory, and anticonvulsant activities	[28–31]
Alstonia scholaris L. R. Br.	Apocynaceae	Ditamine, echitamine, echitenine, alschomine, isoalschomine, tubotaiwine, and N^b-oxide	Anti-ulcer, antirheumatic, carminative, aphrodisiac, and antiperiodic	[32]

(continued)

Table 1 (continued)

Scientific name	Family of the plant	Active chemical compound	Medical importance	Reference
Phyllanthus epiphyllanthus	Phyllanthaceae	Michellamine B (novel alkaloid), gallotannins, and triterpenes	Inhibition of human immunodeficiency virus (HIV), hepatitis B virus, and antibacterial activity against typhoid fever bacteria	[15, 33–35]
Citrus limon L.	Rutaceae	Eriodictyol	Prevention of diabetic retinopathy, antioxidant, anti-inflammatory, and analgesic effects	[36, 37]
Euphorbia hypericifolia L.	Euphorbiaceae	Isomotiol, espinendiol A, ursolic acid, juglangenin A, and teuviscin A	Anticancer activity	[38–41]
Valeriana officinalis L.	Caprifoliaceae	Isovaleric acid, gamma-aminobutyric acid, valerenic acid, and valerine	Relieves mild nervous tension and helps in sleep	[42–44]
Eucalyptus obliqua L'Hér.	Myrtaceae	1,8-cineole, catechins, isorhamnetin, luteolin, kaempferol, phloretin, and quercetin	Anticancer, antioxidant, antiseptic, stimulant, antimalarial, anthelmintic action, anti-inflammatory, and antihistaminic	[45–48]
Panax ginseng C. A.Mey.	Araliaceae	Ginsenosides	Improve phagocytosis, interferon production, and vasodilation, and affects the hypoglycemic activity	[49–51]
Stachytarpheta jamaicensis (L) Vahl	Verbenaceae	Gamma-aminobutyric acid and dopamine	Inhibition of the chicken pox virus	[15, 52]
Moringa oleifera Lam.	Moringaceae	Quercetin, kaempferol glycosides, myricetin, and epicatechin	Hypolipidemic, hypoglycemic, antioxidant, anti-inflammatory, and anticancer properties	[53–55]

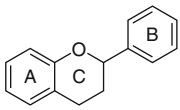

Fig. 1 Basic structure of flavonoids

antibacterial and antioxidant activities [64, 65]. Besides, it is protective against acute lung injuries, cardiovascular diseases, and breast cancer [66–68].

2.1.2 Flavanone

Flavanone is the direct precursor of most flavonoid synthesis. It has a saturated and oxidized C ring. For instance, naringenin and hesperetin are analogue compounds for flavanones and excipients richer in citrus, lemon, grapefruit, and fruit peels. Naringenin is potentially antiviral and antitumoral, preventing cardiovascular disease [69–71]. Hesperetin and its derivatives positively improve acute lung injury, diabetes, and Alzheimer's disease [72–75].

2.1.3 Flavone

Flavone is one of the largest subgroups of flavonoids. Compared to flavanones, besides having a keto group at position four on the C ring, there is also a double bond between the C-2 and C-3 of the C ring. Flavone is present in practically all plant tissue. It has commercial and pharmaceutical value as neuroprotective [76, 77]. For example, apigenin protects neuronal cells from injury by inhibiting microglia cells [78]. In addition, some studies showed that apigenin is safe for humans, which makes it a suitable target for future drug development [79, 80].

2.1.4 Flavanol

Flavanol has a saturated and oxidized C ring and a hydroxyl group in C-3 or C-4 of the C ring. It is mainly found in cocoa, fruits, cereals, and vegetables [81]. Flavanols are important bioactive compounds in *Theobroma cacao*. Researchers have proven its efficacy in anti-inflammatory, neuroprotective, and cardiovascular diseases [82–85]. Recently, Hidalgo et al. [86] investigated the therapeutic activity of epicatechin and epigallocatechin-3-gallate (the main active compound in green tea) flavanols toward nonalcoholic fatty liver disease. Their findings reflected several beneficial properties besides its ability to prevent or treat nonalcoholic fatty liver disease, such as antihyperglycemic, antihypertensive, antithrombotic, anti-inflammatory, and antifibrotic effects. Moreover, following the US Food and Drug Administration classification, they reported its safety on humans as harmless.

2.1.5 Flavonol

Flavonol has a hydroxyl group in C-3 of the C ring, like flavanol. However, there is also a double bond between the second and third carbons in the C ring. Kaempferol and quercetin are representative compounds of flavonols. Both have anxiolytic, antiviral, and anti-inflammatory effects [62, 87]. Tian et al. [88] studied the antioxidant (through the activities of phagocytosis, DPPH, and ABTS radical scavenging)

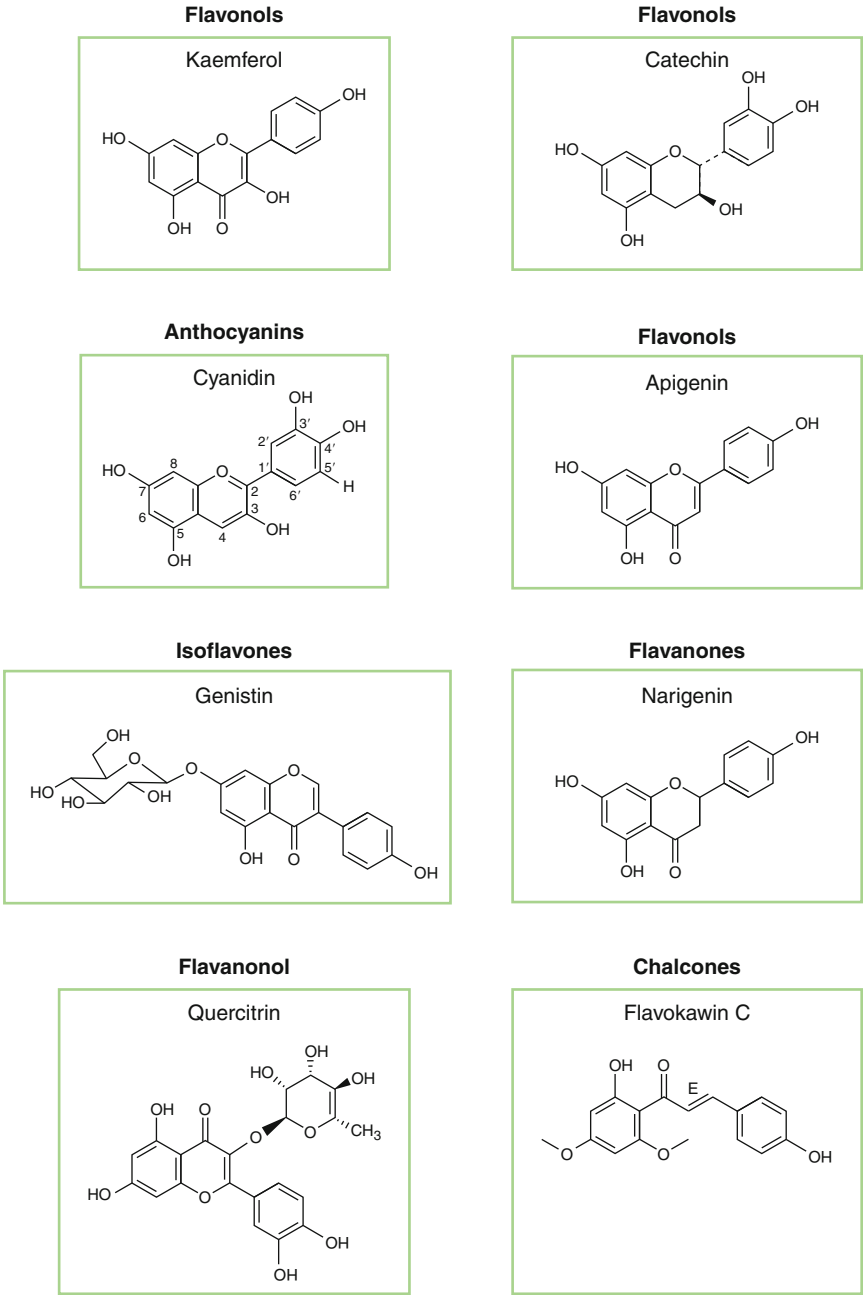

Fig. 2 Examples of different flavonoid categories. (Modified after Bešlo et al. [63])

