Review

Extraction Processes Affect the Composition and Bioavailability of Flavones from Lamiaceae Plants: A Comprehensive Review

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Abstract: Lamiaceae plants are a widespread family of herbaceous plants with around 245 plant genera and nearly 22,576 species distributed in the world. Some of the most representative and widely studied Lamiaceae plants belong to the *Ocimum*, *Origanum*, *Salvia*, and *Thymus* genera. These plants are a rich source of bioactive molecules such as terpenes, flavonoids, and phenolic acids. In this sense, there is a subgroup of flavonoids classified as flavones. Flavones have antioxidant, anti-inflammatory, anti-cancer, and anti-diabetic potential; thus, efficient extraction techniques from their original plant matrixes have been developed. Currently, conventional extraction methods involving organic solvents are no longer recommended due to their environmental consequences, and new environmentally friendly techniques have been developed. Moreover, once extracted, the bioactivity of flavones is highly linked to their bioavailability, which is often neglected. This review aims to comprehensively gather recent information (2011–2021) regarding extraction techniques and their important relationship with the bioavailability of flavones from Lamiaceae plants including *Salvia*, *Ocimum*, *Thymus*, and *Origanum*.

Keywords: flavones; apigenin; luteolin; Lamiaceae; *Origanum*; *Thymus*; *Ocimum*; antioxidants; bioavailability; bioaccessibility

1. Introduction

1.1. Lamiaceae

The Lamiaceae family of plants, also known as the mint family, belongs to the major group Angiosperms, which is a group of herbs and shrubs that are annual or perennial, and most of which are aromatic plants [1–3]. The Plant List database states that around 245 plant genera are included in the Lamiaceae family, with around 7886 species [4], representing the sixth largest family of flowering plants in the world. The Lamiaceae family is distributed around the world and is widely diverse. Moreover, some of the most evaluated plant genera are *Salvia* (986 species), *Ocimum* (66 species), *Origanum* (56 species), and *Thymus* (315 species) [4]. Plants of the Lamiaceae have square stems and opposite leaves, with zygomorphic flowers that have five united petals and five united sepals. These plant species are also known for their aromatic characteristics given by their essential oils and as a source of natural compounds such as terpenes, essential oils, phenolic acids, and flavonoids [5,6].

There is an increasing interest in plant-based natural compounds for pharmacological uses, either as prophylactic or therapeutic agents, due to their antioxidant, anti-inflammatory, anti-obesity, and anti-cancer properties. In this sense, Lamiaceae plants represent an interesting and promising source of natural compounds with bioactive properties; some of the compounds that have attracted attention are flavones, which are described in Section 2.

1.2. Phenolic Compounds

Phenolic compounds are secondary metabolites that are ubiquitously found in plants that act as plant defense metabolites against biotic and abiotic stress. Their distribution in plants depends on the plant species, plant part, place of origin, phenological stage, and environmental factors [7]. Phenolic compounds are derived from pentose phosphate, shikimate, and phenylpropanoid pathways in plants. Furthermore, strictly phenolic compounds are 'secondary metabolites derived exclusively from the shikimate-derived phenylpropanoid and the polyketide pathways, featuring more than one phenolic ring and being devoid of any nitrogen-based functional group' [8]. Phenolic compounds are chemically characterized by having one aromatic ring with -OH radical groups They are also chemically similar to alcohols or aliphatic molecules with -OH attached to carbon atoms. Phenolic compounds are also considered weak acids due to the hydrogen atom lability in the -OH [9,10]. Some of the most studied plants belong to the Lamiaceae genera; these plants and herbs have been used in folk medicine for many purposes. Lamiaceae are a rich source of phenolic compounds such as phenolic acids and flavonoids that are distributed in leaves, flowers, roots, stems, and aerial parts. Flavonoids have been attributed with strong antioxidant, anti-inflammatory, anti-obesity, and anti-cancer properties [5,6,11–13].

Phenolic compounds are classified by their biosynthetic origin and chemical characteristics. Chemically, phenolic compounds can be classified as:

- Flavonoids
  - Flavonols and flavones;
  - Flavanones;
  - Isoflavones;
  - Anthocyanins;
  - Flavan-3-ols.
- Non-flavonoids
  - Hydroxycinnamic acids;
  - Hydroxybenzoic acids;
  - Coumarins;
  - Benzophenones and xanthones;
  - Stilbenes;
  - Chalcones;
  - Lignans.

Flavonoids are produced from the phenylpropanoid pathway [14,15]. During flavonoid biosynthesis, the main flavonoid backbone (a chalcone with a C6-C3-C6 structure), is derived from the shikimic acid pathway and is produced through the action of the enzyme 4-coumaroyl coenzyme A; this generates the synthesis of the B and C rings, and three molecules of malonyl coenzyme A, the precursor of ring A. The resulting flavonoid backbone produces the other flavonoid subclasses, which are further synthesized by the action of reductases, isomerases, hydroxylases, and other enzymes [15,16]. Subsequently, flavones are produced from the flavanone naringenin by catalysis of two oxidoreductases, flavone synthase I and II, introducing a double bond between C2 and C3 [17]. For a more detailed description of the biosynthesis of flavones, we recommend the work by Jiang, Doseff and Grotewold [17].

1.3. Flavones

Flavones are a subtype of flavonoids that are characterized by a double bond in C2-C3 in the flavonoid structure and a ketone group at C4, and a lack of oxygenation at C3 (Figure 1) [18]. Some of the most known flavones are apigenin, cirsimaritin, luteolin, scutellarein, and their derivatives (Figure 2). Flavones can be found in nature with various substitutions, including -OH radicals, methylation, O- and C-alkylation, and glycosylation [10]. These residues may be found alone or in combination with flavones [19]. Many flavones have been reported in Lamiaceae plants, where they mostly accumulate in leaves, aerial parts, and exudates.

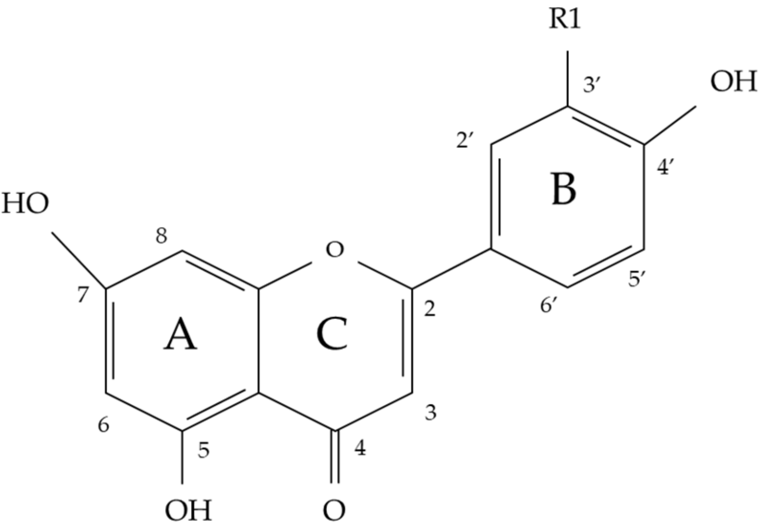

Figure 1. General graphic representation of flavones.

In plants, flavones act as plant defenses against UV radiation, favor pollination, and have an ecological interaction with the soil microbiota [20,21]. However, flavones have also attracted the attention of scientists because their consumption has been associated with beneficial health properties including the prevention of oxidative stress, the prevention of premature aging, the decreased incidence of noncommunicable diseases such as diabetes and different types of cancer, and decreased risk of cardiovascular diseases [17,22]. These noncommunicable diseases represent a global burden in health care systems and are the main cause of death worldwide [23]. The bioactive properties of flavones depend on the number, nature, and position of the substituents in the flavone skeleton, which will modulate their regioselectivity and the way flavones interact with biological targets to exert health-promoting properties [24]. Due to the importance of flavones in human health, several strategies have also been reported to produce them synthetically [24].

Moreover, some of the structural characteristics that facilitate the interaction of flavones with biological molecules to act as antioxidants and exert other bioactive properties are: (a) the presence of catechol on ring B; (b) the 2,3-olefinic bond and the keto group provides electron delocalization from ring B, which facilitates the donation of an electron to free radicals; (c) the -OH groups at C3 and C5 form hydrogen bonds with the keto group; (d) the synergy between flavones and some physiological antioxidants; and (e) the capacity of flavones to chelate metal ions attributed to the -OH at C5 and the C4 keto group [17,20].

Figure 2. Common aglycone flavones in Lamiaceae plants (**a**) apigenin, (**b**) cirsimaritin, (**c**) luteolin, and (**d**) scutellarein [25–28].

2. Literature Research Strategy

To identify relevant information on Lamiaceae flavones, this review was compiled based on recent scientific literature (2011–2021) from the Scopus, Google Scholar, and Web of Science databases. The keywords used for the literature search included the terms Lamiaceae, *Origanum*, *Ocimum*, *Salvia*, *Thymus*, flavones, apigenin, luteolin, scutellarein, cirsimaritin, extraction, supercritical CO_2, ultrasound-assisted extraction, and microwave-assisted extraction (Figure 3).

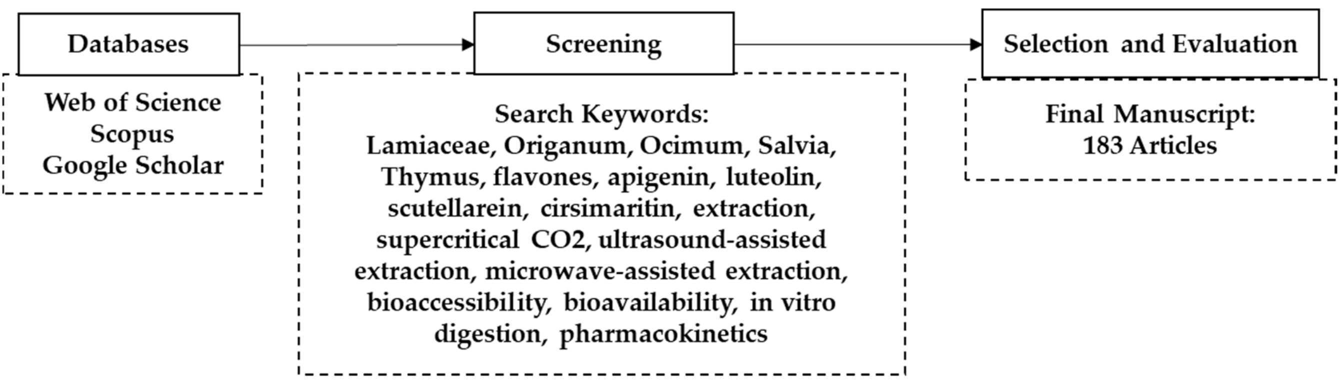

Figure 3. Literature research strategy.

