Chapter

# Secondary Metabolites: Alkaloids and Flavonoids in Medicinal Plants

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## Abstract

Secondary metabolites (SMs) are natural compounds produced mainly by bacteria, fungi, and plants. They are low molecular weight compounds that have a wide range of chemical structures and biological functions. Secondary metabolites are so named because, unlike primary metabolites such as lipids, amino acids, carbohydrates, and nucleic acids, their synthesis is not required for the organism's development and reproduction. Today, the production of secondary metabolites is an important area of research for organic chemists, molecular biologists, and bioinformaticians. In this research, two types of secondary metabolites produced by plants, such as alkaloids and flavonoids, were studied and information was collected on the types of compounds, structures, biological activities, and commercial applications of these two types of secondary metabolites.

**Keywords:** secondary metabolites, types of alkaloids, types of flavonoids

## 1. Introduction

Metabolomics is the study of metabolites in biofluids, cells, tissues, or organisms [1]. Metabolites and their interactions are collectively referred to as the metabolome [2]. Metabolites are tiny molecules formed as a result of metabolic processes; these molecules are either intermediate or final results of metabolic reactions. Natural enzymes found in the cells of organisms accelerate metabolic processes primary and secondary metabolites are compounds that result from primary and secondary metabolism, respectively. Primary metabolites are essential molecules used by organisms for growth, development, and reproduction; these compounds are produced by cells during the growth phase as a result of metabolism. Because of their importance in maintaining normal physiological functions, primary metabolites are called nuclear metabolites. Vitamins ($B_2$ and $B_{12}$), lactic acid, amino acids, polyols, alcohols such as ethanol, nucleotides, organic acids, and other substances are examples of primary metabolites [3].

The present chapter examines the meaning and origins or sources of various significant types of secondary metabolites, such as alkaloids, terpenoids, tannins, flavonoids, saponins, cardiac glycosides, phenolic compounds, and others, as well as their impact on human and animal health.

## 2. Secondary metabolites

Secondary metabolites are organic chemicals created by organisms such as plants, fungi, or bacteria as a result of secondary metabolic processes that result in the creation and accumulation of different chemical compounds known as secondary metabolites. These substances are not essential for the organisms' core metabolic activities [4]. Secondary metabolites are created near the end of the growth phase and hence are not directly engaged in the organism's typical physiologic activities such as growth, development or reproduction. Instead, they boost the organism's survival through the mediation of ecological interaction, which acts as a selection benefit to the organism [4]. Secondary metabolites play crucial roles in interspecies defenses, such as plant defense against herbivory. Secondary metabolites, on the other hand, are used by humans as medications, recreational drugs, flavorings, colors, and so on. Secondary metabolites are generally categorized based on their extensive structural diversity, biosynthesis, and function. Over 2140,000 secondary metabolites have been identified in the literature; secondary metabolites are classified into five types: alkaloids, terpenoids, steroids, polyphenols, fatty-acid-derived compounds, nonribosomal polypeptides, and enzyme cofactors [5].

### 2.1 Alkaloids

Plants offer a large reservoir of active ingredients with substantial therapeutic uses such as antiviral, anticancer, analgesic, and antitubercular [5]. Alkaloids are significant secondary metabolites that were identified and utilized as early as 4000 years ago and are widely known for their medicinal potential [6]. Alkaloids are categorized into many groups based on their heterocyclic ring system and biosynthetic precursors, such as indole, purine, quinoline, isoquinoline, tropane, and imidazole, among others [7, 8]. Alkaloids contain antiproliferative, antimicrobial, and antioxidant properties that can be exploited in medication development [9]. Alkaloids' medicinal potential expands their industrial applicability. Numerous studies on the medicinal characteristics of various alkaloids derived from plants have been conducted. Alkaloids are naturally occurring chemical composites that often include basic nitrogen atoms. They could also have some neutral or mildly acidic substances in them [10, 11]. Several synthesized substances are also classified as alkaloids [12]. Alkaloids, in addition to carbon, nitrogen, or hydrogen, may include sulfur and, in rare cases, bromine, phosphorus, or chlorine. The term "alkaloid" was coined in 1819 by German scientist Carl F. W. Meissner, who derived it from the Arabic name al-Qali, which is related to the plant from which soda was initially extracted [13]. Alkaloids are low-molecular-weight compounds that account for around 20% of plant-based secondary metabolites [7]. So far, over 12,000 alkaloids have been isolated from diverse plant species [7]. Alkaloids are primarily solids that are found in higher plants. They are found in the following botanical families: Apocynaceae, Annonaceae, Amaryllidaceae, Berberidaceae, Boraginaceae, Gnetaceae, Liliaceae, Leguminoceae, Lauraceae, Loganiaceae, Magnoliaceae, Menispermaceae, Papaveraceae, Piperaceae, Rutaceae, Rubiaceae, and Ranunculaceae [14].

#### *2.1.1 Phytochemistry and classification of alkaloids*

Alkaloids exhibit a wide range of variety, not only in their botanical and biological origins but also in structure and pharmacological function. In this regard, different categorization schemes are feasible. Alkaloids can be classified structurally based on their chemical precursor, structures, and sources, or on the biological mechanisms

employed to acquire the molecule. True alkaloids, protoalkaloids, and pseudoalkaloids are the three main kinds of alkaloids. True alkaloids and protoalkaloids are generated from amino acids, but pseudoalkaloids are not.

*2.1.1.1 True alkaloids*

These alkaloids are produced from amino acids and share a heterocyclic ring containing nitrogen. They are biologically active and extremely reactive. They generate water-soluble salts, and many of them are crystalline, forming a salt when conjugated with acid. Except for nicotine, which is a dark liquid, almost all genuine alkaloids have a bitter taste and are solid [15]. Their presence in plants takes three forms: (a) free-state, (b) N-oxide, or (c) salts. Various amino acids like L-phenylalanine, L-tyrosine, L-ornithine, L-histidine, L-lysine, and other amino acids are the main sources of true alkaloids (**Table 1**) [16]. The most prevalent genuine alkaloids found in nature are cocaine, morphine, and quinine.

| Alkaloid type | Major group of alkaloid | Chemical group of alkaloid | Amino acid precursor |
|---|---|---|---|
| Tryptophan-derived alkaloids | True alkaloid | Ergot alkaloids<br>Pyrroloindole alkaloids<br>Indole alkaloids<br>Aspidosperma alkaloids<br>Quinoline alkaloids | L-Threonine<br>L-Proline<br>L-Tryptophan<br>L-Serine |
| | Protoalkaloids | Terpenoid indole alkaloids | --- |
| Arginine-derived alkaloids | True alkaloid | Marine alkaloids | L-Asparagine<br>L-Alanine<br>L-Aspartic acid<br>L-Arginine |
| Ornithine-derived alkaloids | True alkaloid | Pyrrolizidine alkaloids<br>Tropane alkaloids<br>Pyrrolidine alkaloids | L-Ornithine |
| Histidine-derived alkaloids | True alkaloid | Manzamine alkaloids<br>Imidazole alkaloids | L-Histidine |
| Nicotinic acid-derived alkaloids | True alkaloid | Sesquiterpene pyridine alkaloids<br>Pyridine alkaloids | Nicotinic acid |
| Lysine-derived alkaloids | True alkaloid | Indolizidine alkaloids<br>Quinolizidine alkaloids<br>Piperidine alkaloids | L-Lysine<br>L-Leucine<br>L-Isoleucine |
| Anthranilic acid-derived alkaloids | True alkaloid | Acridine alkaloids<br>Quinoline alkaloids<br>Quinazoline alkaloids | Anthranilic acid |
| Tryptophan-derived alkaloids | Protoalkaloids | Terpenoid indole alkaloids | L-Threonine<br>L-Proline<br>L-Tryptophan<br>L-Serine |
| Tyrosine-derived alkaloids | Protoalkaloids | Phenylethylamine alkaloids | L-Tyrosine |

**Table 1.**
*Amino acid and their involvement in alkaloid synthesis.*

| Parent compounds | Precursor compound | Chemical group of alkaloids | Examples |
|---|---|---|---|
| Terpenoid | Geraniol | Terpenoid-alkaloids | Gentianine<br>Aconitine<br>β-Skytanthine<br>Actinidine |
| Sesquiterpene | Acetate | Sesquiterpene-alkaloids | Evonoline<br>Cassinine<br>Evorine<br>Celapanin |
| Phenyl | Ferulic acid | Aromatic alkaloids | Capsaicin |
| Piperidine | Acetate | Piperidine-alkaloids | Pinidine<br>Coniceine<br>Coniine |
| Purine | Adenine/guanine | Purine alkaloids | Theophylline<br>Theobromine<br>Caffeine |

**Table 2.**
*Involvement of parent compound in pseudoalkaloids synthesis.*

*2.1.1.2 Proto alkaloids*

This class of alkaloids has a nitrogen atom obtained from an amino acid but does not belong to the heterocyclic ring system. The major precursors of these categories of alkaloids are L-tryptophan and L-tyrosine. This small category structurally consists primarily of simple alkaloids. The primary alkaloids in this category include yohimbine, mescaline, and hordenine. They are used to treat a variety of medical conditions, including mental illness, pain, and neuralgia [17].