and anti-inflammatory properties of some flavonols (kaempferol, luteolin, quercetin, and apigenin). The results showed that quercetin is a promising anti-inflammatory and antioxidant substance potentially as a therapeutic adjunct for inflammatory disorders and oxidative stress. Furthermore, preliminary findings from this study indicated that antioxidant activity is directly correlated with the number of phenolic hydroxyl groups. A comparison of anti-inflammatory and antioxidant activities revealed that compounds with enol groups were better than those without.

2.1.6 Flavanonol

Flavanonol has a hydroxyl group at position C-3 and a keto group at C-4. Its compounds can exist in free or combined form and are mainly abundant in citrus. Additionally, flavanonols are found in various medicinal herbs families, like Rutaceae, Leguminosae, and Rosaceae [89]. Flavanonol has significant medical value in vascular protection; it has been found that taxifolin has some therapeutic properties, including preventing the damage of vascular structure in diabetic patients, improving capillary microcirculation, and improving blood flow in the retina [90].

2.1.7 Anthocyanidins

Anthocyanidins are water-soluble pigments widely distributed in flowers and can also be detected in leaves, roots, and fruits (strawberry, chokeberry, and elderberry) [91–95]. The soluble pigment helps plants show different colors (red, orange, blue, and green). Consequently, approximately all angiosperm species contain anthocyanins [96, 97]. The structure is characterized by the absence of ketone in the C-4 position of the central heterocyclic ring and the positive charge of the first oxygen atom in the C ring. In flora, anthocyanins are the most prevalent anthocyanidins (containing glycosylated flavylium ion). Up to 300 anthocyanidins have been identified [98], whereas there are approximately 8,000 possible anthocyanins, such as the various anthocyanidin subtypes and the glycosylated [99].

Polyphenolics, especially anthocyanins, have recently become more relevant in treating chronic diseases like cardiovascular diseases [100]. Pergola et al. [101] investigated that the blackberry extract (about 88% of the cyanidin-3-glucoside out of the total anthocyanin content) inhibited the deleterious cardiovascular activity of nitric acid. Moreover, Graf et al. [102] studied the antiatherogenic activity of anthocyanins in the grape-bilberry extract. The results demonstrated that a dose of 1.55 mg/L decreased the total content of cholesterol and triglyceride levels in treated models. Additionally, anthocyanins reflected a physiological disruption of many groups of fatty acids, including a reduction in saturated fatty acids and an elevation in the long-chain fatty acids in plasma. Consequently, these findings showed the antiatherosclerosis activity of anthocyanins-rich grape-bilberry juice.

2.1.8 Chalcones

Chalcones are open-chain flavonoids (alpha, beta-unsaturated ketones) lacking the structural formula's complete C ring. The basic structure of chalcones includes two conformations: cis and trans isomers [103]. It is widely distributed in medicinal

herbs and can be modified into diversified forms (prenylated chalcones (3, 4, 7), licochalcones, and dihydrochalcones). Chalcones and derivatives have been reported for pharmacological activities in the aspect of antiviral, cardiovascular disease prevention, antimicrobial, antioxidant, analgesic, and antidiabetic functions [104–108]. Many researchers reported the pharmaceutical properties of chalcones. Tang et al. [109], Acharjee et al. [110], and Attarde et al. [111] showed the antidiabetic activity of chalcone, piperonal chalcones derivative, and 3-(4-hydroxyphenyl)-1-phenylprop-2-en-1-one (chemically synthesized chalcone) exhibited significant suppression of the activity of α-glucosidase and α-amylase.

2.2 Alkaloids

Alkaloids are a prominent structurally diverse family of heterocyclic substances containing nitrogen in the heterocyclic ring and obtained from amino acids [112]. They exhibit a variety of significant physiological impacts on humans and other mammals. Morphine, strychnine, quinine, ephedrine, and nicotine are prominent alkaloids. Alkaloids are mainly found in plants and are particularly prevalent in certain flowering plant families [113]. Around 20% of higher plant species are estimated to contain alkaloids, with several thousand distinct varieties, besides some other alkaloid-rich families, including Ranuculaceae, Amaryllidaceae, and Solanaceae [114]. They are primarily associated with plant defense against herbivores (feeding deterrence) and pathogens (antibacterial and antifungal activities). Traditional and recent applications of alkaloids range from 25–75% in pharmaceuticals, demonstrating their enormous medicinal potential [115, 116]. The fundamental quality of alkaloids is no longer the requirement for an alkaloid, and the chemical reactivity of nitrogen atoms permits at least four classes of nitrogenous substances.

Moreover, several synthesized substances with equivalent structures are also referred to as alkaloids [117]; however, others can produce salts with organic acids like oxalic and acetic acids. Certain botanical alkaloids, such as solanine in the Solanaceae family, exist in a glycosidic form. The biosynthetic pathway of the alkaloid is involved, especially in the decarboxylation of substances [118]. For example, aspirin is the most common antiplatelet (pain treatment) medicine, prepared mainly from salicin alkaloids originating from the willow plant (*Salix alba* L.) [119].

According to their biochemical precursor and heterocyclic ring arrangement, alkaloids have been categorized into several groups, including indole, piperidine, tropane, purine, pyrrolizidine, imidazole, quinolizidine, isoquinoline, and pyrrolidine [112, 120]. Fig. 3 shows the structural formula of some potent alkaloid substances.

Some pure isolated alkaloids and synthetic analogues (berberine, serotonin, dopamine, and gamma-aminobutyric acid) are employed as fundamental therapeutic agents globally due to their antispasmodic, antimalarial, antibacterial, and analgesic activities [121, 122]. Alkaloids can prevent the beginning of several degenerative disorders by scavenging free radicals or interacting with the oxidation reaction catalyst. Numerous