3. Flavones Distribution in Lamiaceae Plants

3.1. Salvia

3.1.1. Characteristics of the *Salvia* Genus

Salvia L. species constitute the largest genus in the family Lamiaceae with over 1000 species, organized into five subgenera (*Sclarea*, Audibertia, Jungia, Leonia, and *Salvia*); these plants grow in temperate, subtropical, arctic, and sub-arctic areas of the world and are distributed mainly in Central and South America (500 spp.), Central Asia/Mediterranean (250 spp.) and Eastern Asia (100 spp.). Mexico is the country with the largest number of species (about 300). *Salvia* plants are typically 30–150 cm tall. Most species are perennial or annual herbs, they are rarely biennial, although shrubs, and a few trees and vines, also exist, with attractive flowers in various colors that are typically pink, red, or purple to blue [29–34]. Some members of the *Salvia* genus are used as flavoring agents in perfumery and cosmetics; for example, *S. sclarea* and *S. pratensis*. Around 134 of the 1000 *Salvia* species were studied for different functions [29]. Recently, the *Salvia* genus was explored for medical purposes; as the name suggests, the term "*Salvia*" is derived from the Latin "*salvare*" meaning 'to heal or to be safe and unharmed', referring to the medicinal properties of some of the species [33]. In this sense, many species within the genus exhibit antibacterial, antiviral, antioxidative, antimalarial, anti-inflammatory, antidiabetic, cardiovascular, antitumor, and anti-cancer properties [35].

3.1.2. Flavones in *Salvia* Species

Flavones are the most representative flavonoids in *Salvia* species, mostly flavones of apigenin, luteolin, ladanein, and salvigenin, and their corresponding 6-hydroxylated derivatives, flavonols, and their glycosides; these could be found in aerial parts or roots [32,33,36]. The flavones luteolin and salvigenin, identified in several *Salvia* species, are known for their anti-inflammatory effects [33]. In addition, the 6-methoxyflavones (nepetin and hispidulin), and their glycosides, inhibited NO and PGE_2 production, and the expression of the iNOS and COX-2 proteins, through heme oxygenase-1 (HO-1) induction, via the activation of nuclear factor erythroid 2-related factor2 (Nrf2), which suggests in vitro and in vivo anti-inflammatory activities [10]. Other flavones with anti-inflammatory activities are genkwanin, luteolin, cirsimaritin, and salvigenin, isolated from *S. lavandulifolia* [33].

Methoxyflavones isolated from *S. mirzayanii* Rech. f. & Esfand presented chemopreventive activity; these results were better than the hydroxylated ones. They reduced the invasion of tumors and suppressed cancer cell proliferations through proapoptotic properties, thanks to such chemical structures as 5,7-dihydroxy, 5,6,7-trihydroxy, and 5,7-dihydroxy-6-mehoxy at ring A, and 3′, 4′-dihydroxy at ring B [33].

Among *Salvia* bioactivities, the amoebicidal and giardicidal effects and the antidiarrheal properties of *S. divinorum* Epling & Jativa, *S. gesneriiflora* Lindl. & Paxton, *S. herbacea* Benth., *S. microphylla* Kunth, and *S. shannonii* Donn. Sm. have been studied, and it was found that the antiprotozoal activity of flavonoids, such as flavones, appears to be related to the phenolic and hydroxy groups at C-3, C-5, and C-7 of the flavonoid backbone. The change of a hydroxy to a methoxy group or a monosaccharide moiety at C-3 decreases the activity. Especially about flavones, a methoxy group at C-6 was favorable, and when the degree of oxygenation in the B-ring increased, the antiprotozoal activity decreased significantly; it was also observed that the 2,3-double bond was not essential for high antiprotozoal activity, but the stereochemistry could play an important role [37]. In this sense, Bautista, Calzada, Yépez-Mulia, Bedolla-García, Fragoso-Serrano, Pastor-Palacios and González-Juárez [37] determined the antiprotozoal activity of *S. connivens* Epling, against *Entamoeba histolytica* (IC_{50} 0.072 ± 0.006 μM) and *Giardia lamblia* (IC_{50} 0.118 ± 0.006 μM), which was comparable to the drug metronidazole; these results were related to the presence of three flavones: eupatorin, cirsiliol, and nuchensin.

One of the major active compounds in *S. plebeia* is hispidulin, which demonstrated antifungal, anti-inflammatory, antioxidant, antithrombotic, antiepileptic, neuroprotective, and anti-osteoporotic activities [33]. While *S. sharifii* Rech. f. and Esfan. possess two flavones, ladanein and 6-hydroxy-5,7,4′-trimethoxyflavone, both compounds have presented antimicrobial activity, especially in Gram-negative bacteria such as *E. coli*; additionally, these flavones showed antioxidant and cytotoxic activity [32].

There is a large variability of flavonoid structures among the *Salvia* genus, such as flavones; their chemical differentiation might be correlated to the geographical and ecological conditions under which they grow [31]. Researchers often find new structures in *Salvia* species; for example, two new flavone glycosides, with an unusual interglycosidic linkage, were isolated from the petals of *S. uliginosa* [29].

3.2. *Ocimum*

3.2.1. Characteristics of the *Ocimum* Genus

The genus *Ocimum* comprises more than 300 species of annual and perennial herbs and shrubs, and it is considered as one of the largest genera of the Lamiaceae family; this genus comprises many distinct species and varieties [38–40]. The typical characteristics of this genus, as with other members from the same family, are a square stem, and opposite and decussate leaves with many gland dots. The flowers (white, pink, violet) are strongly zygomorphic with two distinct lips; the stamens lie over the lower (anterior) lip of the corolla rather than ascending under the upper (posterior) lip [41]. The genus *Ocimum* is widely distributed in tropical and warm temperate regions over Asia, Africa, and Central and Southern America; this genus requires warmth for growth and should be protected from frost [41]. The name "*Ocimum*" is derived from the Greek meaning "to be fragrant"; therefore, plants of this genus are aromatic and rich in secondary metabolites, which humans have learned to use since antiquity for food preservation, flavoring, and as medicine [1,40].

3.2.2. Flavones in *Ocimum* Species

The flavones apigenin, luteolin, chrysoeriol, 6-hydroxy, and hydroxyl-flavones in glycosidic combination, and lipophilic flavones, such as 5,6,4-trihydroxy-7,3-dimethoxyflavone, were detected in *Ocimum* species [42]. In addition, two unusual flavones from *O. canum* were reported. The identified flavones were navadensin (5,7-dihydroxy-6,8,4′-trimethoxy flavone) and salvigenin (5-hydroxy-6,7,4′-trimethoxyflavone); the amount of these flavones was 0.1% of the dry weight of the material [41]. The flavone xanthomicrol (5,4′-dihydroxy-6,7,8-trimethoxyflavone) was isolated from the leaves of a Nigerian *O. basilicum*; three flavones, eriodictyol, eriodictyol-7-glucoside, and vicenin-2 (apigenin di-C-glycoside), were identified from the leaves of *O. basilicum* grown in Greece; three flavones were also isolated from the leaves of *O. sanctum*, these being vicenin (apigenin-6, 8-Cglycoside), galuteolin (luteolin-5-O-glycoside) and cirsilineol (5,4′-dihydroxy-6,7,3′-trimethoxyflavone) [41].

Due to large variation in the morphological characteristics of species, in addition to human intervention, it has become difficult to identify some species. Therefore, it has been concluded that identification can be conducted in an auxiliary manner through molecular markers, such as the tetrahydroxyflavone luteolin 5-O-glucoside, considered as a chemosystematic element in *O. americanum*, *O. basilicum*, *O. gratissimum*, *O. kilimandscharicum*, *O. lamiifolium*, *O. minimum*, *O. selloi*, *O. gratissimum*, and *O. citriodorum* [38,39].

Ocimum species have been related to many different bioactivities, and most of them have been correlated to essential oils and their components. Nonetheless, a recent study showed that the polymethoxylated flavones 5-demethyl nobiletin and 5-demethyl sinensetin, together with luteolin, isolated from *O. campechianum*, decreased blood glucose in in vivo model; furthermore, it was proposed that these two polymethoxylated flavones can be considered as chemotaxonomical markers for the genus [18]. In addition, luteolin, and luteolin glycosides from *O. sanctum* leaves presented leishmanicidal properties against *L. major*, antituberculosis, and cytotoxic cells of prostate carcinoma in mice, and showed anti-inflammatory and antiproliferative activities [1].

3.3. *Origanum*

3.3.1. Characteristics of *Origanum*

Origanum is an important plant genus that belongs to the Lamiaceae family. Its foremost characteristic species is *Origanum vulgare* L., commonly known as European oregano. The genus *Origanum* comprises 49 taxa and more of 42 species and 18 hybrids [43]. *Origanum* were divided into ten sections: (i) *Amaracus* Bentham, (ii) *Anatolicon* Bentham, (iii) *Brevifilamentum* Ietswaar, (iv) *Longitubus* Ietswaart, (v) *Chilocalys* Ietswaart, (vi) *Majorana* Bentham, (vii) *Campanula ticalix* Ietswaart, (viii) *Elongatispica* Ietswaart, (ix) *Origanum* Ietswaart, and (x) *Prolaticorolla* Ietswaart [44]. The majority of the *Origanum* species are located within the Mediterranean, occurring mainly in Greece and Turkey [43]. This plant grows at altitudes between the 400 and 1800 m, and in sunny areas [45]. *Origanum* species are annual, perennial herbs with oval to small circular leaves, with sometimes toothed margins and obtuse to pointed tips. The flowers might present white, pink or purple colors and are clustered in spikes [46].