*2.1.1.3 Pseudo alkaloids*

Pseudoalkaloids' fundamental carbon skeleton is not generated directly from amino acids. Instead, they are linked to amino acid pathways, where they are produced from forerunners or postcursors of amino acids via amination or transamination processes [16, 18]. Pseudoalkaloids can also be produced by nonamino-acid precursors. They can be generated from phenylalanine or acetate. Pseudoalkaloids are commonly found in capsaicin, caffeine, and ephedrine (**Table 2**).

*2.1.2 Classification established upon the ring structure*

Based on the existence of a fundamental heterocyclic nucleus in their structure, this is the most fully recognized categorization.

*2.1.2.1 Tropane alkaloid*

The tropane ($C_4N$ skeleton) nucleus characterizes this class of alkaloids. They are plentiful in the Solanaceae family. They are created by combining ornithine with acetoacetate. Pyrolines are the structural precursors of these alkaloids. The majority of them are mono, di, and trihydroxytropane esters with a variety of hydroxylation configurations. Cocaine, atropine, scopolamine, and their derivatives have been

extensively researched since the nineteenth century because of their significant pharmacological activities [19–21] (**Figure 1A**).

*2.1.2.2 Pyrrolizidine alkaloids*

The pyrrolizidine nucleus distinguishes this class of alkaloids. They are found in plants of the Asteraceae and Fabaceae families. The majority of pyrrolizidine alkaloids are found in plants as N-oxides; senecionine is the most well-known alkaloid of this kind (**Figure 1B**) [22–27].

*2.1.2.3 Piperidine alkaloids*

The fundamental ring system of this category of alkaloids is the piperidine nucleus. True piperidine alkaloids are distinguished by the presence of monocycle molecules with the $C_5N$ nucleus. Piperidine alkaloids are distinguished by the presence of odor. They cause long-term neurotoxicity. Many of them evolved from plants. Lobeline is an important alkaloid in this class (**Figure 1C**) [28].

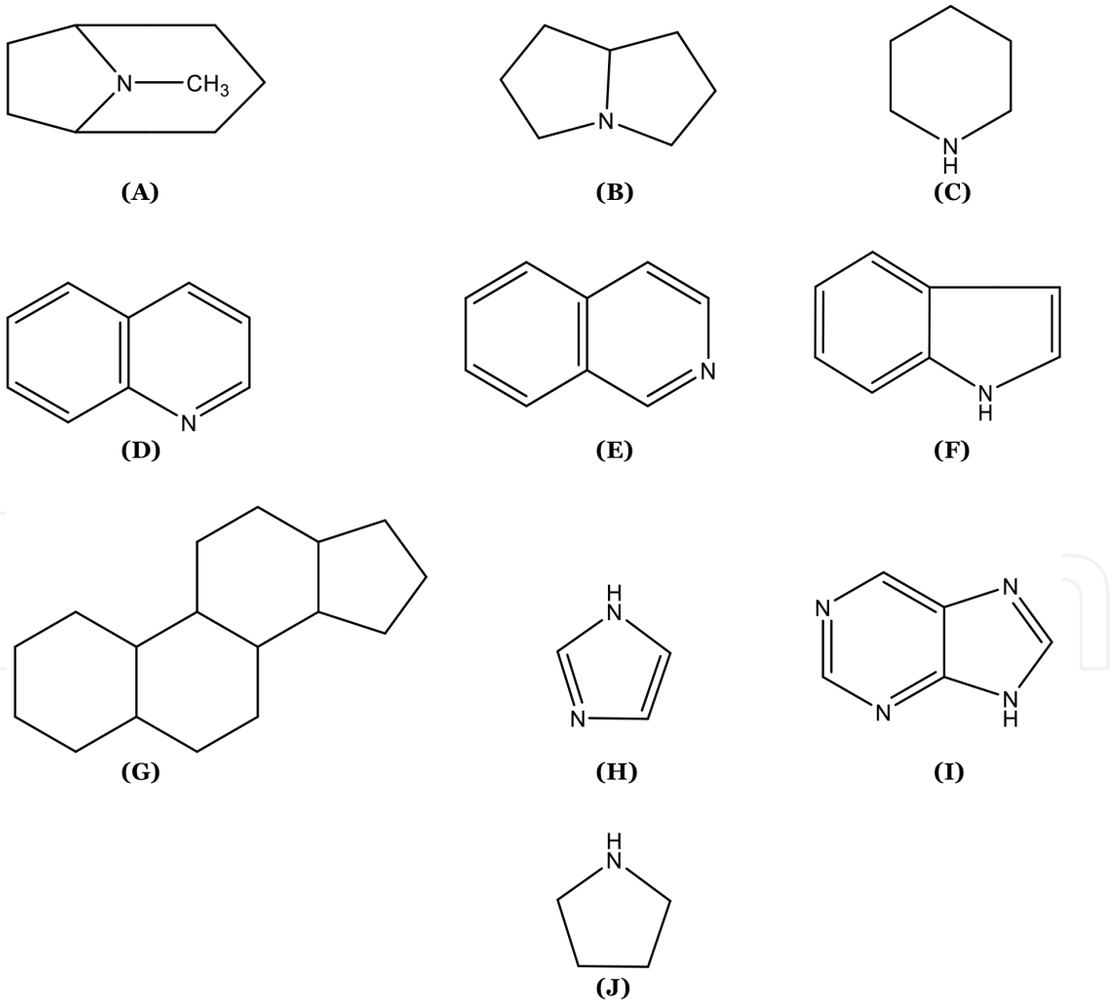


**Figure 1.**
*(A) Basic structure of the tropane nucleus, (B) basic structure of the pyrrolizidine nucleus, (C) basic structure of the piperidine nucleus, (D) basic structure of the quinoline nucleus, (E) basic structure of the isoquinoline nucleus, (F) basic structure of the indole nucleus, (G) basic structure of the steroidal alkaloid nucleus, (H) basic structure of the imidazole nucleus, (I) basic structure of the purine nucleus, (J) basic structure of the pyrrolidine nucleus.*

*2.1.2.4 Quinolines alkaloids*

This quinolone-nucleus-containing alkaloid can only be obtained from the bark of the Cinchona plant. However, many simple heteroaromatic quinolines have been identified from diverse marine sources (4,8-quinolinediol from cephalopod ink and 2-heptyl-4-hydroxyquinoline from a marine pseudomonad). Cinchonine, Cinchonidine, Quinine, and Quinidine are the primary alkaloids in this category (**Figure 1D**) [29, 30].

*2.1.2.5 Isoquinoline alkaloids*

Isoquinoline alkaloids are a diverse category of alkaloids found mostly in higher plants. However, only a few classes of isoquinolinoid marine alkaloids exist. These alkaloids offer a wide range of therapeutic effects, including antiviral, antifungal, anticancer, antioxidant, antispasmodic, and enzyme inhibitor activities. Morphine and codeine are the most well-known and researched isoquinoline alkaloids. They are made from either tyrosine or phenylalanine. They are created by combining a precursor of dopamine (3,4-dihydroxytryptamine) with a ketone or aldehyde. This group of alkaloids is further classified as follows: Simple isoquinoline alkaloids (e.g., salsoline, mimosamycin), benzyl isoquinoline alkaloids (e.g., reticuline, imbricatine), bisbenzyl isoquinoline alkaloids (e.g., fumaricine), manzamine alkaloids (e.g., manzamine a), pseudo benzyl isoquinoline alkaloids (e.g., polycarpine, ledecorine),

Seco bisbenzyl isoquinoline alkaloids (e.g., baluchistanamine), bis benzyl isoquinoline alkaloids containing one ether link (e.g., dauricine), bis benzyl isoquinoline alkaloids containing two ether links (e.g., berbamine), bis benzyl isoquinoline alkaloids containing aryl links only (e.g., pisopowetine), bis benzyl isoquinoline alkaloids containing one aromatic link and one or two ether links (e.g., rodiasine) (**Figure 1E**) [31].