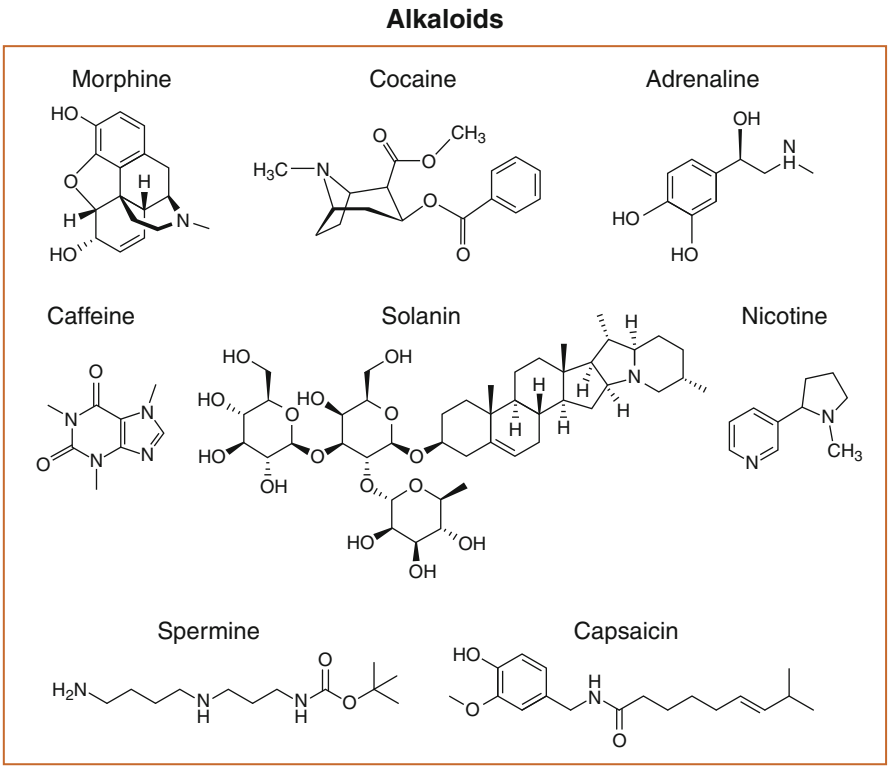

Fig. 3 Examples of some vital alkaloid compounds

studies have evaluated the vast spectrum of pharmacological properties of alkaloids from diverse plants [120]. For instance, the active ingredients of *Papaver somniferum* L., the opium poppy (morphine), and its methyl ether derivatives (codeine) are comparatively nonaddictive analgesics [123]. Moreover, some alkaloids stimulate the cardiovascular or respiratory systems. Uzor [124] reported that quinine, chloroquine, amodiaquine, mefloquine, artemisinin, and artemether are the most vital antimalarial alkaloidal drugs. In addition, Kouam et al. [125] isolated three novel antimalarial indolosesquiterpene alkaloids from the bark extract of *Polyalthia oliveri*. Several studies [112, 126–131] investigated the activity of some active alkaloid constituents, such as atropine (from *Atropa belladonna*) acts as an antidote; ephedrine (from *Ephedra sinica*) can be used as antiasthmatics; and emetine (from *Carapichea ipecacuanha*) as antiprotozoal. Furthermore, noscapine (from *Papaver somniferum*) is used as an antitussive and used as a product in the following names Bequitusin, Degoran, and Tussisedal. In addition to pharmaceutical drugs, some alkaloids have been used as antiplatelet substances. Rutaecarpine, an alkaloid derived from *Evodia rutaecarpa*, was demonstrated as an antiplatelet, and its derivatives (3-methylenedioxyrutaecarpine, 3-chlororutaecarpine, and 3-hydroxyrutaecarpine) reflecting a significant enhancement of its role by interacting with several mediators of coagulation factors [132, 133].

2.3 Terpenoids

Terpenoids are the largest class of phytochemicals (plant-specialized metabolites) with several significant pharmacological effects [134]. They are isoprene-based (5-carbon) metabolites commonly known as isoprenoids. Terpenes can be divided into six categories based on the number of isoprene units in their chemical structure: monoterpene, sesquiterpene, diterpenes, triterpenes, tetraterpenes, and polyterpenoids (Fig. 4) [135]. Terpenoids exist mainly in flowering plants and are responsible for the distinct aroma, flavors, scents, and colors of many species, such as eucalyptus, cinnamon, tomatoes, sunflower, ginger, and clove [136].

Hundreds of terpenoid compounds possess pharmaceutical characteristics; for example, most terpenes in *cannabis* sp. (tetrahydrocannabinol) have diverse pharmacologic effects, including anti-inflammatory, sedative, immunomodulatory, and neuromodulatory properties [137].

2.3.1 Monoterpenoids

The chemical structure of monoterpenes and their derivatives contains two isoprene units. They incorporate three subclasses, acyclic monoterpenes, monocyclic monoterpenes, and bicyclic monoterpenes. For example, the *Cymbopogon citratus*

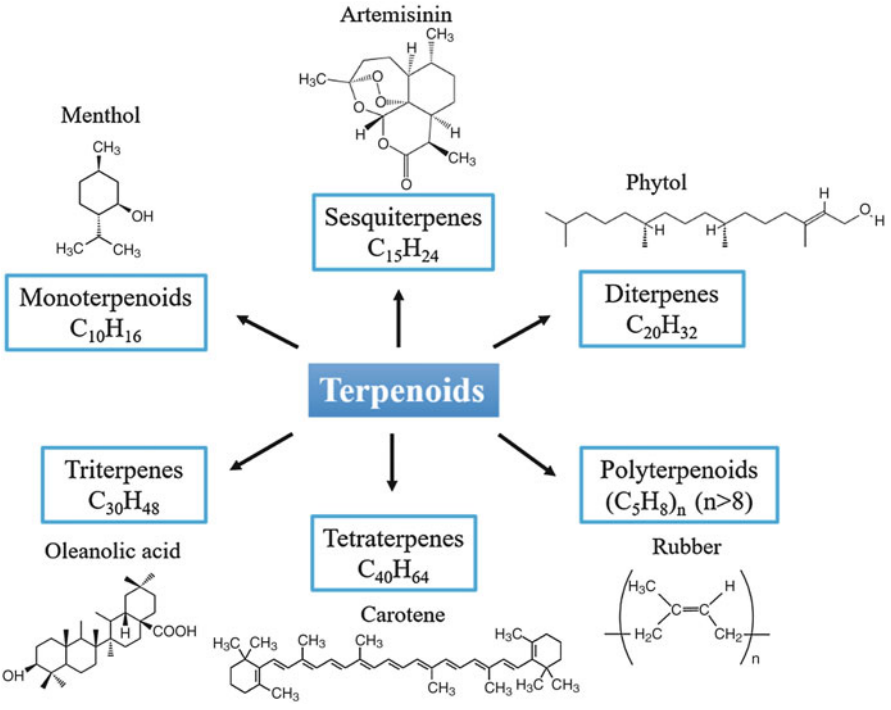

Fig. 4 Chemical structure of some representative terpenoid substances

(lemongrass) produces a large quantity of citronellol (acyclic monoterpene). Santos et al. [138] investigated that citronellol significantly affects bacterial, fungal, allergic, spastic, and diabetic resistance. More acyclic monoterpenes showed antibacterial, anti-inflammatory, and antianxiety properties, such as linalool and its derivatives [139, 140]. In addition, menthol is a monocyclic monoterpene with a prevalent analgesic activity in pain control [141]. α-and β-pinene are representative bicyclic monoterpenoid substances; however, they share the same molecular formula of C10H16, their chemical structures are distinct, and both exhibit anticancer and antimicrobial bioactivity [142–144].

2.3.2 Sesquiterpenes

Sesquiterpene compounds are the most common kind of terpene with three isoprene units. It is subdivided into straight sesquiterpenes (e.g., farnesol and nerolidol) and annular sesquiterpenes based on the stability of the carbon rings (e.g., artemisinin and guaiol). Almost 50% of sesquiterpene compounds contain lactones [145]. It has significant biological and physiological functions. Recent research demonstrated that sesquiterpene lactones could contribute to inflammation and cancer therapies [146, 147].

2.3.3 Diterpenes

Diterpene compounds comprise four isoprene units with one or more carbon rings within their molecular structure. Saha et al. [148] reported that diterpenes had a broad spectrum of microbial inhibition, including bacteria, viruses, and fungi. In addition, several studies reflected that it possesses anticancer, antidiabetic, and antitumor properties [149–153]. Diterpene compounds can not only inhibit the growth and spread of cancer cells but also promote the apoptosis of these cells. Thus, they are widely used to treat liver, lung, breast cancers, and other malignant tumors [151, 154, 155].