3.3.2. Flavones in *Origanum* Species

Much attention has been given to the chemical constituents of essential oils from *Origanum* species. Nevertheless, it was recently reported that polyphenolic components in extracts from these plants might exert beneficial effects [18]. The main phenolic components in *Origanum* species are phenolic acids and flavonoids [47]. Regarding the focus of this review, several studies have been carried out to identify flavones present in plants belonging to the genus *Origanum*. For instance, Gird et al. [48] performed a preliminary study to determine the total flavone content in ethanolic extracts of indigenous *O. vulgare* L. aerial parts and showed 4.21 ± 0.127 g of rutin equivalents/100 g dry extract. In a more profound study, Martins et al. [49] identified and quantified several flavones present in the infusion, decoction, and hydroalcoholic extracts from *O. vulgare* L. flowering aerial parts. The flavones detected were apigenin-6,8-di-*C*-glucuronide (0.52 ± 0.06–0.98 ± 0.00 mg/g extract), luteolin-*O*-glucuronide (12.48 ± 0.09–28.27 ± 0.24 mg/g extract), luteolin-7-*O*-glucoside (20.88 ± 0.00–25.26 ± 0.44 mg/g extract), apigenin-7-*O*-rutinoside (0.74 ± 0.00–1.53 ± 0.06 mg/g extract), apigenin-7-*O*-glucuronide (5.78 ± 0.03–8.63 ± 0.02 mg/g extract), and methylapigenin-*O*-glucuronide (0.61 ± 0.02–1.26 ± 0.13 mg/g extract). Additionally, Milevskaya et al. [50] identified the flavones present in *O. vulgare* extracts using HPLC-ESI-MS. In this case, the flavones detected were apigenin, luteolin, apigenin-7-glucuronide, and luteolin-7-*O*-β-D-glucuronide. Moreover, Tuttolomondo et al. [51] identified and quantified seven flavones, using HPLC-PDA-ESI/MS, in the ethyl acetate extracts from dried aerial parts of 57 biotypes of *O. vulgare* subsp *hirtum* (wild Sicilian oregano). The flavones detected were luteolin (0.15–1.16 mg/kg dry weight), sorbifolin (0.04–2.90 mg/kg dry weight), cirsiliol (0.02–4.61 mg/kg dry weight), apigenin (0.26–2.34 mg/kg dry weight), cirsilineol (0.13–4.08 mg/kg dry weight), cirsimaritin (0.55–8.69 mg/kg dry weight), and xanthomicrol (0.03–9.09 mg/kg dry weight).

Furthermore, Maietta et al. [52] obtained an aqueous infusion from *O. dictaminus* dried herb and identified its flavone components using RP-HPLC-DAD-ESI/MS. The extract presented several flavones, such as 6,8-di-*C*-hexosylapigenin, apigenin-7-*O*-triglucuronide, luteolin-7-*O*-diglucuronide, apigenin-*O*-triglucuronide, apigenin-7-*O*-diglucuronide,

apigenin-7-*O*-glucuronide, luteolin-7-*O*-rutinoside, and xanthomicrol (5,4′-dihidroxy-6,7,8-trimethoxyflavone). Table 1 shows other flavones identified in several plants belonging to the genus *Origanum*.

From these studies, the most frequently identified flavones in the different polyphenolic extracts from *Origanum* species are luteolin and apigenin derivatives, which have shown antioxidant [53,54], anti-cancer [55], and anti-inflammatory properties [56]. Other flavones, such as didymin, isolated from *O. vulgare*, presented biological properties, such as anti-inflammatory activity and a reduction in the hepatic damage induced by CCl_4, in male mice [57].

Table 1. Flavones identified in several *Origanum* species.

Plant Species	Plant Part	Type of Extract	Method of Identification	Flavones	Reference
O. vulgare subsp. *hirtum* (Greek oregano)	Aerial parts	Aqueous, afterward extraction using ethyl-acetate	LC-DAD-MS	Apigenin 7-*O*-glucoside Apigenin Apigenin 7-*O*-glucuronide Luteolin 7-*O*-glucuronide Luteolin Cirsimaritin	[58]
O. vulgare subsp. *viridulum*	Flower buds (without stem)	Water:methanol (6:4)	HPLC-PDA	Luteolin glycosides Apigenin glycosides	[59]
O. vulgare	Unspecified	Pressurized liquid extraction	LC-MS/MS	Luteolin-7-*O*-glucuronide Luteolin Apigenin	[60]
O. dictamnus	Aerial parts	Aqueous, afterward extraction using ethyl-acetate	LC-DAD-MS	Apigenin-7-*O*-glucuronide Cirsiliol Cirsilineol Luteolin-7-*O*-glucuronide	[58]
O. glandulosum	Aerial parts	Microwave-assisted solvent extraction	LC-DAD-ESI-MS/MS	Luteolin-*O*-hexoside Luteolin-6,8-di-*C*-glucoside Luteolin-7-*O*-glucuronide Other luteolin derivatives	[61]
O. majorana L.	Aerial parts	Methanol	UPLC-ESI-QTOF-MS/MS	Luteolin-6,8-*C*-dihexose Apigenin-6,8-di-*C*-hexoside Isoorientin Orientin Vitexin/Isovitexin Luteolin-*O*-glycoside Diosmin Apigenin-*O*-glucuronide Acacetin rutinoside Luteolin Apigenin	[62]
O. mycrophillum	Aerial parts	Aqueous, afterward extraction using ethyl-acetate	LC-DAD-MS	Apigenin-7-*O*-glucoside Apigenin Genkwanin	[58]

3.4. *Thymus*

3.4.1. Characteristics of *Thymus*

The genus *Thymus*, belonging to the Lamiaceae family, consists of over 336 species [63]. *Thymus vulgaris* L., known as common thyme, is the most significant species of this genus [64]. Plants from the *Thymus* genera are native to the Eurasian and the Mediterranean region and are also distributed over North Africa, Australia, and South America [64,65]. *Thymus* species are small perennial shrubs that possess grey to green leaves that might be arranged oppositely or clustered. The flowers present light violet, purple or white coloring [64].

3.4.2. Flavones and Their Significance in *Thymus* Species

As in *Origanum* species, plants belonging to *Thymus* genus are well recognized for their essential oil content. Nevertheless, polyphenolic extracts from this genus were recently studied due to their health-beneficial potential [66]. In this context, Desta et al. [67] used LC-ESI-MS/MS to identify the individual components of polyphenolic extracts from *T. schimperi*. It was determined that the extracts were rich in flavone content; luteolin derivatives were the main constituents (21.83%), and the extracts contained apigenin and chrysoeriol glycosides and other poly-methoxyflavones (unidentified). Afonso et al. [68] determined the total flavone content and the individual constituents of decoction extracts from three *Thymus* species (*T. fragrantissimus*, *T. pulegioides*, and *T. zygis*). *Thymus pulegioides* showed the highest flavone content (55.62 ± 1.05 µg/mg extract), followed by *T. fragrantissimus* (21.67 ± 0.59 µg/mg extract) and *T. zygis* (16.01 ± 0.27 µg/mg extract). The flavone luteolin-*O*-glucuronide was the main component found in the three species of *Thymus* evaluated. In *T. pulegioides*, the main flavones were luteolin-*O*-glucuronide (26.14 ± 0.78 µg/mg extract), chrysoeriol-*O*-hexoside (12.00 ± 0.15 µg/mg extract), apigenin-*O*-glucuronide (9.20 ± 0.21 µg/mg extract), and luteolin-*C*-glucoside (8.27 ± 0.13 µg/mg extract). In *T. fragrantissimus*, the major flavone components were luteolin-*O*-glucuronide (16.86 ± 0.21 µg/mg extract), apigenin-di-*C*-glucoside (2.69 ± 0.50 µg/mg extract), and luteolin-*C*-glucoside (2.00 ± 0.0.02 µg/mg extract), while, in *T. zygis*, luteolin-*O*-glucuronide (7.57 ± 0.05 µg/mg extract), luteolin-*C*-glucoside (4.86 ± 0.03 µg/mg extract), and apigenin-di-*C*-glucoside (1.60 ± 0.32 µg/mg extract) were the predominant flavones. It is clear from this study that the flavone content and composition are affected by the *Thymus* species evaluated. Additionally, it was reported that flavone content varies in *Thymus* species according to the phenological phases. For instance, they determined the effect of the phenological phases on the flavone content in several *Thymus* species (*T. austriacus*, *T. x citriodorus*, *T. longicaulis*, *T. x oblongifolius*, *T. praecox* ssp. *arcticus*, *T. pulegioides*, *T. serpyllum*, and *T. sibtorpii*). The authors analyzed the extracts from *Thymus* species using HPLC-UV and found luteolin-7-rutinoside, luteolin-7-glucoside, and apigenin-7-glucoside to be present. The highest flavones content was described during the flowering phase and a significant diminution was observed throughout the fruit maturation and the end of vegetation. The flavone luteolin-7-glucoside was identified in all species studied, except in *T. austriacus*, while apigenin-7-glucoside was only detected in samples of *T. serpyllum*, *T. sibthorpii*, and *T. praecox* ssp. *arcticus.* Luteolin-7-rutinoside was identified in all *Thymus* species under study [69].

Recently, Kindl et al. [70] analyzed, using LC-DAD-ESI-MS/MS, the polyphenolic composition of extracts from *T. longicaulis* C. Presl, *T. praecox* Opiz subsp. *polytrichus* (A.Kern. ex Borbás) Jalas, *T. pulegioides* L., *T. serpyllum* L. subsp. *serpyllum*, *T. striatus* Vahl, and *T. vulgaris*. These authors found that glycosides of luteolin and scutellarein were the most abundant polyphenolic constituents in the extracts of the *Thymus* spp mentioned. Furthermore, luteolin-7-*O*-hexuronide (4.56 ± 0.03–14.43 ± 0.29 mg/g of dry extract) was the flavone found in all *Thymus* species under study. In contrast, the apigenin derivatives, apigenin-7-*O*-hexuronide (6.86 ± 0.03 mg/g of dry extract) and apigenin-hexoside-hexuronide (1.44 ± 0.01), were only found either in *T. pulegioides* or *T. striatus*, respectively. Other flavones identified in several *Thymus* species are shown in Table 2.