*2.1.2.6 Indole alkaloids*

This is the most significant and intriguing alkaloid group produced from tryptophan. Simple tryptamine derivatives, carbazoles (where the ethanamine chain has been removed), a variety of alkaloids with one or more prenyl residues mixed with tryptamine, and others with the integration of typical monoterpenoid or diterpenoid units are examples of notable alkaloids from this category. Although structural diversity differs depending on the terrestrial and marine sources, traditional research investigations on alkaloids from both sources and the fungal source have been conducted. Polyhalogenation is a characteristic of these alkaloids. They are further classified as follows: simple indole alkaloids (e.g., Aplysinopsin, Gramine), bisindoles (e.g., Indirubin, 6,6′-dibromoindigotin), simple tryptamine alkaloids (e.g., tryptamine), cyclotryptamine alkaloids (e.g., Physostigmine), quinazolinocarbazole alkaloids (e.g., Rutaecarpine), β-carboline alkaloids (e.g., Harman), carbazole alkaloids (e.g., ekeberginine), indolonaphthyridine alkaloids (e.g., Canthin-6-one), ergot alkaloids (e.g., ergotamine) (**Figure 1F**) [32–38].

*2.1.2.7 Steroidal alkaloids*

The 1,2-Cyclopentane phenanthrene ring structure is unique to this class of alkaloids. They are mainly derived from higher plants of the Liliaceae, Solanaceae, Apocynaceae, and Buxaceae families, although some have also been isolated from

amphibians. These alkaloids are further subdivided into several subtypes, the most basic of which are various forms of aminopregnanes. The others types of steroidal alkaloids are Salamandra type (e.g., cyclo neosamandione), jerveratrum type (e.g., jervine), spirosolane type (e.g., soladulcidine), solanidine type (e.g., rubijervine), cerveratrum type (e.g., 3,6-cevanediol), conanine type (e.g., didymeline), Buxus type (e.g., cyclobuxine), pregnane type (e.g., 20α-dimethylamino-3β-senecioylamino-16β-hydroxy-pregn-5-ene), cephalostatins/ritterazines (e.g., ritterazinesa), miscellaneous steroidal alkaloids (e.g., bufotoxin) (**Figure 1G**) [39–43].

*2.1.2.8 Imidazole alkaloids*

This class of alkaloids is distinguished by its imidazole ring structure. Because the imidazole ring of these alkaloids is already formed at the precursor stage, they are exempt from the structural transformation operation. This class of alkaloids includes several structurally distinct instances, notably among marine and microbial alkaloids. They exhibit a diverse range of biological activity as well as great medicinal promise. Pilocarpine is the most important imidazole alkaloid in medicine (**Figure 1H**) [44, 45].

*2.1.2.9 Purine alkaloids*

Purine is a nitrogenous nucleotide (a building unit of DNA and RNA) that consists of a purine ring, pentose sugar, and another base, pyrimidine. Purine alkaloids include caffeine, theophylline, and theobromine. They are well-known as plant alkaloids, but they may also be found in marine species as substituted purines (e.g., Phidolopin) and a variety of terpenoid-purine alkaloids, including the age lines and others (**Figure 1I**) [46, 47].

*2.1.2.10 Pyrrolidine alkaloids*

The fundamental nucleus of pyrrolidine alkaloids is pyrrolidine ($C_4N$ skeleton). Plants have a large number of pyrrolidine alkaloids. Some examples of this class of alkaloids are Hygrine (biosynthesized from ornithine), Ficine (where the pyrrolidine ring is associated with a flavone nucleus), and Brevicolline (where it is coupled to a ß-carboline unit) (**Figure 1J**) [48].

*2.1.3 The biological activity of alkaloids*

Plant secondary metabolites are a broad group of physiologically active compounds with a variety of pharmacological activities such as antibacterial, stimulant, analgesic, anthelmintic, anticoagulant, antiacne, and antioxidant [49, 50]. For many millennia, humans from practically every culture have used plant-derived substances to predict and manage a variety of health problems.

*2.1.3.1 The biological activity of indole alkaloids*

The most important indole alkaloids are reserpine (an antihypertensive agent) from Rauvolfia serpentine [51] vinblastine and vincristine (an anticancer lead) from Catharanthus roseus [52]. Other indole alkaloids have important and powerful pharmacological activity such as antibacterial, antifungal, CNS stimulant, and antiviral properties. They have antiparasitic, cytotoxic, serotonin and antagonistic realms, anti-inflammatory,

and antiviral properties [53]. This unique class of phytochemicals has a variety of medicinal and pharmacological properties, which will be addressed in this section.

*2.1.3.1.1 Anti-cancer activity*

The vinca alkaloids, vincristine, and vinblastine have mostly been employed as chemotherapeutic agents in cancer therapy. They possibly limit the development of several cancer cell lines, such as neuroblastoma cells in mice, human leukemia HL-60 cells, HeLa cells, S49 lymphoma cells from mice, and $IC_{50}$ values for mouse leukemia L1210 cells were 33 and 15 nM, respectively. 4.1 and 5.3 nM, 1.4 and 2.6 nM, 5 and 3.5 nM, 4.4 and 4.0 nM, respectively. The cytotoxic activity of vinca alkaloids (vincristine and vinblastine) is mostly related to the disruption of mitotic spindle construction via interactions with tubulin in the microtubules that compose the mitotic spindles, resulting in metaphase arrest [54–58].

Vallesiachotamine (derived from the leaves of Palicourea rigida) exhibits substantial anticancer efficacy against human (SK-MEL-37) melanoma cells via an apoptotic mechanism [59]. Eudistomin K (derived from the Caribbean ascidian Eudistoma olivaceous) is an indole alkaloid with a new oxathiazepine ring that is an anti-tumor in L-1210, A-549, HCT-8, and P-388 cell lines [53]. Topsentin (discovered from the Caribbean deep-sea sponge Spongosorites ruetzleri) has in vitro cytotoxic effect against P-388 with $IC_{50}$ of 3.0 and 20 μg/mL for human tumor cells, respectively (HCT-8, A-549, and T47D). At concentrations of 150 mg/kg and 37.5 mg/kg, the drug also exhibits in vivo anticancer efficacy against P-388 (T/C 137 percent) and B16 melanoma (T/C 144 percent) [53]. Dragmacidin D, a bis (indole)-derived sponge metabolite (isolated from the sponge Spongosorites sp. Dragmacidin D), has anticancer activity in vitro against P-388 and A-549, with $IC_{50}$ values of 1.4 and 4.4 μg/mL, respectively [53]. Gelliusines A and B (derived from the deep-water New Caledonian sponge Gellius or Orina sp.) showed anticancer efficacy against KB, P-388, P-388/dox, HT-29, and NSCLCN-6 cell lines, with $IC_{50}$ values ranging from 10 to 20 μg/mL [53, 60]. Kapakahine B, a peptide derived from the marine sponge Cribrochalina olemda, has shown promising anticancer activity against P-388 murine leukemia cells, with an $IC_{50}$ value of 5.0 μg/mL [53]. Convolutamydine A (derived from the marine bryozoan Amathia convolute) has shown anticancer efficacy against HL-60 (human promyelocytic leukemia cells). At concentrations ranging from 0.1 to 25 μg/mL, this indole alkaloid alters culture plate adherence, produces growth arrest, and stimulates phagocytosis [53].

*2.1.3.1.2 Anti-oxidant activities*

The DPPH radical-scavenging test revealed that reserpine inhibits the DPPH radical by 42%. Lind et al. investigated the antioxidant activity of Barettin using two distinct biochemical tests, FRAP (Ferric-Reducing Antioxidant Power) and ORAC (Oxygen Radical Absorbance Capacity). According to their findings, Barettin has a possible antioxidant profile that is dose-dependent. Barettin showed FRAP and ORAC values of 77 and 5.5 μM Trolox equivalents (TE) at a concentration of 30 μg/mL, respectively [61].