2.3.4 Triterpenes

Triterpene chemicals refer to six isoprene units–containing terpenes. The most common triterpene molecules are tetracyclic and pentacyclic, which have four- and five-carbon rings, respectively. Triterpenes showed potential medical activities; for example, oleanolic acid might combat diabetes by suppressing the function of α-glucosidase [156]. Moreover, Sohag et al. [157] revealed that lupeol (pentacyclic triterpene) safeguard against cardiovascular, renal, liver, and skin disorders. Sun et al. [158] summarized the effect of *Centella asiatica* triterpenes in treating common diseases and the underlying mechanisms, such as Alzheimer's disease, acne, chronic and recurrent liver injuries, pelvic inflammatory disease, and rheumatoid arthritis.

2.3.5 Tetraterpenes

Tetraterpenes are one of the isoprenoids containing eight isoprene units with molecular formula C40H64 – they involve many pigmentary substances (carotenoids) [159] and nonpigmentary compounds (poduran) [160]. Carotene is the first isolated tetraterpene discovered in carrots. Furthermore, beta-carotene has significant

antioxidant effects that help in the treatment of many chronic diseases, such as optical diseases and particular cancers [161]. Zerres and stahl [162] reported that carotenoids are characterized by UV-absorbing properties and can be used as photoprotectants. They revealed that carotenoids provide comprehensive photoprotection after supplementation or consuming carotenoid-rich meals. Additionally, lycopene offers therapeutic potential to treat human malignancies [163].

2.3.6 Polyterpenoids

Polyterpenoid molecules have more than eight isoprene units and have a greater molecular weight than other terpenes. These can be extracted from some citrus oils or tree sap, and their yields fluctuate according to the growing seasons (e.g., rosin and its derivatives) [164]. Few investigations have been carried out on the pharmacological characteristics of polyterpenoids. Rubber is a natural polyterpenoid compound with between 1500 and 15000 isopentenyl units. de Barros et al. [165] and Mendonca et al. [166] showed that it influences wound healing and oxytocin-sustained release.

2.4 Phenolic Components

Phenolic acids are a large family of secondary aromatic metabolites. They are extensively distributed in their seeds, roots, stems, and leaves and are associated with xylans, pectin, and lignin. Similarly, to flavonoids, phenolic acids are essential members of the phenolic family. They comprise the most frequently distributed nonflavonoid phenolic molecules in plants and exist in various forms, like free, conjugated soluble, and insoluble bound. Phenolic compounds are the derivatives of benzoic and cinnamic acids [167]. The most common benzoic acid derivatives are p-hydroxybenzoic acid, salicylic acid, gallic acid, and ellagic acid, whereas the most prevalent derivatives of cinnamic acid are p-coumaric acid, caffeic acid, and ferulic acid [168]. Phenolic acids compounds can be classified into two fundamental subclasses hydroxybenzoic and hydroxycinnamic acids (Fig. 5).

In hydroxybenzoic acid, one of the hydrogens on the benzene ring is substituted by the carboxyl group (—COOH). The majority of hydroxybenzoic acid compounds exist as free acids, while a few occur as esters or glycosides. Hydroxycinnamic acids comprise a three-carbon chain connected to the benzene ring (C6H5CHCHCOOH) with at least one hydrogen atom that an OH group can replace [169]. In drug development technology, phenolic components have a significant interest worldwide due to their diverse chemical structures and biological activities. They play a crucial function in antihypertensive, antidiarrheal [170], neuroprotective, antidepressant, anti-inflammatory, anticancer, and antihyperglycemic drugs [171]. In addition, phenolic acids can suppress the activity of acetylcholinesterase and butyrylcholinesterase, which play a crucial role in treating Alzheimer's disease [172].

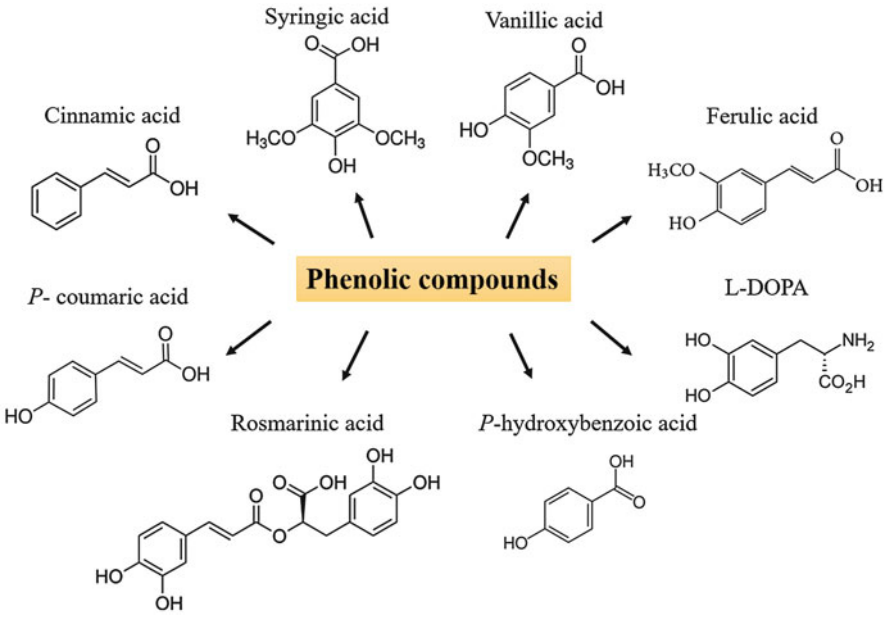

Fig. 5 Examples of some phenolic compounds

2.4.1 Hydroxybenzoic Acids

Hydroxybenzoic acid comprises a benzene ring, a carboxyl group, and additional hydroxyls, methyl (CHn), or methoxy (CHnO) groups attached to the benzene ring. The primary components of hydroxybenzoic acids include gallic, p-hydroxybenzoic, protocatechuic, and vanillic-hydroxybenzoic acid components produced as a resultant product of aromatic amino acids through the shikimic acid pathway [173]. Here, chloroformate intermediate is used to convert shikimic acid to L-phenylalanine. Consequently, L-phenylalanine is translated into p-hydroxybenzoic acid (a precursor to other phenolic acid metabolites) [174]. Moreover, the hydroxylation and methylation of its benzene ring produces other hydroxycinnamic acids (including ferulic and caffeic acids) or hydroxybenzoic acids (such as protocatechuic and p-hydroxybenzoic acids). It is hypothesized that hydroxybenzoic acid is synthesized by hydroxycinnamic acid with a similar structure via CoA-dependent (oxidative) or CoA-independent (nonoxidative) or a mixture of both mechanisms [169].

P-hydroxybenzoic acid, its derivatives, and vanillic acid are the major phenolic acids in many plant species, including cereals, flaxseeds, chia, and sunflower seeds [175–177]. Most of the hydroxycinnamic acid derivatives in chokeberry are chlorogenic and neochlorogenic acids. At the same time, strawberries and red raspberries involve predominant types of hydroxybenzoic acids, such as p-coumaric acid, p-hydroxybenzoic acid, and ellagic acid, respectively [168]. Hydroxybenzoic acid has contributed to significant medical research advances. Adefegha et al. [178] reported that some hydroxybenzoic acids have

antidiabetic properties. For instance, gallic and protocatechuic acids inhibit the activity of type 2 diabetes–related enzymes (amylase and glucosidase). Furthermore, Yi et al. [179] investigated that the last mentioned acids (extracted from muscadine grapes) exhibited anticancer activities against cervical cancer.