Polyphenolic extracts containing flavones from several *Thymus* species have been evaluated to determine their biological properties. For instance, it was demonstrated that decoction extracts containing glucosides of luteolin and apigenin from *T. herba-barona*, *T. pseudolanuginosus*, and *T. caespititius* possess antioxidant, anti-inflammatory, and antibacterial activities [71].

Table 2. Flavones identified in several *Thymus* species.

Plant Species	Plant Part	Type of Extract	Method of Identification	Flavones	Reference
T. vulgaris (common thyme)	Leaves	Ultrasound-assisted maceration with methanol; afterward, liquid–liquid extraction using ethyl acetate	RP-HPLC-ESI-MS/MS	Luteolin-*O*-hexoside Luteolin Eupatorine Poly-methoxyflavones	[72]
	Aerial parts	Methanol	RP-HPLC–DAD	Luteolin-hexoside Luteolin-7-*O*-glucoside Luteolin-7-*O*-hexuronide	[70]
	Deodorized leaves	Pressurized hot water extraction	HPLC-ESI-Q-TOF	Apigenin-6,8-di-*C*-glucoside Luteolin Luteolin-7-*O*-glucoside Luteolin-7-*O*-glucuronide Apigenin-7-*O*-glucuronide Cirsimaritin Cirsilineol 5,6-Dihydroxy-7,8,3′,4′-tetramethoxyflavone	[73]
T. algeriensis	Aerial parts	Infusion, decoction or ethanol:water (80:20)	LC-DAD-ESI/MS	Apigenin-6,8-*C*-dihexoside Apigenin-8-*C*-glucoside Luteolin-7-*O*-glucuronide Apigenin-7-*O*-glucuronide	[74]
T. capitatus	Leaves	Methanol	UHPLC-DAD-ESI-MS	Apigenin-*C*-di-hexoside	[75]
T. x citriodorus	Aerial parts	80% ethanol	HPLC–DAD-ESI–MS	Luteolin-5-β-*O*-glucoside Luteolin-7-α-*O*-glucuronide Luteolin-7-*O*-glucoside Chrysoeriol-7-β-*O*-glucoside Apigenin-7-β-*O*-glucuronide	[76]
T. lotocephalus	Aerial parts	Water, water:ethanol (1:1) or ethanol	HPLC-DAD	Luteolin Apigenin	[77]
T. pseudolanuginosus	Aerial parts	Decoction extracts (water)	UHPLC-DAD-ESI-MS	Luteolin-*C*-glucoside Luteolin-*O*-glucuronide Apigenin-*O*-glucoside Apigenin-*O*-glucuronide	[71]
T. puligioides	Aerial parts	Decoction extracts (water)	UHPLC-DAD-ESI-MS	Luteolin-*C*-glucoside Scutellarein-*O*-glucuronide Luteolin-*O*-glucuronide Chrysoeriol-*O*-hexoside Apigenin-*O*-glucuronide	[68]
	Aerial parts	70% ethanol	HPLC-UV	Luteolin-7-rutinoside Luteolin-7-glucoside	[69]
T. serpyllum	Obtained as herbal tea	95% ethanol	HPLC-DAD	Luteolin-7-*O*-glucoside Luteolin Apigenin	[78]
	Whole plant	Aqueous extract	HPLC-DAD	Luteolin Apigenin	[79]
	Unspecified	Pressurized liquid extraction	LC-MS/MS	Luteolin-7-*O*-glucoside Luteolin-7-*O*-glucuronide Apigenin-7-*O*-glucuronide Luteolin Apigenin Cirsimaritin	[60]

4. Extraction Methods of Flavones from Lamiaceae Plants

4.1. Conventional Methods

Flavones are usually extracted by conventional techniques, including maceration, Soxhlet extraction, hydrodistillation, and boiling, among others [80]. In almost all extraction, it is necessary to decrease particle size to help the process [81]; the plant is dried and pulverized to obtain a powder used for the extraction. Table 3 summarizes the conventional extraction techniques used to obtain flavones in Lamiaceae species; we encourage the reading of each specific research paper to obtain detailed information about the extraction process, identification technique, and compound identification. In general, apigenin, luteolin, and their glucosides are widely distributed in the genera analyzed and can be extracted by various conventional methods. Moreover, the aerial parts (leaves, stems, and flowers) are the most used in these extractions; separately, however, leaves, roots, flowers, and residues from previous processes can also be used to obtain flavones.

In *Salvia* species, hydrophilic solvents are widely used to extract flavones. For instance, methanolic, ethanolic, and aqueous mixtures have been used to extract various compounds, mostly luteolin and apigenin derivatives, including glucoside and glucuronides, along with hydroxylated and methylated derivatives [36,82–92]. In contrast, other polar solvents such as acetone and ethyl acetate are less used to extract these compounds [32,37,93–95], while dichloromethane is even less common [96,97]. Furthermore, the use of hot water to extract flavones is generally used to simulate the usual way in which these plants are consumed (infusion or decoction), with good results found when obtaining apigenin and luteolin derivatives [90], and other flavones such as cirsimaritin [98]. To improve the separation of desired compounds, it is necessary to fractionate the extracts by subsequent extractions using solvents with different polarity or by column chromatography, as seen in the hot water extract of *Salvia absconditiflora*, which was sequentially fractionated with ethyl acetate and *n*-butanol, and was found to be rich in flavones in the ethyl acetate fraction [98]. Similarly, the n-hexane extract of *Salvia chloroleuca* fractionated with ethyl acetate and methanol showed the first fraction as the best one to obtain these compounds. Moreover, flavones such as salpleflavone were found in the ethyl acetate fraction of the ethanolic extract of *Salvia plebeian* [92]. In addition, further fractionation of the ethanolic extract was useful to isolate the flavones neocafhispidulin and 6″-*O*-acetylhomoplantaginin, among others [86]. Similarly, the fractionation of the acetone extract of *Salvia connivens* was useful to isolate three bioactive flavones [37]. Meanwhile, fractionation was also used for less polar solvents such as the dichloromethane extract of *Salvia circinata* [97].

Polar solvents such as methanol, ethanol, and aqueous mixtures have been used to obtain extracts from species including *O. basilicum*, *O. gratissimum*, *O. sanctum*, and *O. tenuiflorum* with good results [84,99–104]. Less used, but also effective in the extraction of flavones, are solvents such as diethyl ether, which is useful to extract such flavones as nevadensin and salvigenin in *O. basilicum* [105]. Fewer studies were observed with other solvents such as hot water extract that showed similar results to hydromethanolic and hydroethanolic extractions in the same plant [106]. On the other hand, some studies further fractionated the extract to isolate the compounds, as seen in the infusion of *O. campechianum* [107] and the methanolic extract of *O. gratissimum* and *O. sanctum* [100,101].

Water extracts are effective in the extraction of flavones of *Origanum* species; numerous studies show the presence of mostly apigenin and its derivatives in the aqueous extracts of *O. acutidens*, *O. majorana*, *O. minutiflorum*, and *O. vulgare* [108–112]; while methanolic and hydroethanolic extracts can also extract luteolin derivatives in *O. vulgare* and *O. majorana* [112–115]. Furthermore, fractionation with diverse solvents, in addition to chromatography, is effective in isolating some flavones, such as cirsiliol and cirsilineol, that were only found in *O. dictamnus* after fractionation [58,116].

For *Thymus* species, multiple studies have been conducted using mostly ethanol, methanol, water, and their mixture as solvents, in which not much variety was observed in the flavones extraction of such species as *T. alternans*, *T. caespititius*, *T. fragrantissimus*, *T. mastichina*, *T. pulegioides*, *T. serpyllum*, and *T. vulgaris*, among others [68,71,117–121]. However,

using fractionation techniques, it is possible to obtain flavones that have not been identified in crude extracts such as 7-methoxyapigenin (genkwanin) [122] and nobiletin [123,124], while, by using dichloromethane, hydroxyluteolin and hydroxyapigenin derivatives can be extracted from *T. mastichina* [125]. Furthermore, the water residue from hydrodistillation from *T. vulgaris* process has shown to be a valuable source of flavones such as luteolin and apigenin glucuronide derivatives [126].

Table 3. Conventional solvent extraction methods of flavones from *Salvia*, *Ocimum*, *Origanum*, and *Thymus* species.

Source	Part	Extraction Method	Identification Method	Flavone/Flavone Derivative	Reference
Salvia absconditiflora	Aerial parts	Hot water, subsequent fractionation	^{1}H NMR, ^{13}C NMR, HPLC-TOF/MS	Cirismaritin Apigenin-7-*O*-β-glucoside Luteolin Luteolin-7-*O*-β-glucoside	[98]
Salvia apiana	Aerial parts	Ethanolic extract (95%)	^{1}H NMR, ^{13}C NMR, HRMS	Cirismaritin Salvigenin	[127]
Salvia chloroleuca	Aerial parts	Sequentially extracted with n-hexane, ethyl acetate, and methanol	^{1}H NMR, ^{13}C NMR, HPLC-PDA	Salvigenin Luteolin Cirsiliol	[95]
Salvia chrysophylla	Aerial parts	Dichloromethane extract	^{1}H NMR, ^{13}C NMR, HRESIMS, FT-IR, UV-Vis	Salvigenin	[96]
Salvia circinata	Aerial parts	Acetone extract, subsequent fractionation	^{1}H NMR, ^{13}C NMR	Apigenin 6-Dihydroxy-7,3′,4′-trimethoxyflavone	[93]
	Aerial parts	Dichloromethane-methanol extract, subsequent fractionation	^{1}H NMR, ^{13}C NMR, IR, HRESIMS, ECD	Pedalitin Apigenin-7-*O*-β-D-glucoside 2-(3,4-Dimethoxyphenyl)-5,6-dihydroxy-7-methoxy-4H-chromen-4-one	[97]
Salvia connivens	Leaves	Acetone extract, subsequent fractionation	^{1}H NMR, ^{13}C NMR, HMBC, ESIMS	Eupatorin Cirsiliol Nuchensin	[37]
Salvia elegans	Aerial parts	Decoction	UHPLC-DAD-ESI-MS^n	Hydroxyluteolin-glucuronide Scutellarein-*O*-glucuronide Luteolin-7-*O*-glucuronide Apigenin-glucuronide	[90]
Salvia fruticosa	Not specified	Ethyl acetate extract	HPLC-SPE-NMR	Hispidulin Cirsimaritin Salvigenin	[128]
	Aerial parts	Methanolic extract	HPLC-ESI-QTOF-MS	Nepetin Luteolin Apigenin Hispidulin Cirsimaritin Genkwanin Luteolin-*O*-glucuronide Luteolin-*O*-glucoside Apigenin-*O*-glucuronide	[87]
Salvia greggii	Aerial parts	Decoction	UHPLC-DAD-ESI-MS^n	Luteolin-C-hexoside Luteolin-7-*O*-glucoside Apigenin-*C*-hexoside Apigenin-hexoside	[90]