*2.1.3.1.3 Anti-hypertensive activities*

Reserpine is widely used as first-line therapy in the treatment of primary hypertension. A reserpine dosage of 0.5 mg/day or higher resulted in statistically significant

SBP (systolic blood pressure) effects [62]. The fundamental mechanism of reserpine's antihypertensive activity is that it lowers the levels of catecholamines in peripheral sympathetic nerve terminals. Reserpine has a greater affinity for VMAT2 (vesicular monoamine transporter), binds to their receptors irreversibly, and inhibits VMAT2 irreversibly [63]. VMATS transports released and liberated nor-adrenaline or nor-epinephrine, dopamine, and serotonin (5-HT) from the presynaptic nerve terminal cytoplasm into storage vesicles for subsequent release into the synaptic cleft [64, 65]. Reserpine has a greater affinity for VMAT2 and binds to their receptors permanently. It is an effective antihypertensive and sedative, but long-term use promotes prolactin secretion and causes breast cancer.

*2.1.3.2 The biological activity of tropane alkaloids*

*2.1.3.2.1 Effect on asthma*

Atropine is extracted from the dried leaves and blooming tops of Datura metal, a member of the Solanaceae family. It works against Nocturnal Asthma. Atropine methyl nitrate can successfully cure nocturnal asthma, atropine sulfate [66], atropine in combination with metaproterenol [67], and albuterol Correspondingly. Atropine inhalation can enhance lung mucociliary function in humans.

*2.1.3.2.2 Activity against hyperglycemia and parkinsonism*

Atropine reduces hyperglycemia caused by neostigmine [68]. Atropine affects diabetes individuals' vagal tone [69]. Atropine can relieve tremors in a monkey model of parkinsonism.

*2.1.3.2.3 Anti-cancer and anti-inflammatory activity*

Colchicine is beneficial against chronic myelocytic leukemia and gout at toxic or almost toxic doses [70].

*2.1.3.3 The biological activity of isoquinoline alkaloids*

*2.1.3.3.1 Anti-bacterial activity*

Berberine has antibacterial action at a minimum inhibitory concentration (MIC) of 78 μg/mL by severely disrupting bacterial cell membrane structure by inhibiting cellular proteins, as proven by TEM and SDS-PAGE. This substance influenced bacterial DNA synthesis. It also inhibits methicillin-resistant S. aureus (MRSA) biofilm development in a concentration-dependent manner ranging from 1 to 64 μg/mL by reducing phenol soluble modules (PSMs) aggregation into amyloid fibrils.

*2.1.3.3.2 Anti-diabetic activity*

Berberine (methanolic extract) has anti-diabetic activity at a dosage of 500 mg/kg. Berberis aristata (methanolic extract) has potential effects on glucose metabolism, as well as HDL and cholesterol levels, in addition to anti-diabetic action [71].

*2.1.3.3.3 Anti-osteoporosis activity*

Berberine has modest laxative and hypocholesterolemic properties [72]. Berberine and its methanolic extract have strong antiosteoporosis action, which supports its ethnic usage in the treatment of postmenopausal osteoporosis [73].

*2.1.4 Current and potential industrial applications of alkaloids*

*2.1.4.1 Pharmaceutical application*

Alkaloids have led to the development of herbal remedies and their components based on the medical approach. The alkaloidal structure is changing chemically to improve therapeutic response. In general, synthetic medications perform better after modification than natural pharmaceuticals. Alkaloids, on the other hand, play an important part in phototherapy, homeopathy, and alternative medicine [15]. Indole, isoquinoline and tropane compounds are clinically important. In the pharmaceutical business, natural medications are transformed into medical goods to get a greater therapeutic response than synthetic pharmaceuticals. Physicians are interested in prescribing herbal treatments for the treatment of various ailments. Tropane derivatives such as atropine, hyoscine, and hyoscyamine are widely advocated for both recreational and therapeutic uses. Atropinol, for example, comprises the active component of atropine sulfate. Buscopan is a hyoscine derivative. Transdermal plasters include it. Another component of Bella sanol is hyoscyamine [15, 74]. Key alkaloids including boldine, codeine, narceine, and morphine have important roles in clinical care. Oxyboldine and Bold oval have morphine-like pharmacological effects. Codeine is a common ingredient in over 250 medicinal medications on the market. Codicaps and Codipront can be used for the same thing. Every single product is derived from opium. Narceine-containing drugs are related to codeine. It is mainly used for cough treatment [15, 75]. Tubocurarine derivatives such as tubarine and jexin have been used to relax muscles. Morphine-containing medicines, such as morphalgin and spasmofen, are utilized in extreme circumstances like surgical procedures and postoperative care [15]. The indole alkaloid chemical constituents such as ephedrine, ergotamine, ergometrine, and yohimbine are used in various combination formulations. Ephedrine is the primary active component of Dorex or Endrine. It is used for a variety of applications, including the treatment of nasal cold symptoms and bronchial asthma [15]. Ergotamine is the primary chemical ingredient of ergot. Because of its several uses; ergotamine is widely accessible on the market. Ergostat and Migral are commercialized ergotamine-based medications. These alkaloids are used in the treatment of migraines. Yohimbine is the primary active molecule in aphrodyne or yohimex. Based on this alkaloid, at least 20 distinct compounds have been created. These medications are used to treat male impotency. Alkaloids have a wide range of applications. Strychnine, for example, is used to treat a variety of illnesses, including eye ailments. Strychnine, which is used in clinical quantities, is the active component of Dysurgal or Pasuma [15, 76].

*2.1.4.2 Agricultural application*

Alkaloids are a source of worry and debate in food crops due to potential health risks and the fact that they must be eliminated from plants through breeding, particularly hybridization. As a result, alkaloid-rich (bitter) and alkaloid-poor (sweet)

cultivars are created [77]. Total alkaloids cannot be eliminated by breeding. However, by employing an appropriate application, alkaloid content can be reduced. Industrial processing also removes alkaloids from raw materials [15]. Alkaloids are sometimes used as biological fertilizers in agriculture.

Alkaloids are high in nitrogen and carbon. Nitrogen and carbon, on the other hand, play an essential role in organic farming. The balance of macro and micronutrients is critical in carbon and nitrogen-based soil management methods.

## 2.2 Flavonoids

Flavonoids are secondary metabolites that are abundant in plants, fruits, and seeds and are responsible for color, aroma, and flavor. Flavonoids have several roles in plants, including controlling cell development, attracting pollinators and insects, and defending against biotic and abiotic stressors [78]. These chemicals have been linked to a wide range of health advantages in humans, including anti-inflammatory, anticancer, anti-aging, cardioprotective, neuroprotective, immunomodulatory, antidiabetic, antibacterial, antiparasitic, and antiviral effects [79–81]. Flavonoids have a $C_6-C_3-C_6$ flavone skeleton with two benzene rings (A and B) connected by a three-carbon pyran ring (C). The location of the catechol B-ring on the pyran C-ring, as well as the quantity and position of hydroxy groups on the catechol group of the B-ring, affect the antioxidant activity of flavonoids [82]. Flavonoids' functional hydroxy groups can donate electrons through resonance to stabilize free radicals and mediate antioxidant protection [83]. Flavonoids are categorized into six primary types based on their structure: Flavan-3-ols, Flavones, Flavonols, Flavanones, Isoflavones, and Anthocyanins [83]. Because of their remarkable antioxidant qualities, Flavonoids are used in the food, cosmetic, and pharmaceutical industries [84].

### *2.2.1 Flavonoids biosynthesis, structure, and classification*

Flavonoids are phenolic chemicals or polyphenols that have over 6000 distinct configurations [83]. Flavonoids are generated from two biochemical processes in plants: the phenylpropanoid system, which generates the phenylpropanoid skeleton ($C_6-C_3$), and the polyketide pathway, which generates blocks for polymeric $C_2$ units [85]. Almost all flavonoids have a $C_6-C_3-C_6$ structure with two benzene rings, A and B, linked by an oxygen-containing heterocycle pyrene ring (C). Flavonoids are classified into two broad groups based on the degree of central heterocyclic ring saturation [79]. Anthocyanidins, Flavones, Flavonols, and Isoflavones, for example, have a $C_2{=}C_3$ unsaturation, whereas Flavanones, Dihydroflavonols, and Flavan-3-ols are saturated flavonoids (**Figure 2**).