2.4.2 Hydroxycinnamic Acids

From a structural perspective, hydroxycinnamic acids contain functional groups that can contribute to the coordination, like phenolic hydroxyl and carboxyl groups [180]. In addition, some compounds have phenolic hydroxyl groups and carboxyl groups of hydroxycinnamic acid and have one or two methoxy groups adjacent to phenolic hydroxyl groups on the benzene ring that have multiple coordination sites (which is crucial to the formation of complex and diverse compounds) [181]. Hydroxycinnamic acid is produced by lignin's metabolic pathway, which provides mechanical support for the plant cell wall [182]. It is catalyzed by phenylalanine ammonia-lyase, which deaminases L-phenylalanine to generate (E)-cinnamic acid. Then it undergoes further enzymatic transformations to create some related metabolites [183].

Recently, hydroxycinnamic acids' antioxidant, anti-inflammatory, and antibacterial properties have been investigated and employed in various pharmaceutical domains [184]. Many studies focused on vasodilation, antioxidant activity, and inflammation characteristics of hydroxycinnamic acid. Recent research showed that hydroxycinnamic acid compounds could reduce the severity of cardiovascular diseases [185, 186], hypertension [187, 188], depression [189], and diabetes [190]. Moreover, Tresserra-Rimbau et al. [179] and Adriouch et al. [180] studied that the high-intake percentages of hydroxycinnamic acids in daily meals significantly reduced the risks of cardiovascular disease in two countries (Spain and France).

2.5 Phytosterols

Phytosterols are cholesterol-like molecules found in various plants, with high concentrations occurring in the cell membranes of vegetables, fruits, and other plants. Phytosterol is a 3-hydroxy compound of cyclopentaphthene. The structure of phytosterols is similar to cholesterol; the main difference is that sterols are usually connected with a methyl or ethyl group at C-24, and common sterols have unsaturated double bonds between C-22 and C-23. Their structure comprises a steroid skeleton characterized by the saturated bond between C-5 and C-6 of sterol moiety [191]. Their aliphatic side chains are connected to C-17, while the hydroxyl groups are attached to the C-3 atom. They can be divided into sterols and stanols, representing unsaturated and saturated molecules. Phytosterols exist in four forms in plants, in the form of fatty acid esters, free alcohols, sterol glycosides, and acylated sterol glycosides [192]. They mainly exist in free and esterified forms (in edible oils), are found in plants, and cannot be synthesized in the human body. People mostly get phytosterols by ingesting dietary fiber, such as vegetable oil,

beans, nuts, vegetables, and fruits [193]. Phytosterols show the characteristics of directly inhibiting tumor growth, including reducing cell cycle progression, inhibiting tumor metastasis, and inducing apoptosis, such as reducing the risk of oesophagal and ovarian cancers [194]. Campesterol, β-sitosterol, ergosterol, and stigmasterol are four representative compounds widely studied in treating diseases (Fig. 6).

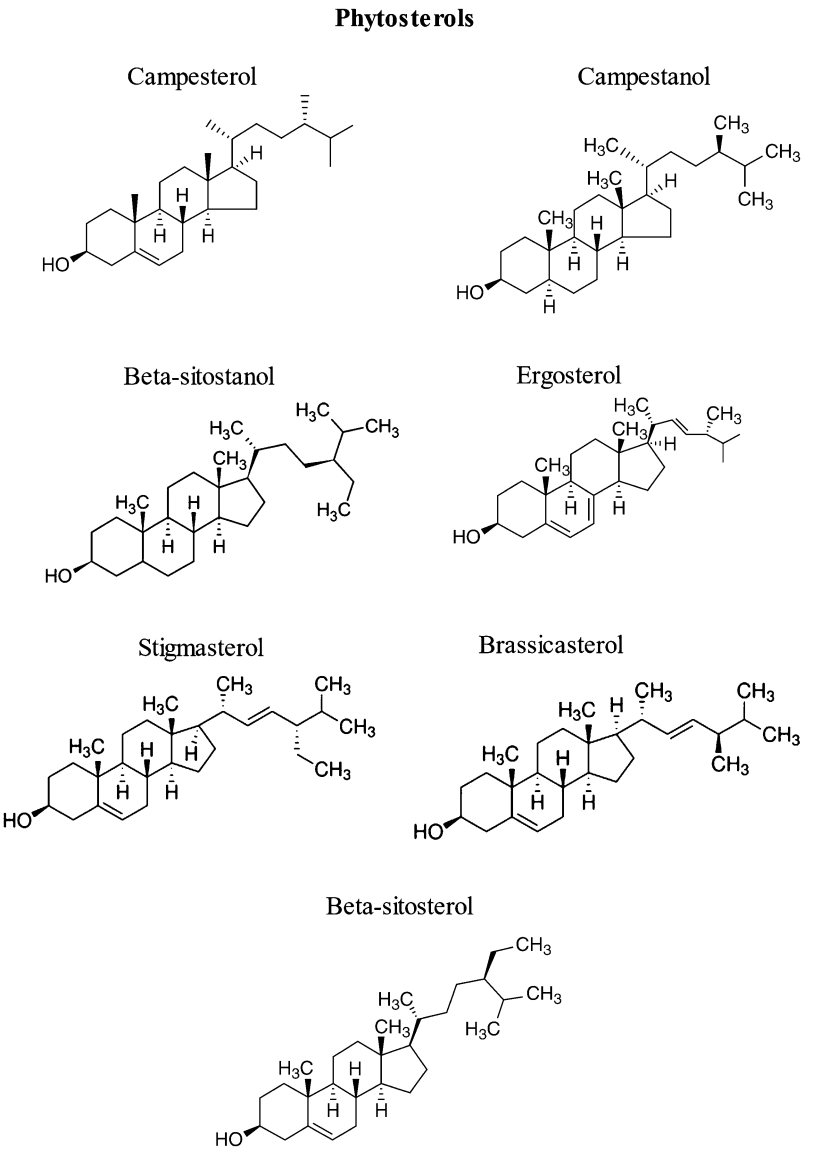

Fig. 6 Examples of some phytosterol compounds

Campesterol is abundant in canola and corn oils [195]. Campesterol has played an important role in inhibiting the proliferation of ovarian cancer cells and has the potential as a new antiovarian cancer drug. It was isolated from *Strychnos innocua* (Delile) and has been found to potentially affect antibacterial activity [196].

β-sitosterol has an unsaturated double bond on C5-C6, easily oxidized by active oxygen. Because of this structural characteristic, oxyphytosterols are one of the most common phytosterols in plants. Oxyphytosterols can play an important role as anti-inflammatory and antivirus agents. β-sitosterol can interfere with various cell signaling pathways, including cell cycle, proliferation, anti-inflammatory, hepatoprotective, and antioxidation [197]. Moreover, von Holtez et al. [198] discovered that low concentrations of β-sitosterol in cancer treatment dimensioned the development of cancer cells and even caused cancer cell death.

Ergosterol is the major steroidal component of the cell membrane of filamentous fungi and is not present or a minor component in most higher plants. It also exists in yeast cell walls and the mitochondrial membrane [193]. Its content has been widely used as an estimate of fungal biomass in soil and the aquatic environment because it was found that there was a strong correlation between ergosterol content and dry fungal biomass [194].

Stigmasterol is mainly found in soybeans. In addition to reducing cholesterol activity, stigmasterol has anti-inflammatory effects. Gabay et al. [199] showed that stigmasterol extracted from the bark of *Butea monosperma* (Lam.) Taub. has hypoglycemic, antiperoxidative, and thyroid-inhibiting effects.