Table 3. *Cont.*

Source	Part	Extraction Method	Identification Method	Flavone/Flavone Derivative	Reference
Salvia judaica	Aerial parts	Ethanolic extract	^{1}H NMR, ^{13}C NMR, UV-Vis, FT-IR	Luteolin-3′-methyl ether Apigenin Salvigenin Cirsilineol	[82]
Salvia macrosiphon	Aerial parts	Ethyl acetate and methanolic extracts	^{1}H NMR, ^{13}C NMR, MS	Apigenin-7, 4′-dimethyl ether Apigenin-7-*O*-glucoside Luteolin-7-*O*-glucoside Salvigenin	[36]
Salvia officinalis	Leaves	Ethanolic (30–70%) and acetone (30–70%) extracts	HPLC-UV/PDA	6-Hydroxyluteolin-7-glucoside Luteolin-7-glucuronide Luteolin-7-glucoside Apigenin-7-glucunoride Apigenin-7-glucoside Luteolin-3-glucuronide	[94]
	Aerial parts	Decoction	UHPLC-DAD-ESI-MS^{n}	Apigenin-6-*C*-glucoside-7-*O*-glucoside Apigenin-glucuronide Apigenin-diglucuronide Luteolin-7-*O*-glucuronide Scutellarein-*O*-glucuronide Apigenin-rutinoside	[90]
	Aerial parts	Methanolic extract	^{1}H NMR, UPLC -QTOF-MS	Cirsiliol Luteolin	[91]
Salvia plebeia	Aerial parts	Methanol: water: formic acid (50:45:5, *v*/*v*/*v*)	UPLC-DAD-QTOF-MS	Apigenin Apigenin-7-*O*-glucoside Hispidulin Hispidulin-7-*O*-glucoside Luteolin Luteolin-5-*O*-glucoside Luteolin-7-*O*-glucoside 6-Hydroxyluteolin 7-*O*-glucoside Nepetin Nepetin-7-*O*-glucoside	[88]
	Whole plants	Ethanolic (95%) extract, subsequent fractionation	HR-DART-MS, ^{1}H NMR, ^{13}C NMR, HMBC	Neocafhispidulin 6″-*O*-Acetylhomoplantaginin Sorbifolin Jaceosidin Nepetin Pectolinarigenin Hispidulin (2S)-5,7,4′-Trihydroxy-6-methoxy-flavanone-7-*O*-β-D-glucopyranoside Galuteolin Nepitrin Homoplantaginin	[86]
	Aerial parts	Ethanolic extract (95%), subsequent fractionation	^{1}H NMR, ^{13}C NMR, 1H–1H COSY, HMQC, HMBC, NOESY, HR-ESI-MS, IR	Salpleflavone 6-*O*-Methyl-scutellarein	[92]
Salvia pomifera	Aerial parts	Methanolic extract	HPLC-ESI-QTOF-MS	Luteolin Apigenin Hispidulin Cirsimaritin Genkwanin Luteolin-*O*-hexoside	[87]

Table 3. *Cont.*

Source	Part	Extraction Method	Identification Method	Flavone/Flavone Derivative	Reference
Salvia rosmarinus	Leaves	Methanolic extract	HPLC-ESI-MS	Hispidulin Cirsimaritin	[83]
	Not specified	Acidified water extract	HPLC-DAD, HPLC-ESI-QTOF-MS	Luteolin 3′-(3″-acetylglucuronide)	[109]
Salvia sharifii	Aerial parts	Ethyl acetate-methanol extract	^{1}H, ^{13}C NMR, EI-MS, UV	Ladanein 6-Hydroxy-5,7,4′-trimethoxyflavone	[32]
Salvia splendens	Leaves	Methanolic extract (80%), subsequent fractionation	^{1}H NMR, ^{13}C NMR, ESI-MS, UV	Luteolin Luteolin 7-*O*-(4″, 6″-di-*O*-α-L-rhamnopyranosyl)-β-D-glucopyranoside Apigenin Apigenin 7-*O*-β-D-rutinoside Cosmosiin Cinaroside Pedalitin Crisiliol	[89]
Salvia trichoclada	Aerial parts	Methanolic extract	^{1}H NMR, ^{13}C NMR	Apigenin-7-*O*-rhamnoside	[84]
Ocimum basilicum	Leaves	Ethanolic extract (80%)	^{1}H NMR, ^{13}C NMR, ESI-MS	Apigenin Luteolin Vitexin Isovitexin 3″-*O*-Acetylvitexin	[99]
	Leaves and flowers	Diethyl ether extract	HPLC-PDA	Nevadensin Salvigenin	[105]
	Leaves	Hot water extract	UPLC-ESI-MS/MS	Apigenin Apigenin-*O*-glucoside Apigenin-*O*-glucuronide Luteolin Luteolin 7-*O*-glucuronide Luteolin acetylglucuronide	[106]
	Leaves	Methanolic extract	HPLC-UV/Vis	Luteolin Apigenin	[103]
	Aerial parts	Ethanolic extract (70%)	HPLC-MS	Luteolin	[104]
Ocimum campechianum	Leaves	Infusion, subsequent fractionation	^{1}H NMR, ^{13}C NMR, COSY, HSQC, HMBC	5-Demethyl nobiletin 5-Demethyl sinensetin Luteolin	[107]
Ocimum gratissimum	Leaves	Methanol extract, subsequent fractionation	HPLC-DAD	Luteolin	[101]
Ocimum sanctum	Leaves	Methanolic extract (50%), subsequent fractionation	LC-QTOF-MS	Vicenin 2 Luteolin-7-*O*-glucuronide Isorientin Orientin Galuteolin Apigenin-7-*O*-glucuronide Isovitexin Luteolin Apigenin Cirsimaritin	[100]
	Leaves	Methanolic extract	HPLC-UV/Vis	Luteolin Apigenin	[103]
Ocimum tenuiflorum	Leaves	Methanolic extract	HPLC-MS	Luteolin Diosmetin Nevadensin Xanthomicrol	[102]

Table 3. *Cont.*

Source	Part	Extraction Method	Identification Method	Flavone/Flavone Derivative	Reference
Origanum acutidens	Aerial parts	Hot water, subsequent fractionation	HPLC-TOF-MS	Apigenin-7-glucoside	[112]
Origanum dictamnus	Aerial parts	Fractionation with various solvents	LC-DAD-MS	Cirsiliol Cirsilineol	[58]
Origanum majorana	Leaves	Methanolic extract, subsequent fractionation	UPLC-ESI-MS/MS	Luteolin-7-*O*-glucoside	[113]
	Aerial parts	Hot water extraction, subsequent fractionation	HPLC-TOF-MS, UV, ^{1}H NMR, ^{13}C NMR	5,6,3′-Trihydroxy-7,8,4′-trimethoxyflavone	[111]
	Leaves	Methanolic extract	HPLC-UV	Apigenin Luteolin-7-*O*-rutinose	[115]
Origanum microphyllum	Aerial parts	Fractionation with various solvents	LC-DAD-MS	Apigenin Apigenin-7-*O*-glucoside Genkwanin	[58]
Origanum minutiflorum	Aerial parts	Hot water extraction, subsequent fractionation	^{1}H NMR, ^{13}C NMR, LC-TOF-MS	Apigenin Apigenin-7-*O*-glucuronide Vicenin-2 Luteolin	[110]
Origanum rotundifolium	Aerial parts	Fractionation with various solvents	LC-TOF-MS, UV, ^{1}H NMR, ^{13}C NMR	Apigenin Vitexin	[116]
Origanum vulgare	Shoots	Water extract	UPLC-MS/MS	Apigenin	[108]
	Not specified	Acidified water extract	HPLC-DAD, HPLC-ESI-QTOF-MS, FT-IR	Apigenin 7-*O*-glucuronide	[109]
	Aerial parts	Ethanolic extract (50%)	HPLC-DAD	Luteolin glycosides Apigenin glycoside	[114]
	Aerial parts	Hot water, ethyl acetate, methanolic, hexane extract	HPLC-TOF-MS	Apigenin-7-glucoside	[112]
	Aerial parts	Fractionation with various solvents	LC-DAD-MS	Apigenin Apigenin glucosides Apigenin glucuronides Luteolin Luteolin glucosides Luteolin glucuronides Cirsimaritin	[58]
Thymus algeriensis	Aerial parts	Infusion, decoction or ethanolic extract (80%)	UPLC-DAD-ESI-MS^{n}	Apigenin-6,8-*C*-dihexoside Apigenin-8-*C*-glucoside Apigenin-7-*O*-glucuronide Luteolin-7-*O*-glucuronide	[74]
Thymus alternans	Aerial parts	Methanolic extract	HPLC-MS^{n}, ^{1}H NMR COSY, HSQC-DEPT, HMBC, TOCSY, NOESY	Luteolin-3-*O*-glucopyranoside Luteolin-7-*O*-glucopyranoside Luteolin-7-*O*-rutinoside Chrysoeriol-hexoside Methoxy luteolin-hexoside Chrysoeriol-7-*O*-hexosyl-deoxyhexoside Apigenin-7-*O*-glucopyranoside	[117]