#### *2.2.1.1 Anthocyanins*

Anthocyanins are responsible for the hues of flowers, which range from pink to blue, but they are also found in leaves, fruits, and roots. Anthocyanins are the anthocyanidins O-glycosides from a chemical standpoint, as previously stated. Anthocyanidins (**Figure 2g**), which are highly oxidized 2-aryl-3-hydroxychromenylium, are also colored pigments, but they are less stable, so there are fewer examples in nature. The most common derivatives are cyanidin, which is responsible for red to magenta colors, delphinidin, which is responsible for purple to blue colors and pelargonidin, which is responsible for orange to pink colors (**Figure 3**). The presence

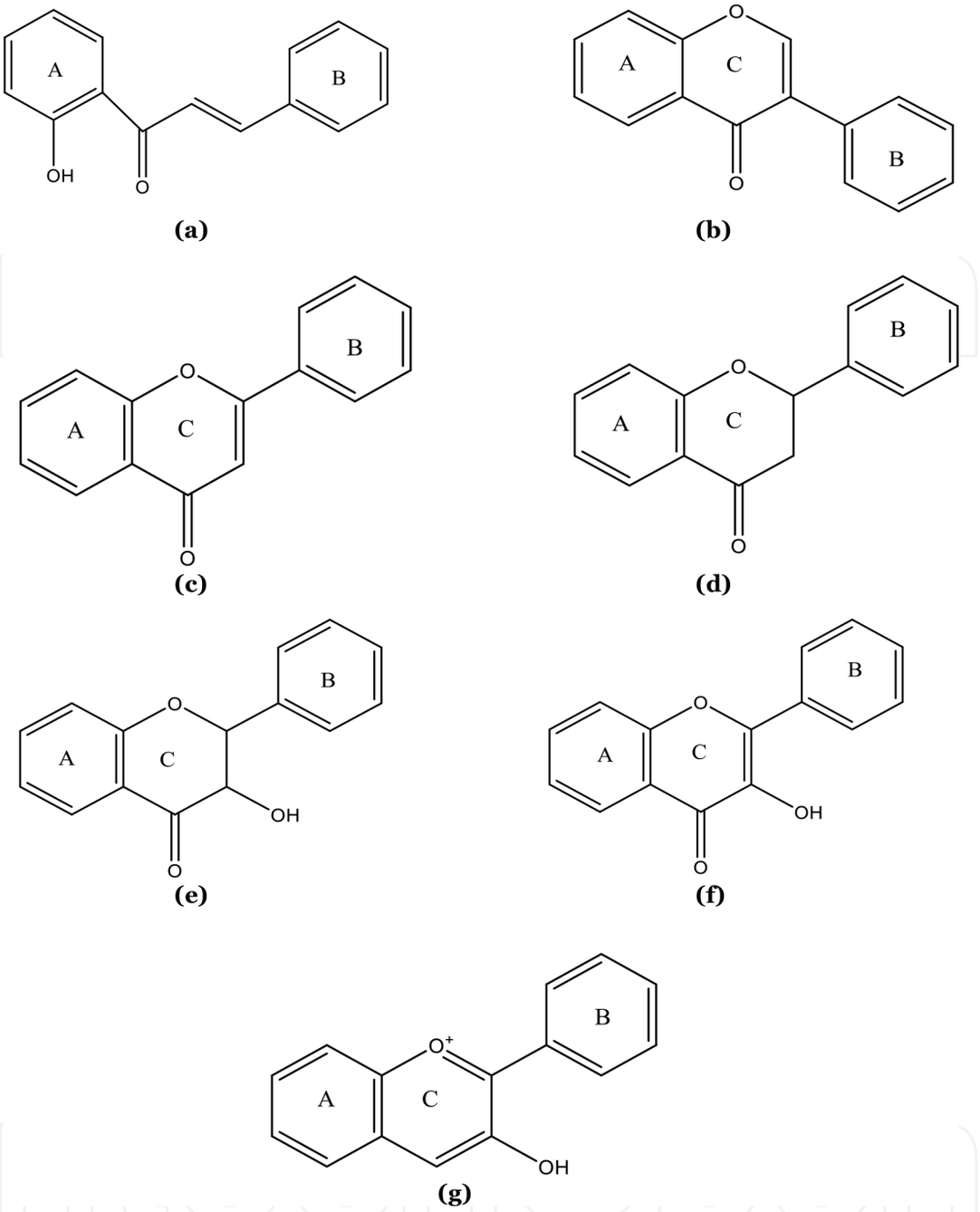


**Figure 2.**
*Types of Flavonoids (a) Chalcone, (b) Isoflavone, (c) Flavone, (d) Flavanone, (e) Dihydroflavonol, (f) Flavonols and (g) Anthocyanins.*

of a sugar moiety causes several color brightness alterations. The most frequent sugar with a β-linkage is glucose, but galactose, rhamnose, and xylose are also present [86].

*2.2.1.2 Flavanones and dihydroflavonols*

Flavanones, 2-arylchroman-4-ones (**Figure 2d**), are formed via ring closure isomerization of 20-hydroxychalcones, which results in a stereogenic center at carbon $C_2$. As a result, naturally occurring flavanones are optically active, mostly with a (2S) stereogenic structure, as in naringenin (**Figure 4**), a structure seen in natural flavanones. Many natural flavanones are also connected to sugars, mainly

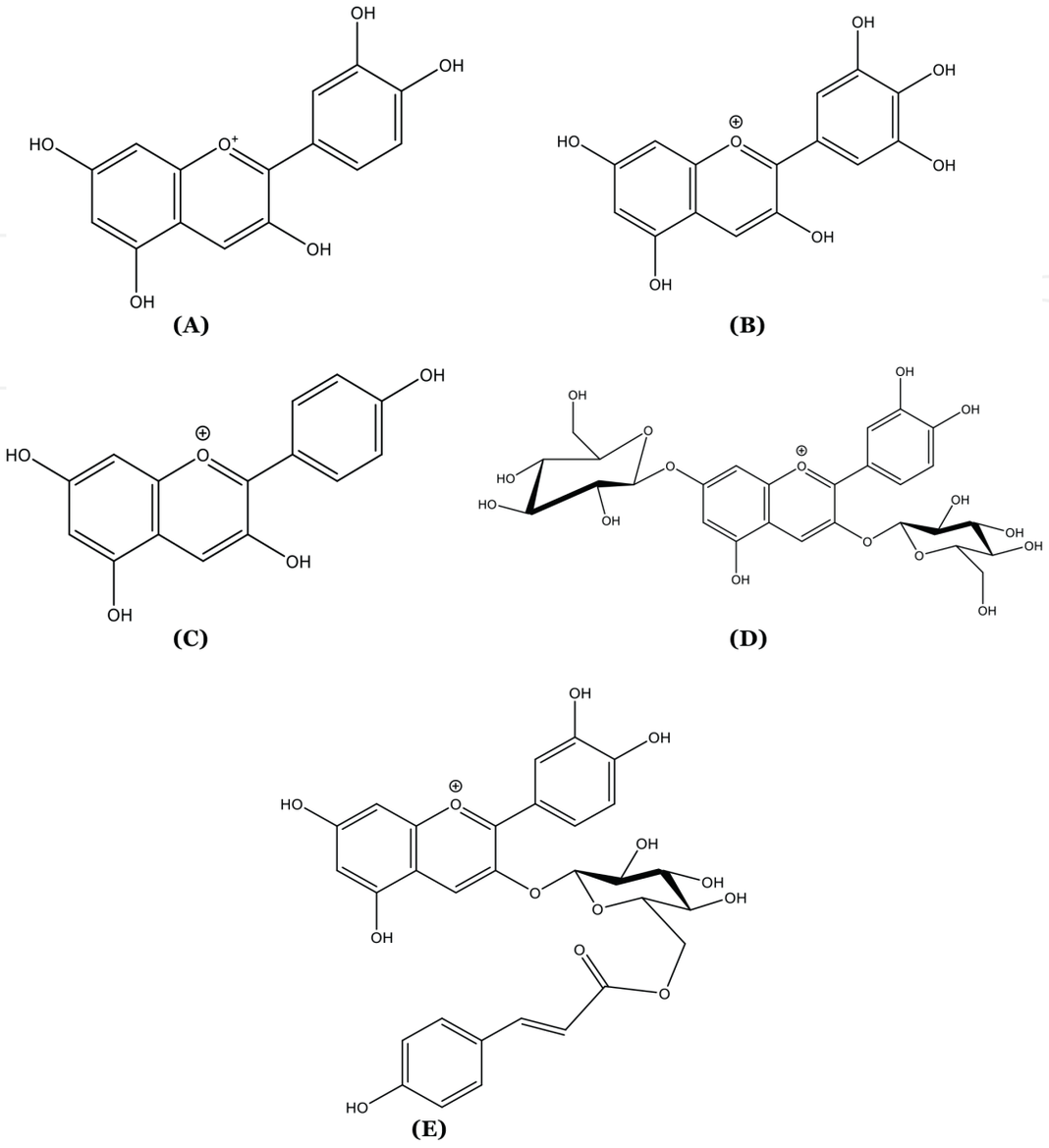


**Figure 3.**
*Examples of representative anthocyanidins and anthocyanins. (A) Cyanidin, (B) Delphinidin, (C) Pelargonidin, (D) Seranin, (E) Hyacinthin.*

as 7-O-glycosides, although others include prenyl side chains [87]. Dihydroflavonol, 2-aryl-3-hydroxychroman-4-one (**Figure 2e**), the biosynthesis of flavanones requires an oxidative hydroxy group addition at the C-3 position, which is why they are sometimes referred to as 3-hydroxyflavanones. Taxifolin is a common derivative that also serves as the principal scaffold for various other naturally occurring dihydroflavonols (**Figure 4**). These flavonoids are also discovered connected to sugars, with astilbin being an important example, as it has outstanding anti-inflammatory action [88] and is related to other groups such as prenyl and methoxy groups.