3 Role of Secondary Metabolites in Diseases Treatment

Phytochemicals have been increasingly studied in disease treatment globally. In this section, the role of some phytochemicals in treating some disorders, including hepatic, renal, and cardiovascular disorders, cancer treatment, antimicrobial, anti-inflammatory activities, and neurological disorders, are discussed.

3.1 Hepatic Disorders

Nowadays, alternative therapy methods for several ailments are being embraced that use phytochemicals derived from natural resources. Despite significant developments in contemporary medicine, a persistent issue has been the lack of suitable and effective hepatoprotective medication [200]. Recent research has focused mostly on phytochemical screening to identify distinct types of biological activity. Recent years have seen a tremendous increase in interest in phytotherapy research as researchers look for new pharmacological cures. Numerous phytochemical substances, especially from medicinal herbs, are incorporated into the treatment of liver problems, including *Hedyotis corymbos*, *Rosa damascene*, *Casuarina equisetifolia*, *Cajanus cajan*, *Trichosanthes dioica*, *Glycosmis pentaphylla*, *Justicia gendarussa*, *Tinospora crispa*, *Bixa orellana*, *Moringa oleifera*, *Premna esculenta*,

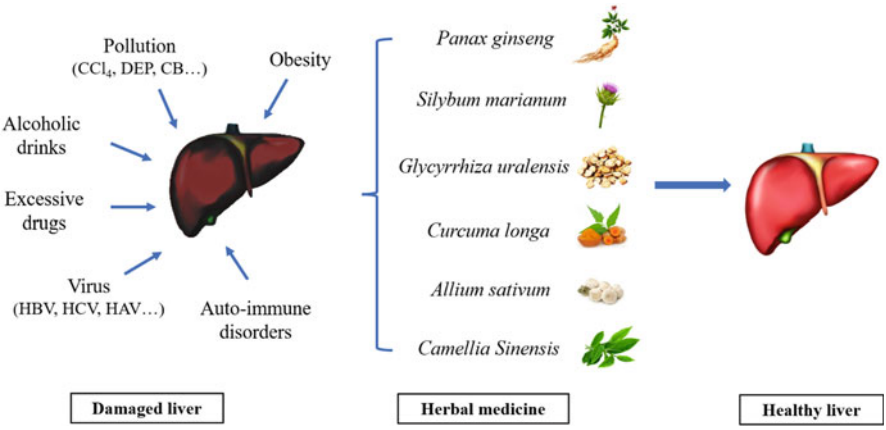

Fig. 7 Some vital phytochemicals support the hepatic disorders treatment. (modified after Das et al. [202])

Dendrophthoe pentandra, *Argemone mexicana*, *Leea macrophylla*, *Physalis minima*, *Synedrella nodiflora*, *Hylocereus polyrhizus*, *Caesalpinia bonduc*, *Piper chaba*, and *Bombax ceiba* (Fig. 7) [201].

Aguirre et al. [203] investigated some polyphenol components, like resveratrol (trans-3,4′,5-trihydroxystilbene) and stilbenoid involved in the enhancement of glycemic control and glucose tolerance, decrease in lipid levels, as well as anti-lipogenic, anti-inflammatory, and antioxidant properties. In addition, thymohydroquinone exhibited hepatoprotective characteristics toward drug-induced hepatotoxicity [204].

3.2 Renal Disorders

Renal damage and chronic kidney disorders are severe medical cases globally; the average number of patients increased by 8–16%. Besides Chinese herbal medicine metabolites, bioflavonoids, resveratrol, quercetin, and curcumin were demonstrated to be potential in chronic kidney disorders [205]. Green tea contains various polyphenolic substances, among them is epigallocatechin-3-gallate. Many reports showed the reactivity of epigallocatechin-3-gallate in renal damage treatment by delaying lupus nephritis via boosting the antioxidant Nrf2 pathway and diminishing the NLRP3 inflammasome activation. Additionally, ursolic acid (pentacyclic triterpenoid) is frequently found in fruit peels, herbs, and spices. Kunkel et al. [206] investigated that ursolic acid has a protective activity against chronic kidney disorders by suppressing the activity of STAT3 and the NF-B mechanism, hence decreasing the inflammatory activity. Moreover, allicin (organosulfur compound) enhances renal function by modifying the AT1, Nrf2/Keap1, and eNOS pathways and lowering CKD-mediated systemic hypertension [207].

3.3 Cardiac Disorders

According to current epidemiological forecasts, the globe is on course to experience a vascular typhoon of cardiovascular disease burden. In emerging nations, coronary heart disease raised by 120% in women and 137% in men in 2020 [208]. Therefore, researchers searched for natural plant-derived cardiovascular medicines. Soya bean isoflavones reported a powerful ability to manage the risk factors for cardiovascular disorders. Key isoflavones found in soya beans are present as glycosides (e.g., genistein, daidzein, and glycitin) and support cardiac function through various methods [209]. Many epidemiological, clinical, and experimental investigations revealed a positive correlation between green tea consumption and cardiovascular health, as green tea contains a high yield of catechins [210]. In addition, an epidemiological study suggests dietary carotenoids may lower the incidence of ischemic stroke, myocardial infarction, and coronary heart disease. Several phytochemical components, such as glucoraphanin, cucurbitacins, diosgenin, sulforaphane, and tocopherols, provide cardiovascular protection, reduce oxidative stress, enhance lipid profiles, and lower the blood pressure [211, 212].

3.4 Cancer Treatment

The number of cancer patients is still rising yearly, despite research into many ways to prevent and treat the disease. Reregulating cellular processes has been the focus of cancer treatment. Many clinical trials have examined cancer treatments using radiation, chemotherapy, antibody therapy, and immunotherapy. Because they cause deleterious effects on healthy cells, radiation and chemotherapy have serious adverse effects. Immunotherapy and antibody therapy exhibit exact cancer-targeting abilities, but they have a small therapeutic window and are sometimes expensive [213]. About 25% of medications utilized in cancer therapeutic settings come from plants (anticancer activity). For example, Lestari et al. [214] reported the anticancer activity of curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) (isolated from *Curcuma longa*) in colorectal cancer treatment.

Additionally, curcumin can be investigated as an antiangiogenic, anti-inflammatory, and antioxidant drug. Polyphenol flavonoid resveratrol (3,4,50-hydroxystilbene) can stop the growth of *H. pylori* and the division of gastric NSCLC cells preventing/treating gastric cancer [215]. Recent research revealed that the secondary metabolite hypericin from the plant *Hypericum* L. inhibited the overexpression of the ABC transporter in the HL-60 subclone leukemia cells via accelerating mitoxantrone-induced cell death [216]. Furthermore, β-carotene has been demonstrated to enhance the suppression activity of the anticancer drug (5-FU) on the development of tumors by oesophagal carcinoma (Eca109) [217].

3.5 Antimicrobial Activity

In the past 50 years, the development of vaccines and antibiotics has successfully eliminated infectious diseases such as *Mycobacterium tuberculosis* and smallpox, saving many lives. Plant secondary metabolites, such as flavonoids, phenolic, alkaloids, organic acids, and essential oils, have a significant role in antimicrobial properties. *Saussurea gossypiphora* contains multiple secondary metabolites, including apigenin and luteolin, which have antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus* [218]. Other examples of heterologous expression of phytochemical pathways have shown it is possible to develop plants into pharmaceutical production platforms. *Crocosmia* spp. is an ornamental plant found to produce montbretin A, a potent inhibitor of human pancreatic amylase, which is a promising treatment for type II diabetes pending clinical validation.