Table 3. *Cont.*

Source	Part	Extraction Method	Identification Method	Flavone/Flavone Derivative	Reference
Thymus austriacus	Aerial parts	Ethanolic extract (70%)	HPLC-UV	Luteolin-7-rutinoside	[69]
Thymus caespititius	Aerial parts	Decoction	UHPLC-DAD-ESI-MS^n	Apigenin di-*C*-glucoside Luteolin-*O*-rutinoside Luteolin-*O*-glucuronide Chrysoeriol-*O*-rutinoside Apigenin-*O*-glucuronide	[71]
Thymus caramanicus	Aerial parts	Methanolic extract (80%)	HPLC-UV	Luteolin	[129]
	Aerial parts	Methanolic extract	HPLC-UV	Apigenin Luteolin-7-*O*-glucoside	[130]
Thymus capitatus	Leaves	Methanolic extract	UHPLC-DAD-ESI/MS^n	Apigenin-C-di-hexoside	[75]
Thymus daenensis	Aerial parts	Methanolic extract	HPLC-UV	Apigenin Luteolin-7-*O*-glucoside	[130]
Thymus fallax	Aerial parts	Methanolic extract	HPLC-UV	Apigenin Luteolin-7-*O*-glucoside	[130]
Thymus fedtschenkoi	Aerial parts	Methanolic extract	HPLC-UV	Apigenin Luteolin-7-*O*-glucoside	[130]
Thymus fragrantissimus	Aerial parts	Decoction	UHPLC-DAD-ESI-MS^n	Apigenin-di-*C*-glucoside Luteolin-*C*-glucoside Luteolin-*O*-di-glucoside Luteolin-*O*-glucuronide Apigenin-*O*-glucuronide	[68]
Thymus herba-barona	Aerial parts	Decoction	UHPLC-DAD-ESI-MS^n	Luteolin-*C*- glucoside Luteolin-*O*-rutinoside Luteolin-*O*-glucuronide Chrysoeriol-*O*-glucoside Apigenin-di-*C*- glucoside Apigenin-*O*-glucoside Apigenin-*O*-glucuronide	[71]
Thymus kotschyanus	Aerial parts	Methanolic extract	HPLC-UV	Apigenin Luteolin-7-*O*-glucoside	[130]
Thymus marschallianus	Aerial parts	Ethanolic extract (70%)	HPLC-DAD-ESI-MS	Luteolin Luteolin-7-*O*-glucuronide Apigenin Apigenin-7-*O*-glucuronide	[131]
Thymus mastichina	Aerial parts	Methanolic extract	HPLC-DAD	Apigenin Luteolin	[118]
	Aerial parts	Dichloromethane, ethanolic extract	^{1}H NMR, ^{13}C NMR, FT-IR, MS, $[\alpha]_D{}^t$ values	6-Hydroxyluteolin-7-*O*-β-glucopyranoside 6-Hydroxyapigenin-7-*O*-β-glucopyranoside	[125]
	Leaves and flowers	Methanolic extract (50%)	HPLC-DAD	Luteolin Luteolin glucoside	[132]
Thymus migricus	Leaves	Water, methanolic extract	RP-UHPLC-ESI-MS/MS	Acacetin Amentoflavone Apigenin Cynaroside Luteolin	[133]
	Aerial parts	Methanolic extract	HPLC-UV	Apigenin Luteolin-7-*O*-glucoside	[130]

Table 3. *Cont.*

Source	Part	Extraction Method	Identification Method	Flavone/Flavone Derivative	Reference
Thymus longicaulis	Aerial parts	Methanolic extract	LC-DAD-ESI-MS/MS	6-Hydroxyluteolin-hexoside Scutellarein-7-*O*-hexoside Luteolin-7-*O*-glucoside Luteolin-7-*O*-hexuronide	[70]
	Aerial parts	Ethanolic extract (70%)	HPLC-UV	Luteolin-7-rutinoside Luteolin-7-glucoside	[69]
Thymus lotocephalus	Aerial parts	Water, ethanolic or mixture extract	HPLC-DAD	Luteolin Apigenin	[77]
Thymus pallescens	Aerial parts	Infusion	HPLC-DAD-ESI/MS	Apigenin-6,8-*C*-dihexoside Apigenin-*O*-glucuronide Luteolin-*O*-diglucuronide Luteolin-*O*-diglucuronide Luteolin-7-*O*-rutinoside Luteolin-7-*O*-glucuronide	[134]
Thymus praecox	Aerial parts	Methanolic extract	LC-DAD-ESI-MS/MS	Scutellarin Scutellarein-7-*O*-hexoside Luteolin-7-*O*-hexuronide	[70]
	Aerial parts	Ethanolic extract (70%)	HPLC-UV	Luteolin-7-rutinoside Luteolin-7-glucoside Apigenin-7-glucoside	[69]
	Aerial parts	Methanolic extract, subsequent fractionation	^{1}H NMR, ^{13}C NMR, HPLC-DAD	Luteolin-5-*O*-β-D-glucopyranoside	[135]
	Aerial parts	Fractionation with various solvents	HPLC-DAD, LC-ESI-QTOF-MS/MS	Luteolin-7-*O*-glucoside Apigenin 7-*O*-glucuronide	[136]
Thymus pseudolanuginosus	Aerial parts	Decoction	UHPLC-DAD-ESI-MS^{n}	Apigenin-di-*C*- glucoside Luteolin-*C*- glucoside Luteolin-*O*-glucuronide Apigenin-*O*-glucoside Chrysoeriol-*O*-glucoside Apigenin-*O*-glucuronide	[71]
Thymus pubesence	Aerial parts	Methanolic extract	HPLC-UV	Apigenin Luteolin-7-*O*-glucoside	[130]
Thymus pulegioides	Aerial parts	Methanolic extract	LC-DAD-ESI–MS/MS	Luteolin-hexoside Luteolin-7-*O*-hexuronide Apigenin-7-*O*-hexuronide	[70]
	Aerial parts	Decoction	UHPLC-DAD-ESI-MS^{n}	Apigenin-di-*C*-glucoside Luteolin-*C*-glucoside Scutellarein-*O*-glucuronide Luteolin-*O*-glucuronide Chrysoeriol-*O*-hexoside Apigenin-*O*-glucuronide	[68]
	Aerial parts	Ethanolic extract (70%)	HPLC-UV	Luteolin-7-rutinoside Luteolin-7-glucoside	[69]
	Aerial parts	Decoction, ethanolic extract (80%)	HPLC-DAD, HPLC-ESI-MS^{n}	Luteolin-7-*O*-glucoside (only in ethanolic extract) Luteolin-*O*-hexuronide Luteolin-*O*-hexuronide Apigenin-glucuronide	[121]
Thymus saturoides	Leaves	Acetone extract (80%), subsequent fractionation	HRESI-MS, UV/Vis, ^{1}H NMR, ^{13}C NMR, IR	8-Methoxycirsilineol Nobiletin Luteolin Chrysin	[124]

Table 3. *Cont.*

Source	Part	Extraction Method	Identification Method	Flavone/Flavone Derivative	Reference
Thymus schimperi	Not specified	Methanolic extract, subsequent fractionation	HPLC-ESI-MS/MS	Luteolin Luteolin-7-*O*-glucoside Luteolin-4′-*O*-(rhamnosyl)glucoside Luteolin-6-*C*-pentoside-8-*C*-hexoside Luteolin-6-*C*-glucoside Chryseoriol-7-*O*-glucoside Luteolin-7-*O*-(2″-apiosyl-acetyl)glucoside Luteolin-6-*C*-pentoside Luteolin-7-*O*-(acetyl-apiosyl)xyloside Luteolin-7-*O*-(dipentosyl)glucuronide Luteolin-7-*O*-glucuronide-3′-*O*-glucoside Luteolin-7-*O*-glucoronide Dihydroxytrimethoxy flavone Apigenin-7-*O*-(acetyl-apiosyl)glucoside Hispidulin Trihydroxy-dimethoxyflavone Hydroxy-trimethoxyflavone Trihydroxy-trimethoxyflavone	[67]
Thymus serpyllum	Commercial herbal tea	Ethanolic extract (95%)	RP-HPLC-DAD	Luteolin Luteolin-7-*O*-glucoside Apigenin	[78]
	Aerial parts	Methanolic extract	LC-DAD-ESI-MS/MS	6-Hydroxy luteolin-hexuronide Scutellarin Luteolin-7-*O*-hexuronide	[70]
	Aerial parts	Ethanolic extract (70%)	HPLC-UV	Luteolin-7-rutinoside Luteolin-7-glucoside Apigenin-7-glucoside	[69]
	Aerial parts	Methanolic extract	HPLC-UV	Apigenin Luteolin-7-*O*-glucoside	[130]
	Whole plant	Methanolic extract (75%)	HPLC-ESI-MS/MS	Apigenin 6,8-di-*C*-glucoside Apigenin *O*-glucuronide Luteolin Luteolin-*O*-diglucuronide Luteolin 7-*O*-glucuronide Luteolin 7-*O*-glucoside	[137]
Thymus sibthorpii	Aerial parts	Fractionation with various solvents	UV-Vis, ^{1}H NMR, ^{13}C NMR	Apigenin 7-Methoxyapigenin	[122]
	Aerial parts	Ethanolic extract (70%)	HPLC-UV	Luteolin-7-rutinoside Luteolin-7-glucoside Apigenin-7-glucoside	[69]
Thymus sipyleus	Aerial parts	Methanolic extract	RP-HPLC-DAD	Apigenin	[138]
	Aerial parts	Infusion, decoction	HPLC-UV	Luteolin-7-*O*-glucoside	[139]