*2.2.1.3 Isoflavones*

Isoflavones, also known as 3-aryl-4H-chromen-4-ones (**Figure 2b**), are synthesized from flavanones by a rearrangement that favors 2,3-aryl migration followed by dehydrogenation. Although the word isoflavonoids is derived from the isolation of other

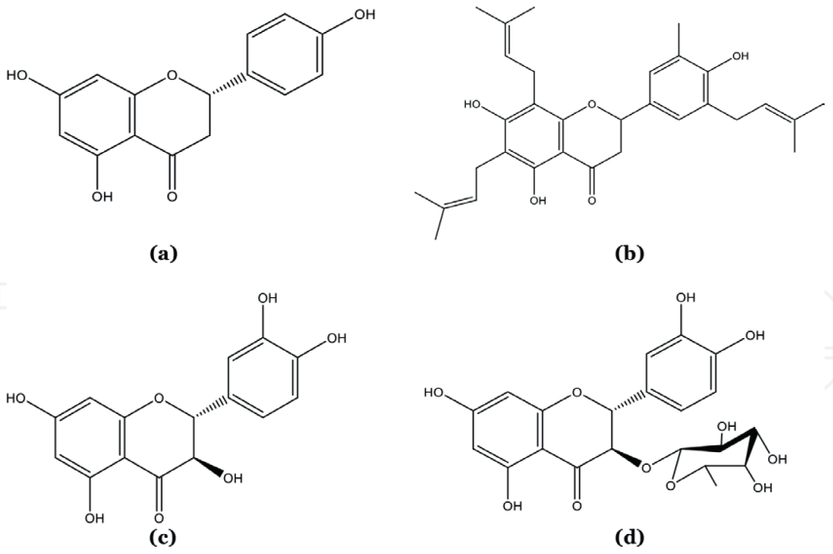


**Figure 4.**
*Examples of representative Flavanones and Dihydroflavonols. (a) (2S)-Naringenin, (b) Amorisin, (c) (2R,3R)-Taxifolin and (d) Astilbin.*

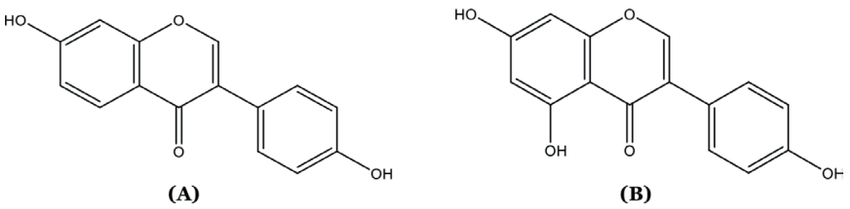


**Figure 5.**
*Examples of representative isoflavones. (A) Daidzein (B) Genistein.*

chemicals, such as isoflavanones or isoflavans, isoflavones remain the most prevalent. Isoflavones are still found only in a few subfamilies of the Leguminosae family [89]. Nonetheless, these metabolites have significant estrogenic action [90], and the anti-inflammatory benefits of several therapeutic plants are due to their isoflavone content [91]. The most prevalent scaffolds are daidzein and genistein (**Figure 5**), which are also discovered coupled to sugars however, there are just a few cases.

### *2.2.1.4 Flavones and flavonols*

Flavones, 2-aryl-4H-chromen-4-ones (**Figure 2c**), and flavonols, 2-aryl-3-hydroxy-4H-chromen-4-ones (**Figure 2f**), are formed via dehydrogenation of flavanones and dihydroflavonols, respectively. Flavones are the most common and typical class of flavonoids, moreover if it is considered that flavonols are 3-hydroxyflavones. Flavones have piqued the curiosity of scientists due to their abundance in nature and documented biological activity [92]. Flavones are further classified based on their substitution pattern and wide dispersion, such as O-methylated, C-methylated, and isoprenylated, among others. Flavones are members of the flavonoid family that exist as both O- and C-glycosides, with the most common aglycones being apigenin and luteolin (**Figure 6**). Although various sugar moieties have been identified, glucose is the most prevalent, and the flavone-preferred O-glycosylation site is $C_7$. It's worth noting that many sugar units can be connected to C-glycosides, as shown in carlinoside (**Figure 6d**), the most common flavonol is quercetin (**Figure 6e**), which has

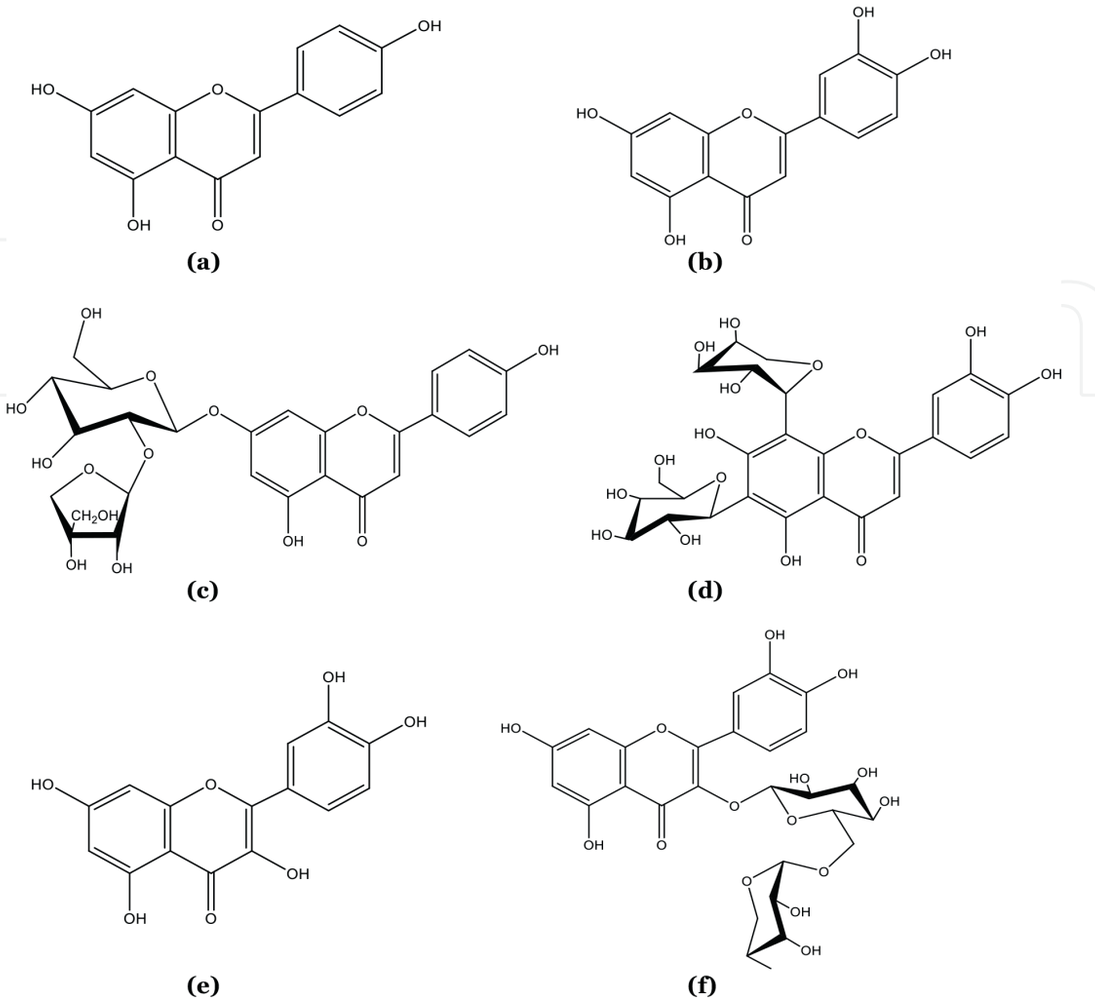


**Figure 6.**
*Examples of representative flavones and flavonols. (a) Apigenin, (b) Luteolin, (c) Apiin, (d) Carlinoside, (e) Quercetin and (f) Rutin.*

numerous biological features established [93], and which exists in both aglycone and oglycoside forms. In the case of rutin, O-glycosylation occurs at $C_3$ (**Figure 6f**). The most common flavonol glycoside in the plant kingdom.