Moreover, rosmarinic acid extracted from *Origanum vulgare* L. has significant antibacterial activity against *Helicobacter pylori* associated with an ulcer [219]. Flavonoids have multitarget characteristics, which can target bacterial plasma membranes to inhibit drug-resistant bacteria through different sterilization mechanisms. Isoprenylation of flavonoids plays a crucial role in antibacterial activity. Both α-mangostin and isobavachalcone target phospholipids, which destroy the membrane homeostasis and combine with the outer membrane permeabilizer against gram-positive bacteria. In addition, the antibacterial activity of phenolic secondary metabolites is attributed to the acidic characteristics of hydroxyl groups. The compounds change the permeability of cells, interfere with the enzymes involved in productivity, interrupt protein synthesis, and eventually lead to cell death [220]. Alkaloids affect the integrity of the cell wall of *Candida albicans*, leading to mitochondrial dysfunction, which in turn leads to the upregulation of oxidative stress. Similarly, essential oils have antimicrobial mechanisms that affect the ATP concentration and peptidoglycan of *Escherichia coli* and *Staphylococcus aureus*, resulting in cell wall damage [221].

3.6 Anti-Inflammatory Activity

Inflammation is the common process in the body's defensive response to hazardous stimuli, such as biological factors (bacteria, fungi, parasites, and viruses), physical factors (ultraviolet rays, extreme temperature, radioactive substances, and mechanical damage), chemical elements (a poisonous gas), and others. The uncontrolled inflammatory reaction is one of the main causes of allergies, cardiovascular diseases, and autoimmune diseases. Inflammation can cause various conditions, such as asthma, arteriosclerosis, and arthritis, which greatly threaten health [222]. Treating some inflammation-related diseases depends on steroidal and nonsteroidal anti-inflammatory drugs but treating such drugs will have several side effects. Therefore, using natural herbal medicines in treatment is particularly important. How to develop drugs with anti-inflammatory activity by using natural herbal medicine has become the hotspot of research. Natural herbal medicines can synthesize various

anti-inflammatory compounds, including flavonoids, terpenoids, alkaloids, and essential oils.

Turmeric has anti-inflammatory and anti-arteriosclerosis effects. In India, turmeric is a traditional medicine used to treat rheumatic diseases [223]. It is reported that the genus *Ipomoea* and *Alstonia* species in Egypt have anti-inflammatory activity with little side effects. Furthermore, *Ipomoea pescaprae* extract has a therapeutic impact on dermatitis caused by jellyfish sting and oedema caused by ethyl phenylpropionate in experimental animals [224]. Studies illustrated this activity is due to the separation of some lipid and phenolic compounds.

In addition, licorice is the most frequently used traditional Chinese medicine; it can produce a variety of bioactive secondary metabolites, such as flavonoids, polysaccharides, and triterpenes. They have anti-inflammatory activity and are important as antibacterial, antiviral, and hepatoprotective substances [225]. Stilbenoids are found in tea, grapes, nuts, and berries. Resveratrol, pterostilbene, and piceatannol are well-known stilbenoids with indisputable anti-inflammatory activity in vitro and in vivo. Stilbene compounds are a group of plant phytoalexin polyphenols that can protect plants against pathogenic bacteria [226]. In folk medicine, these compounds are extensively used to treat skin inflammation, hepatitis, and stomachache. At the same time, they also have anticancer, neuroprotective, and antiviral properties. Recent studies reported that phenylpropanoids in essential oils have anti-inflammatory activities. Phenylpropionic acids are organic substances produced by plants that play an important role in preventing and treating trauma and infection. They are widely used in the medical field due to their corresponding pharmacological characteristics [227]. For instance, *Cinnamomum cassia* is commonly used to treat gastritis, anti-inflammation, and dyspepsia [228].

Moreover, alkaloids are widely distributed in *Menispermum dauricum* DC., *Tripterygium wilfordii*, and *Begonia kunmingshanensis* [229]. Wei et al. [230] stated that alkaloids have strong anti-inflammatory activity and are commonly used in treating ankylosing spondylitis, systemic lupus erythematosus, and other diseases. Berberine, sinomenine, dauricine, tetrandrine, stephanine, and lycorine in isoquinoline alkaloids have good anti-inflammatory effects. Piperidine alkaloids have anti-inflammatory, anti-arrhythmia, and anticancer effects. In addition to anti-inflammation, terpenoid alkaloids have antipyretic, analgesic, and antihypertensive effects [231].

3.7 Neurological Disorders

Neurological disorders affect the central nervous system and its peripheral nerves. The symptoms of neurological disorders include headaches, memory loss, slowness of movement, speech disorders, limb weakness, or pain. The causes of the disease are complicated; some neurological diseases have obvious heritability. Furthermore, environmental factors and age also affect nervous system health. The active ingredients in plants are very important in preventing and treating neurological diseases. Herbal medicines can delay or reduce the symptoms of neurological disorders. For

example, tea polyphenols are a well-known active ingredient in tea. It can inhibit acetylcholinesterase and butyrylcholinesterase in improving Alzheimer's disease. In addition, tea polyphenols can modulate and shape gut microbiota to boost immunity and enhance sleep quality by the gut-brain axis. Phenolic substances extracted from grapes have a good antioxidant effect, which can reduce the formation of free radicals and prevent damage to protective cells, helping to alleviate neurological disorders and brain aging. Moreover, numerous research reported that cannabinoids (isolated from *Cannabis Sativa*) have sedative, anti-inflammatory, and analgesic effects. Thus, it can potentially relieve various neurological diseases [232, 233].

4 Artificial Phytochemicals Production

Herbal medicines have been utilized since antiquity, and several therapeutic plant secondary metabolites are employed directly as medications and raw resources for semisynthetic alterations. Their structural diversity, which frequently limits the cost-effective chemical synthesis and relatively low extracted content of many plant species, mandates the field-cultivated materials. The novel biotechnological fabrication techniques of these chemicals offer a variety of benefits, including predictable, steady, and longtime sustainable production, adaptability, and more straightforward isolation and purification [234]. Many researchers use genetic engineering to manipulate plant metabolism to manufacture artificial phytochemicals. This entails the introduction of genes that encode enzymes involved in synthesizing specific bioactive components in plants. For instance, scientists have successfully modified plants to generate secondary Taxol® (paclitaxel) metabolite. It is an isoprenoid extracted mainly from *Taxus brevifolia* plant and widely used in cancer treatment [235–237]. Moreover, the artificial synthesis of phytochemicals involves using genetically engineered microbes or "cell factories" engineered to manufacture certain compounds, including carotenoids, flavonoids, and terpenoids. The extracted chemicals are subsequently utilized as dietary supplements or food additives to enhance their nutritional value.

Plant synthetic biology attempts to avoid several challenges by overexpressing bioactive chemicals for large-scale synthesis and purification. The complete characterization of the biosynthetic process for the target molecule is the critical step in synthetic biology. Recognizing the interactions between produced intermediates and identifying the necessary components of a biosynthetic route based on conventional classes of enzymes can assist in completing several fragmented molecular mechanisms [238]. Moreover, contemporary sequencing technology has progressed, so whole genome sequencing and phylogenetic analyses of nonmodel species are now feasible [239]. For example, Natt et al. [240] identified a biosynthetic mechanism for producing and extracting colchicine (alkaloid) from *Gloriosa superba*. The study was conducted through previously derived RNA sequencing data of many plant species following metagenomics to ascertain eight critical genes in the pathway and to reassemble a 16-gene scheme in *Nicotiana benthamiana* with overexpression to generate N-formyldemecolcine (the colchicine precursor).