Table 3. *Cont.*

Source	Part	Extraction Method	Identification Method	Flavone/Flavone Derivative	Reference
Thymus striatus	Aerial parts	Methanolic extract	LC-DAD-ESI-MS/MS	6-Hydroxyluteolin-hexoside Luteolin-7-*O*-hexoside-hexuronide Apigenin-hexoside-hexuronide Luteolin-7-*O*-glucoside Luteolin-7-*O*-hexuronide Luteolin-3′(4′)-*O*-hexuronide	[70]
Thymus transcaspicus	Aerial parts	Methanolic extract	HPLC-UV	Apigenin Luteolin-7-*O*-glucoside	[130]
Thymus trautvetteri	Aerial parts	Methanolic extract	HPLC-UV	Apigenin Luteolin-7-*O*-glucoside	[130]
Thymus vulgaris	Aerial parts	Methanolic extract, subsequent fractionation	HPLC-ESI/MS	Apigenin Nobiletin	[123]
	Aerial parts	Methanolic extract	LC-DAD-ESI-MS/MS	Luteolin-hexoside Luteolin-7-*O*-glucoside Luteolin-7-*O*-hexuronide	[70]
	Leaves	Methanolic extract	HPLC-DAD	Luteolin-7-*O*-glucoside	[140]
	Aerial parts	Ethanolic extract (45%)	HPLC-PDA-ESI-MS	Luteolin-7-*O*-glucuronide Apigenin-7-*O*-glucuronide	[126]
	Post-distillation waste	-			
	Leaves	Methanolic extract	HPLC-UV	Apigenin Luteolin-7-*O*-rutinose	[115]
	Leaves	Water extract	HPLC-PDA-ESI-MS	Luteolin Luteolin-7-*O*-glucoside Apigenin Apigenin-7-*O*-glucoside Acacetin	[119]
	Aerial parts	Methanolic extract	HPLC-UV	Apigenin Luteolin-7-*O*-glucoside	[119]
	Leaves	Infusion	HPLC-PDA-ESI-MS	Apigenin 6,8-di-*C*-glucoside Luteolin-7-*O* glucoside Luteolin-*O*-diglucuronide Luteolin-diglucuronide-glucuronide Luteolin-7-*O*-glucuronide Apigenin-*O*-glucuronide Luteolin	[120]
Thymus zygis	Aerial parts	Decoction	UHPLC-DAD-ESI-MS^n	Luteolin-*C*-glucoside Luteolin-di-*C*-glucoside Scutellarein-*O*-glucuronide Luteolin-*O*-glucuronide Chrysoeriol-*O*-hexoside Apigenin-*O*-glucuronide	[68]
	Aerial parts	Decoction, ethanolic extract	RP-HPLC-DAD, HPLC-ESI-MS^n	Apigenin-(6,8)-*C*-diglucoside Luteolin-*O*-hexoside Luteolin-*O*-hexoside Luteolin-*O*-hexorunide	[141]

4.2. Alternative Methods (Environmentally Friendly)

Alternative extraction methods aim to limit the use of organic solvents, thereby reducing environmental damage and improving extraction efficiency. The most common alternative extraction techniques include ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), pressurized liquid extraction (PLE, also known as accelerated solvent extraction), and supercritical fluid extraction (SFE), among others [142]. These technologies have been shown to be effective for extracting flavones from Lamiaceae, mostly apigenin and luteolin derivatives; the aerial parts are the most used for this. However, other parts, such as roots and even residues from previous processes, are rich in flavones. A summary of these extraction methods to obtain flavones in Lamiaceae species is shown in Table 4.

PLE has been widely used to obtain flavones from diverse *Salvia* species using water or ethanol as a solvent, obtaining similar compounds in them [143]. Although MAE can obtain a good variety of flavones [144], UAE was demonstrated to be more effective than MAE in some cases, because it is less time consuming [145]. On the other hand, SFE with ethanol as cosolvent was proven to be a more selective technique for the extraction of flavones such as cirsimaritin, genkwanin and salvigenin from *Salvia rosmarinus* leaves, compared to PLE, which obtained a greater variety of flavones [146]. Similarly, more flavone diversity was observed in the extract of roots from *Salvia viridis* obtained from UAE and MAE than from SFE [144]. For *Origanum* species, *O. glandulosum* (leaves and flowers) and *O. majorana* (leaves) have been extracted by MAE and UAE, respectively, with apigenin and luteolin derivatives in the former, but only luteolin derivatives in the latter [61,147]. However, in *O. vulgare* aerial parts, the same flavones profile was found using UAE, PLE, and MAE [148], while fewer flavones were found in another extract obtained by PLE [60,149]. With regard to *Thymus* genus, UAE is a popular extraction method to extract flavones from species such as *T. marschallianus*, *T. seravschanicus*, and *T. serpyllum*, and *T. vulgaris* [150–152]. Nevertheless, PLE is also effective in the extraction of flavones from *Thymus* species [149], including cirismaritin from *T. serpyllum* [60], which was also detected in *T. Vulgaris* after a combination of alternative extraction methods, namely pulsed electric field followed by ultrasound-assisted extraction [153]. A study by Palmieri et al. [154], with different conventional methods involving PLE and rapid solid–liquid dynamic extraction, showed that the aforementioned methods obtain better extract yield from *T. vulgaris* leaves and stems [154]. Subsequently, the extraction of flavones from *Thymus* residues using these technologies was studied, as seen in the extracts that were rich in flavones derived from steam distillation residues from *T. mastichina* [155], and the herbal dust and hydrodistillation residue from *T. serpyllum* and *T. vulgaris* obtained by PLE, respectively [73,156]. Finally, not many studies have been recently conducted regarding the extraction of flavones from *Ocimum* species using alternative methods. In this regard, the extract, obtained by UAE, of *O. tenuiflorum* leaves showed higher quantities of apigenin and luteolin, compared with a conventional ethanolic extract [157]; this demonstrates the high potential of these kinds of techniques in the extraction of flavones from *Ocimum* species.

Table 4. Alternative extraction methods of flavones from *Salvia*, *Ocimum*, *Origanum*, and *Thymus* species.

Source	Part	Extraction Method	Identification Method	Flavone/Flavone Derivative	Reference
Salvia amplexicaulis	Not specified	Pressurized liquid extraction with ethanol or water	UPLC-QTOF-MS	Apigenin-7-*O*-β-D-glucuronide	[143]
Salvia austriaca	Not specified	Pressurized liquid extraction with ethanol or water	UPLC-QTOF-MS	Apigenin-7-*O*-β-D-glucuronide	[143]

Table 4. *Cont.*

Source	Part	Extraction Method	Identification Method	Flavone/Flavone Derivative	Reference
Salvia sclarea	Not specified	Pressurized liquid extraction with ethanol or water	UPLC-QTOF-MS	Apigenin-7-*O*-β-D-glucuronide Luteolin-7-*O*-β-D-glucuronide	[143]
Salvia forsskaolii	Not specified	Pressurized liquid extraction with ethanol or water	UPLC-QTOF-MS	Apigenin-7-*O*-β-D-glucuronide Luteolin-7-*O*-β-D-glucuronide	[143]
Salvia fruticosa	Not specified	Ultrasound-assisted extraction with various solvents	HPLC-DAD-ESI-MS^n	Luteolin-7-*O*-rutinoside Apigenin-6-*C*-glucoside-7-*O*-glucoside Luteolin-diglucuronide	[145]
	Aerial parts	Deep eutectic solvent extraction with lactic acid and sodium citrate dibasic	LC-DAD-MS/MS	Luteolin 7-*O*-glucuronide	[158]
Salvia glutinosa	Not specified	Pressurized liquid extraction with ethanol or water	UPLC-QTOF-MS	Apigenin-7-*O*-β-D-glucuronide	[143]
Salvia nemorosa	Not specified	Pressurized liquid extraction with ethanol or water	UPLC-QTOF-MS	Apigenin-7-*O*-β-D-glucuronide Luteolin-7-*O*-β-D-glucuronide	[143]
Salvia officinalis	Not specified	Ultrasound-assisted extraction with various solvents	HPLC-DAD-ESI-MS^n	Luteolin-7-*O*-rutinoside Apigenin-6-*C*-glucoside-7-*O*-glucoside Luteolin-diglucuronide	[145]
	Leaves	Microwave-assisted extraction with various solvents	HPLC-UV/PDA	6-Hydroxyluteolin-7-glucoside Luteolin-7-glucuronide Luteolin-7-glucoside Luteolin-3′-glucuronide Apigenin-7-glucuronide Apigenin-7-glucoside	[159]
	Leaves	Ultrasound-assisted extraction with ethanol (30%)	HPLC-UV/PDA	6-Hydroxyluteolin-7-glucoside Luteolin-7-glucuronide Luteolin-7-glucoside Luteolin-3-glucuronide Apigenin-7-glucuronide Apigenin-7-glucoside	[85]
	Not specified	Pressurized liquid extraction with ethanol or water	UPLC-QTOF-MS	Apigenin-7-*O*-β-D-glucuronide Luteolin-7-*O*-β-D-glucuronide	[143]
Salvia pomifera	Not specified	Ultrasound-assisted extraction with various solvents	HPLC-DAD-ESI-MS^n	Luteolin-7-*O*-rutinoside Apigenin-6-*C*-glucoside-7-*O*-glucoside Luteolin-diglucuronide	[145]
Salvia pratensis	Not specified	Pressurized liquid extraction with ethanol or water	UPLC-QTOF-MS	Apigenin-7-*O*-β-D-glucuronide	[143]

Table 4. *Cont.*

Source	Part	Extraction Method	Identification Method	Flavone/Flavone Derivative	Reference
Salvia rosmarinus	Leaves	Supercritical CO_2 extraction with ethanol as cosolvent	HPLC–DAD-MS	Cirismaritin Genkwanin Salvigenin	[146]
		Pressurized liquid extraction with water or ethanol		Luteolin Luteolin-3′-*O*-(*O*-acetyl)-β-D-glucuronide Scutellarein Scutellarein-7-*O*-β-glucuronide Nepitrin Apigenin Apigenin-7-*O*-glucoside Homoplantaginin Cirsimaritin-4′-glucoside Hispidulin Cirsimaritin Genkwanin	
	Hydrodistillation residue	Ultrasound-assisted extraction with ethanol	LC-PDA-ESI-MS	Scutellarein Apigenin Cirismaritin Acacetin Genkwanin	[160]
Salvia stepposa	Not specified	Pressurized liquid extraction with ethanol or water	UPLC-QTOF-MS	Apigenin-7-*O*-β-D-glucuronide	[143]
Salvia verticillata	Not specified	Pressurized liquid extraction with ethanol or water	UPLC-QTOF-MS	Apigenin-7-*O*-β-D-glucuronide Luteolin-7-*O*-β-D-glucuronide	[143]
Salvia viridis	Roots	Microwave-assisted extraction with ethanol (96%)	UHPLC-ESI-MS/MS	Luteolin-*C*-hexoside-*C*-pentoside Luteolin-*C*-hexoside-*O*-pentoside Apigenin-*C*-hexoside-*O*-pentoside Luteolin-*O*-(pentosyl)hexoside Luteolin-*O*-glucuronide Luteolin-7-*O*-glucoside (Cynaroside) Luteolin-*O*-(deoxyhexosyl)hexoside Apigenin-*O*-(deoxyhexosyl)hexoside Cosmosiin (Apigetrin, Apigenin-7-*O*-glucoside) Apigenin-*O*-glucuronide Luteolin Luteolin-*O*-(coumaroyl)hexoside Apigenin Chrysoeriol Genkwanin	[144]