### *2.2.2 Sources of flavonoids*

Flavonoids may be found in a variety of drinks and foods, including wine, beer, and tea, but the largest concentrations of natural flavonoids can be found in fruits, vegetables, flowers, and seeds [94]. The quantity of these chemicals, however, is determined by various factors, including plant cultivar/genotype, growing environment circumstances, soil characteristics, harvest, and storage. Green leaves, fruits, and grains are high in flavonols such as quercetin, kaempferol, fisetin, isorhamnetin, and myricetin (**Table 3**) [95, 96]. Lettuce, cranberry, apple, peaches, and red pepper, for example, are high in quercetin and kaempferol [97]. Rutin, spinacetin glycosides, and patuletin glycosides are abundant in spinach leaves but kaempferol 3-O-glycosides are abundant in broccoli, kale, endive, potatoes, onions, grapes, and tomatoes [98]. Myricetin can be found in a variety of foods, including nuts, berries, tea, and red wine [98, 99]. Flavones, which include luteolin, apigenin, sinensetin, isosinensetin, nobiletin, tangeretin, galangin, and chrysin, are among the most significant flavonoids (**Table 3**) [95].

| No. | Flavonoid classes | Examples | Food sources |
|---|---|---|---|
| 1 | Flavonols | Quercetin-Kaempferol-Fisetin-Isorhamnetin-Myricetin | Cranberry-Apple-Peaches-Grapes-Red pepper-Lettuce-Broccoli-Kale-Endive-Potatoes-Onions-Tomatoes-Nuts-Tea |
| 2 | Flavones | Luteolin-Apigenin-Sinensetin-Isosinensetin-Nobiletin-Tangeretin-Galangin-Chrysin-Baicalin | Citrus fruits-Green Tea-Red pepper-Lettuce-Broccoli-Oliveoil-Oregano-Thyme-Rosemary-Peppermint-Parsley-Cacao |
| 3 | Flavanols | Catechin-Epicatechin-Epicatechin gallate-GalloCatechin-EpigalloCatechin-EpigalloCatechin gallate | Tea-Cocoa-Raspberry-Apple-Red grape- Nectarine-Peach-Mango-Pear-Plum |
| 4 | Flavanones | Naringenin-Naringin-Hesperetin-Hesperidin-Eriodicytol | Orange-Mandarin-Lime-Lemon-Grape fruit |
| 5 | IsoFlavones | Daidzein-Genistein-Daidzin | Soyabean-Lupin-Fava beans-Chickpeas-Common beans- Kudzu roots-Peanuts |
| 6 | Anthocyanins | Pelargonidin-Cyanidin-Delphinidin-Peonidin-Petunidin-Malvidin | Cranberries-Blueberries-Raspberries-Bilberry-Strawberries-Blackberries-Red cabbage-Grapes-Cherries-Plums-Red turnip-Black beans-Purple corn |

**Table 3.**
*Flavonoid classes and examples of natural food sources*

These chemicals are mostly found in leaves, flowers, and fruits as apigenin, luteolin, and diosmetin glucosides [96]. Apigenin-7-O-glycoside, for example, is plentiful in celery, while luteolin and apigenin glycosides are abundant in numerous citrus fruits, green and red peppers, lettuce, broccoli, olive oil, cocoa, oregano, thyme, rosemary, peppermint, and parsley [98]. Flavanols, also known as flavan-3-ols, are a group of compounds that include catechin, epicatechin, epicatechin gallate, gallocatechin, epigallocatechin, and epigallocatechin gallate (**Table 3**) [100]. Flavanols such as (−)-epigallocatechin gallate, (−)-epicatechin gallate, (−)-epigallocatechin, and (−)-epicatechin are abundant in Camellia sinensis, the tea plant, and tea drinking is one of the most significant sources of these flavonoids [101]. Furthermore, fruits high in (+)-catechin, (−)-epicatechin, and (−)-epigallocatechin include apples, red grapes, peaches, mangoes, pears, plums, nectarines, and raspberries. Catechins can be found in cocoa and red wine [97, 98]. Flavanones, also known as dihydroflavones, is a kind of flavonoid found in citrus fruits (**Table 3**). Flavanone glycosides such as naringin, naringenin, and naringenin 7-O-neohesperidoside may be found in grapefruits, hesperidin, hesperetin, and hesperetin 7-O-rutinoside in oranges, mandarins, limes and lemons, and eriocitrin, eriodictyol, and eriodictyol 7-O-rutinoside in lemons [96, 97]. Isoflavones have a more restricted distribution in plants, being generated mostly in legumes [102]. Soybeans are high in genistin, glycitin, and daidzin glycosides, as well as malonylated isoflavones [98] (**Table 3**). Genistin can also be found in lupin, fava beans, and kudzu roots. Isoflavones are found in small amounts in common beans, peanuts, and chickpeas [102]. Anthocyanins are flavonoids that give some flowers, foliage, and fruits their blue, purple, red, and orange colors. This family of chemicals is found in anthocyanidin glycosides such as cyanidin, pelargonidin, delphinidin, peonidin, petunidin, and malvidin [97]

(**Table 3**). Cranberries, blueberries, raspberries, bilberries, strawberries, blackberries, plums, grapes, cherries, and sweet potatoes for example contain significant levels of anthocyanins [98]. Red cabbage, red turnips, and purple sweet potatoes are high in acylated anthocyanins. Furthermore, black beans, and purple maize contain cyanidin 3-O-glucoside [96]. Some flowers are blue because of delphinidin, while others are orange because of pelargonidin. Natural flavonoids can be isolated and utilized in the food business instead of manufactured chemicals to improve food quality.

In recent years, restrictions on the use of some synthetic antioxidants, such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and propyl gallate, have increased interest in natural flavonoids, owing to their ability to slow oxidative degradation of lipids, improve food quality and nutritional value and reduce toxicity [103]. Flavonoids can be utilized as food preservatives, preventing lipid oxidation and safeguarding vitamins and enzymes, as microbial growth inhibitors in foods, as additions in human nutritional supplements and animal feed, as flavorings, and colorants and as flavorings and colorants (e.g., anthocyanins) [103]. Some flavonoids also decrease fungal spore germination and have been recommended as a fungal disease control agent in certain meals [104]. Flavonoids are extremely adaptable, with photochemical capabilities that can be employed to protect drinks against light-induced color loss [105]. Because flavonoids are natural chemicals with low toxicity, plentiful in plants, and affordable, their rising usage as food additives in place of synthetic preservatives will contribute to the sustainability of the food business.