5 Recent Advances in Herbal Medicine

To understand the most recent advances in herbal medicine achievements, in this part, groups of studies conducted on the potentiality of plant secondary metabolites activity in disorders treatment are discussed. Several natural products derived from Chinese herbal medicine display anticancer properties, such as antiproliferative, proapoptotic, antimetastatic, and antiangiogenic effects, as well as the ability to regulate autophagy, modify multidrug resistance, balance immunity, and augment chemotherapy in vitro and in vivo. For instance, the therapeutic activity of curcumin, epigallocatechin gallate, berberine, artemisinins, ginsenosides, ursolic acid, silibinin, emodin, triptolide, cucurbitacins, tanshinones, ordonin, shikonin, gambogic acid, artesunate, wogonin, β-elemene, and cepharanthine has been discussed in more than 100 published research articles [241]. Curcumin has been found to possess diverse pharmacological effects, such as anticancer, anti-inflammatory, and anti-xidative activities, as supported by clinical data and comprehensive research [242, 243].

Curcumin and its derivatives have demonstrated promising potential as therapeutic agents for various malignant conditions, including cancer. Several research studies have demonstrated that curcumin and its derivatives can impede the growth of tumors in different human body regions, such as the head, neck, skin, ovarian, and gastric cancers[244–246]. Liu et al. [243] reported that the natural polyphenol curcumin (extracted from turmeric rhizome) suppressed the Janus kinase/signal transducers and activators of the transcription (JAK/STAT) pathway in cultured oesophagal squamous cell carcinoma (ESCC) cells. The attachment of cytokines to receptors activates JAKs, which phosphorylates STATs. STATs are translocated into the nucleus after being dimerized and phosphorylated to regulate gene expression. These genes, including cyclins and antiapoptosis proteins, are crucial for cell proliferation and survival [242]. The results showed that curcumin inhibits JAK2 activation, downregulating STAT3 signaling, suppressing cell proliferation and colony formation, cell cycle arrest, and apoptosis. In addition, curcumin substantially reduced tumor growth in xenografts derived from ESCC patients. These findings indicated that curcumin is a powerful agent for preventing ESCCs harboring constitutively active STAT3 proteins. In addition, curcumin substantially reduced tumor growth in xenografts derived from ESCC patients. These findings indicated that curcumin is a powerful agent for preventing ESCCs harboring constitutively active STAT3 proteins. A study by Sivanantham et al. [247] reflected the anticancer activity of curcumin and its role in treating head and neck squamous cell carcinoma (HNSCC). They combined curcumin with three anticancer drugs, including docetaxel, doxorubicin, 5-fluorouracil, and diammine dichloroplatinum (II) (cisplatin), and evaluated their joint influence on the HNSCC cell line NT8e. The outcomes showed that the combined administration of 5- fluorouracil or doxorubicin with curcumin significantly inhibited NT8e cancer cell proliferation and enhanced apoptosis. NT8e cells treated with 5-fluorouracil or doxorubicin in combination with curcumin exhibited apoptosis via inhibition of Bcl-2 and elevation of Bax, caspase-3, and poly-ADP ribose polymerase. The researchers undergo some confirmation experiments to ensure the results are obtained through DAPI staining

and decreased red/green fluorescence by JC-1 observations of apoptotic cell features, such as membrane blebbing, nuclear condensation, and cell contraction.

Some phenolic substances collaborate with nonsteroidal anti-inflammatory drugs to block pro-inflammatory mediators' functioning or gene expression, such as cyclooxygenase (COX). Diverse phenolic components can also act on transcription factors, like nuclear factor-B (NF-B) and nuclear factor-erythroid factor 2-related factor 2 (Nrf-2), to upregulate or downregulate antioxidant response pathway constituents. Moreover, they may suppress enzymes involved in developing human diseases and have been utilized for treating various common human disorders, such as hypertension, metabolic issues, incendiary infections, and neurological disorders [247]. Hypertension is a prevalent and frequently progressive condition associated with a high risk of heart failure and complications [248]. According to estimates, up to 25% of adults struggle with hypertension globally [249]. Hypertension is a serious and becoming more prevalent global health issue. Multiple investigations have demonstrated that polyphenol-rich foods effectively prevent and treat hypertension, particularly through angiotensin-converting enzyme (ACE) inhibition [250]. Patten et al. [235] recently discovered about 74 plant families with substantial ACE inhibitory activity. Similarly, Han et al. [251] proved that some cocoa polyphenols, including catechins, flavonol glycosides, anthocyanins, and procyanidins, are bioavailable substances with antihypertensive properties by inhibiting ACE [252].

In addition, an in vitro study carried out by Bhandari et al. [253] investigated the antidiabetic efficacy of two soluble active compounds(−)-3-O-galloylepicatechin and(−)-3-O-galloylcatechin found in the ethyl acetate Bergenia ciliate extract served as catalysts for the dose-dependent suppression of porcine pancreatic amylase and rat intestinal maltase activation. The half-maximal inhibitory concentration (IC_{50}) value is the compound concentration required for inhibiting enzyme activity by 50%. The in vivo and in vitro suppressive enzyme activity of these compounds against α-glucosidase and α-amylase indicate that they have outstanding prospects for development as a treatment for type 2 diabetes [254].

Aging can be described as an accumulation of multiple detrimental changes in cells and tissues, which increases the risk of disease and mortality with advancing age. The free radical and oxidative stress theory [255] represents one of the most commonly accepted hypotheses for the aging mechanism. Despite normal conditions, oxidative damage occurs; however, as antioxidative and restoration processes become less effective with age, the rate of oxidative destruction rises [256, 257]. Plasma antioxidant capacity is correlated with antioxidant dietary consumption; it has been observed that a diet rich in antioxidants can mitigate the negative effects of aging and behavior. Multiple investigations suggest that a combination of antioxidant/anti-inflammatory polyphenolic substances found in fruits and vegetables may be effective antiaging compounds [258]. Anthocyanins, a category of flavonoids, are exceptionally abundant in brightly colored fruits, like berries, Concord grapes, and grape seeds. Anthocyanins have potent anti-inflammatory and antioxidant effects and inhibit lipid peroxidation and COX-1 and -2, which are inflammatory mediators. The antioxidant activity of formulations

of flavonoid-rich fruits and vegetables, including spinach, strawberries, and blueberries, is very high. According to the results of Shukitt-Hale et al. [259], supplemental nutrition with spinach, strawberry, or blueberry extracts in a control diet was similarly effective in restoring age-related deficits in the brain and behavioral function of geriatric rats. Moreover, tea catechins have potent antiaging characteristics, and drinking green tea abundant in these catechins could potentially delay the advent of aging [260].

6 Conclusion

Natural plant secondary metabolites (phytochemicals) have unique chemical structures with a wide range of diversity in medicinal and biological characteristics. They significantly treated some diseases and chronic disorders (cancers, cardiovascular, hyperglycemic, and type 2 diabetes). Moreover, they are involved in many pharmaceutical industries, like cosmetics and food supplements. The classification and the taxonomic position of each group and plant species are crucial in understanding each phytochemical's distinct function and characteristics (physical and chemical properties, synthesis pathways, and extraction methods). Furthermore, nature may have more based on the number of secondary metabolites identified and extracted. Considering the developments in synthesis technology as well as the invention of more advanced isolation and analysis approaches, it should be possible to identify a significant amount of these additional phytochemicals. Moreover, artificial phytochemical manufactoring also offers the potential to increase the effectiveness and safety of natural phytochemicals. Scientists can confirm the absence of impurities and pollutants by synthesizing molecules in a sterile atmosphere. In addition, they can alter the structure of a substance to increase its efficacy or decrease its toxicity. Recently, many researchers reflected on the potency of many isolated active metabolites in treating some vital disorders and may replace commercial and chemically synthesized drugs, especially those offered for tumor treatment.

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