### *2.2.3 Biological activity of flavonoids*

Flavonoids have been demonstrated to have various health advantages in humans and a diet high in these substances can help avoid several chronic illnesses [94]. Flavonoids have numerous functions, but the capacity to scavenge free radicals and serve as antioxidants is unquestionably the most important. The antioxidant potential of flavonoids varies depending on the kind of functional group and its placement around the nuclear structure [106]. The amount and location of hydroxy groups in the catechol B-ring, as well as their position on the pyran C-ring, affect free radical scavenging capabilities [82]. Flavonoids' antioxidant activity methods include (a) direct scavenging of ROS, (b) suppression of ROS creation via trace element chelation (e.g., quercetin possesses iron-chelating and iron-stabilizing capabilities), or inhibition of enzymes involved in free radical production (e.g., glutathione S-transferase, microsomal monooxygenase, mitochondrial succinoxidase, NADH oxidase, and xanthine oxidase) and (c) antioxidant defense activation (e.g., upregulation of antioxidant enzymes with radical scavenging ability) [97, 106]. The majority of flavonoids occur as glycosides and the number and position of linkages with the sugar determine the flavonoid's antioxidant effects [107]. However, aglycone forms have a stronger antioxidant capability but are less available. In addition to antioxidant capabilities, flavonoids have been shown to have anti-inflammatory, anticancer, cardioprotective, antibacterial, and antiviral activities (**Table 4**). Inflammation develops as a result of a variety of factors, including tissue physical damage or trauma, chemical exposure, and microbial infection. In most circumstances, inflammation is brief and self-limiting, but in rare cases, continuous inflammation contributes to the development of chronic or degenerative illnesses such as cancer, diabetes, cardiovascular and neurological diseases, and obesity [108]. Flavonoids can serve as antioxidants in an inflammatory process, (a) scavenging ROS or lowering free radical buildup, (b) inhibitors of regulatory enzyme activity (e.g., protein kinases and phosphodiesterase), and

| No. | Flavonoid classes | Compounds | Biological activities |
|---|---|---|---|
| 1 | Flavonols | Quercetin-Myricetin-Kaempferol-Isorhamnetin | Anti inflammatory-anticancer-cardioprotective-antifungal-anti bacterial-antiviral |
| 2 | Flavones | Apigenin-Luteolin-Chrysin-Baicalin-Acacetin | Anti inflammatory-anti cancer-cardioprotective-anti bacterial- antifungal-antiviral |
| 3 | Flavanols | Catechin-Epigallocatechin-Epicatechin-Epigallocatechin gallate | Anti cancer-anti bacterial-antiviral |
| 4 | Flavononones | Hesperetin-Hesperidin-Naringenin | Anti inflammatory-anti cancer-cardioprotective-antifungal |
| 5 | IsoFlavones | Genistein-Daidzein-Glabridin | Anti cancer-anti bacterial-antifungal-antiviral-cardioprotective |
| 6 | Anthocyanins | Cyanidin | Anti inflammatory-Anti Cancer |

**Table 4.**
*Flavonoid classes and some examples of their biological activities.*

transcription factors involved in the regulation of mediators involved in the inflammatory process, and (c) immune cell activity modulators (e.g., suppression of cell activation, maturation, signaling transduction, and secretion processes) [108]. The inflammatory process is influenced by both hereditary and environmental factors.

Several studies have shown that a nutritious diet rich in fruits and vegetables, as well as non-processed and low-sugar meals, along with an active lifestyle, might help avoid inflammatory disorders [108]. Some flavonoids, such as flavonols (e.g., quercetin, rutin, and morin), flavanones (e.g., hesperetin and hesperidin), flavanols (e.g., catechin), isoflavones (e.g., genisten), and anthocyanins (e.g., cyanidin) have been demonstrated to exhibit anti-inflammatory functions during in vitro and in vivo experiments and clinical studies.

*2.2.3.1 Cardiovascular protection*

Flavonoids can protect the heart by reducing oxidative stress (preventing the oxidation of low-density lipoproteins), causing vasodilation, and regulating apoptotic processes in the endothelium [109]. Flavonoids can interact with lipid metabolism and minimize platelet aggregation, hence avoiding a variety of cardiovascular disorders [110]. Some research has shown that quercetin, naringenin, and hesperetin have vasodilator characteristics, with naringenin lowering blood pressure and relaxing vascular smooth muscles [108]. Isoflavones appear to protect against inflammatory vascular disorders and quercetin possesses cardioprotective characteristics against heart damage as well as an atheroprotective activity linked to oxidative stress reduction [108]. Baicalin has been shown to prevent apoptosis in heart tissue and alleviate cardiac dysfunction [111]. Chrysin inhibits platelet activity, while genistein has antihypertensive characteristics [109]. Anthocyanins reduce the risk of myocardial infarction in humans, enhance systolic blood pressure, and lower triglyceride total, and LDL cholesterol levels [112]. Furthermore, quercetin lowers systolic blood pressure and LDL cholesterol levels [81].

*2.2.3.2 Antiviral action*

Flavonoids can inhibit virus binding and penetration into cells, interfere with viral reproduction or translation and impede virus release [113]. Apigenin, for example, has been shown to inhibit viral protein synthesis in various DNA and RNA viruses, including herpes simplex virus, types 1 and 2, hepatitis C and B viruses, and the African swine fever virus [114]. Baicalein can inhibit avian influenza $H_5N_1$ virus multiplication in humans [115], while luteolin can inhibit HIV-1 reactivation [115]. Epigallocatechin gallate has an antiviral impact at several stages of the HIV-1 life cycle [115]. By interfering with HIV-mediated actin dynamics, genistein can prevent HIV infection of CD4 T cells and macrophages [116]. In addition, kaempferol can limit HIV replication in target cells [117] and prevent herpes simplex virus types 1 and 2 from adhering to and entering the host cell [116]. Wu et al. demonstrated the antiviral activity of quercetin, kaempferol, and epigallocatechin gallate against different influenza virus strains [118].

*2.2.3.3 Antibacterial action*

Flavonoids have multiple methods of action against bacteria. They can damage bacterial membranes and hinder many activities such as biofilm development, cell envelope creation, nucleic acid synthesis, electron transport chain, and ATP generation [119].

Catechin, epicatechin, and epigallocatechin gallate, as well as the flavonol quercetin, appear to cause an oxidative burst, boosting ROS generation and thereby increasing membrane permeability and damage [120]. Apigenin can disrupt membrane structure by disordering and disorienting membrane lipids, resulting in membrane leakage [119]. Flavonoids such as apigenin, chrysin, naringenin, kaempferol, quercetin, daidzein, and genistein limit biofilm development, whereas luteolin, myricetin and baicalein hinder bacterial DNA replication [119]. Epigallocatechin gallate and baicalein may limit bacterial ATP production [121].

*2.2.3.4 Antifungal action*

Flavonoids have several antifungal mechanisms, including disruption of the plasma membrane, activation of numerous mitochondrial dysfunctions, and suppression of cell wall production, cell division, and RNA and protein synthesis [122]. Apigenin and Baicalein can serve as antifungals by lowering lipid peroxidation and preventing membrane disruption [123]. Some isoflavones, such as glabridin, can impede the formation of fungal cell wall components such as β-glucans and chitin [124]. Quercetin can influence numerous mitochondrial activities, including the suppression of oxidative phosphorylation and the modification of ROS generation [125]. Apigenin disrupts the cell cycle, whereas myricetin, kaempferol, quercetin, luteolin, naringenin, and genistein inhibit DNA, RNA, and protein synthesis [126].

*2.2.4 Conclusions*

Alkaloids are of enormous medicinal and societal importance as a source of innovative leading chemicals for medication development against a variety of severe illnesses. Among them, the indole, tropane, and isoquinoline alkaloids are widely known for their medicinal potential in the treatment of hypertension, cancer, microbial infection,

neurological disorders, and other conditions. They are structurally distinct bioactive compounds with potential therapeutic properties. Finally, an extensive study on their metabolic transformation, the introduction of a wide variety of scientific instruments, and the collaborative collaboration of specialists from other scientific fields will speed up research on this hotspot and give new and significant healthcare chances. Also, flavonoids as another secondary chemical have different roles in growth and development as well as stress prevention. A greater understanding of the positive effects of flavonoids on human health has led to increased consumption and interest in using flavonoids in food processing and for medicinal purposes. Flavonoids are abundant in vegetables, flowers, and seeds, and methods have been developed to extract these compounds from these natural sources for use as food additives and preservatives. The recognition of natural flavonoids as a good and safer source of antioxidants provides new avenues for further research on these chemicals, focusing on new structures, new approaches and technologies, and other new natural sources.

## Acknowledgements

In this section, I'd like to thank my dear parents for all of their hard work on my behalf.

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[103] Saul R. Flavonoids: Important Biocompounds in Food N2 - Flavonoids are abundant secondary metabolites found in plants and fungi that have various roles in these organisms, including pigmentation, cell signalling, plant defence and inter-organism communication. Due to their abundance in nature, flavonoids are also important components of the human diet, and the last four decades have seen an intense study focused on the structure characterization of flavonoids and on their roles in mammal metabolism. This book reviews most of the well-established activities of flavonoids, and we also present more recent research studies on the area of flavonoids, including the chemical aspects of structure characterization of flavonoids, the biosynthesis of flavonoids in model plants as well as their role in abiotic stress situations and in agriculture, the role of flavonoids in metabolism and health and their importance in foods, from consumption to their use as bioactive components. 2017: Chapter 16

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