Table 4. *Cont.*

Source	Part	Extraction Method	Identification Method	Flavone/Flavone Derivative	Reference
Salvia viridis	Roots	Ultrasound-assisted extraction	UHPLC-ESI-MS/MS	Luteolin-*C*-hexoside-*C*-pentoside Luteolin-*C*-hexoside-*O*-pentoside Apigenin-*C*-hexoside-*O*-pentoside Luteolin-*O*-(pentosyl)hexoside Luteolin-*O*-glucuronide Luteolin-7-*O*-glucoside (Cynaroside) Apigenin-*C*-hexoside-*O*-deoxyhexoside Apigenin-*O*-(deoxyhexosyl)hexoside Apigenin-*O*-(deoxyhexosyl)hexoside Apigenin-*O*-glucuronide Luteolin Luteolin-*O*-(coumaroyl)hexoside Apigenin (4′,5,7-trihydroxyflavone) Chrysoeriol Genkwanin Apigenin-4′,7-dimethyl ether	[144]
	Roots	Supercritical CO_2 extraction	UHPLC-ESI-MS/MS	Genkwanin Apigenin-4′,7-dimethyl ether	[144]
Ocimum tenuiflorum	Leaves	Ultrasound-assisted extraction with ethanol (55.34%)	HPLC-UV/Vis	Luteolin Apigenin	[157]
Origanum glandulosum	Leaves and flower	Microwave-assisted extraction with water	HPLC-DAD-ESI-MS/MS	Luteolin-*O*-hexoside Luteolin-6,8-di-*C*-glucoside Luteolin-7-*O*-glucuronide	[61]
Origanum majorana	Leaves	Ultrasound-assisted extraction with water	RP-HPLC-DAD	Luteolin-7-*O*-glucoside Apigenin-7-*O*-glucoside	[147]
Origanum vulgare	Not specified	Pressurized liquid extraction with water, ethanol or mixture	HPLC-DAD-ESI-MS/MS	Apigenin Luteolin Luteolin-7-*O*-glucuronide	[60]
	Not specified	Pressurized liquid extraction with methanol	HPLC-ESI-MS/MS	Apigenin Luteolin	[149]

Table 4. *Cont.*

Source	Part	Extraction Method	Identification Method	Flavone/Flavone Derivative	Reference
Origanum vulgare	Aerial parts	Ultrasound-assisted extraction with ethanol Microwave-assisted extraction with ethanol Pressurized liquid extraction with ethanol	UHPLC-LTQ OrbiTrap MS	Luteolin Luteolin-7-*O*-hexosyl-hexoside Luteolin-7-*O*-pentosyl-hexoside Luteolin-7-*O*-pentosyl-acetyl-hexoside Luteolin-7-*O*-acetyl-hexosyl-acetylhexoside Apigenin Apigenin-7-*O*-hexosyl-acetyl-hexoside Apigenin-7-*O*-hexuronide Apigenin-7-*O*-pentosyl-acetyl-hexoside Acacetin Acacetin-7-*O*-hexosyl-acetyl-hexoside Acacetin-7-*O*-pentosyl-hexoside Acacetin-7-*O*-hexuronide Acacetin-7-*O*-pentosyl-acetyl-hexoside Diosmetin-7-*O*-pentosyl-acetyl-pentoside	[148]
Thymus fontanesii	Aerial parts	Microwave-assisted extraction with ethanol	HPLC-DAD-ESI-MS/MS	Luteolin-*O*-hexoside Luteolin-6,8-di-*C*-glucoside Luteolin-7-*O*-glucuronide	[61]
Thymus marschallianus	Aerial parts	Ultrasound-assisted extraction with ethanol	RP-HPLC-PDA, HPLC-ESI-QTOF-MS	Luteolin Luteolin-7-*O*-rutinoside Luteolin-7-*O*-glucoside Luteolin-7-*O*-glucuronide Luteolin-7-*O*-dipentoside Luteolin-7-*O*-(6″-3-hydroxy-3-methyl-glutaryl)-glucoside Apigenin Apigenin-7-*O*-glucoside Apigenin-7-*O*-glucuronide Apigenin-7-*O*-rhamnoglucuronide Diosmetin-glucuronide	[151]
Thymus mastichina	Steam distillation residues	Ultrasound-assisted extraction with ethanol	LC-DAD-ESI-MS	Luteolin Luteolin-glucoside Apigenin Apigenin-7-O-glucoside	[155]
Thymus seravschanicus	Aerial parts	Ultrasound-assisted extraction with ethanol	RP-HPLC-PDA, HPLC-ESI-QTOF-MS	Luteolin-7-*O*-rutinoside Luteolin-7-*O*-glucoside Luteolin-7-*O*-glucuronide Luteolin-7-*O*-(6″-3-hydroxy-3-methyl-glutaryl)-glucoside Apigenin-7-*O*-glucuronide Diosmetin glucuronide	[151]
Thymus serpyllum	Aerial parts	Ultrasound-assisted extraction with ethanol	RP-HPLC-DAD, HPLC-MS	6-Hydroxyluteolin-7-*O*-glucoside Luteolin-7-*O*-glucuronide Apigenin-glucuronide	[150]

Table 4. *Cont.*

Source	Part	Extraction Method	Identification Method	Flavone/Flavone Derivative	Reference
Thymus serpyllum	Not specified	Pressurized liquid extraction with water	HPLC-DAD-ESI-MS/MS	Luteolin Luteolin-7-*O*-glucoside Luteolin-7-*O*-glucuronide Apigenin Apigenin-7-*O*-glucuronide Cirsimaritin	[60]
	Herbal dust (industrial waste from filter-tea production)	Pressurized liquid extraction with ethanol	HPLC-Orbitrap-ESI-MS/MS	Luteolin	[156]
Thymus vulgaris	Not specified	Ultrasound-assisted extraction with water	UPLC-TOF-MS/MS	Luteolin-7-*O*-glucuronide Luteolin-7-*O*-malonyl-glucoside Apigenin Apigenin-7-*O*-glucuronide Chrysoeriol-7-*O*-(6-malonyl-apiosyl-glucoside)	[152]
	Leaves and stems	Rapid solid–liquid dynamic extraction with ethanol	HPLC-UV	Luteolin Apigenin	[154]
		Ultrasound-assisted extraction with ethanol	HPLC-UV	Luteolin Apigenin	[154]
	Not specified	Pressurized liquid extraction with methanol	HPLC-ESI/MS/MS	Apigenin Luteolin	[149]
	Leaves and stems	Pulsed electric field followed by ultrasound-assisted extraction with ethanol	UPLC-ESI-MS/MS	Luteolin Luteolin-7-*O*-glucuronide Luteolin-rutinoside Luteolin-7-*O*-glucoside Cirsimaritin	[153]
	Leaves residue from hydrodistillation	Pressurized hot water extraction	HPLC-ESI-QTOF-MS	Apigenin-6,8-di-*C*-glucoside Apigenin-7-*O*-glucuronide Luteolin Luteolin-7-*O*-glucoside Luteolin-7-*O*-glucuronide Cirsimaritin	[73]

5. Bioavailability and Bioactivity Relationship of Flavones in Lamiaceae

As previously mentioned, the chemical structure of flavones determines their bioactivity since it establishes the way in which they interact with biological molecules through different mechanisms of action [17,20,24]. Thus, any changes in the structures of flavones can affect (positively or negatively) their antioxidant, anti-inflammatory, anti-obesity, and anti-cancer properties. Once consumed, flavones enter the body and travel through the gastrointestinal tract. Here, flavones can be affected by physiological and biochemical conditions such as changes in pH, and interaction with other food constituents and digestive enzymes. These physiological conditions can alter the chemical structures of flavones by partial hydrolysis from the food matrix, by deprotonation of the -OH radicals of the flavone molecule, or through interaction with digestive enzymes, which will affect their bioactive properties [161,162].

Thus, it is important to evaluate the bioaccessibility and bioavailability of flavones to improve our understanding of their mechanisms of action and bioactive effects, and to develop strategies to enhance their bioavailability. Bioaccessibility is the amount of a food constituent that is released during gastrointestinal digestion and is accessible to be absorbed or pass through the enterocytes. Additionally, bioavailability is defined as

the amount of the food constituent or molecule that is absorbed through the enterocytes into the bloodstream, distributed, metabolized, and excreted [161]. Bioaccessibility is assessed using simulated gastrointestinal protocols coupled with cell-based assays (Caco-2, HepG2), and bioavailability is assessed using in vivo assays that measure pharmacokinetic parameters [163–167].

In this sense, once consumed, flavones pass by the mouth where the saliva is present, and mastication occurs. Saliva is mainly constituted by water, electrolytes, proteins, and digestive enzymes. After that, the compounds are transported to the stomach, where pH drops to 2–4, facilitating the partial hydrolysis of these molecules from the matrix. Then, the chyme is transported from the stomach to the small intestine, passing through the duodenum, where the pH stabilizes to 7. Additionally, the small intestine is the major site of absorption for nutrients and phenolic compounds such as flavones [161,168]. The enterocytes in the small intestine are also a site of metabolism attributed to the phase I and phase II xenobiotic metabolic enzymes [169]. Generally, phenolic compounds have low bioaccessibility and bioavailability; most are degraded, metabolized, and excreted. Several factors can affect the bioavailability of flavones and phenolic compounds in general; these factors are related to the molecule and the food matrix, and others are related to the host, such as intestinal and systemic factors [170].

It was reported that aglycone flavones are more rapidly absorbed than their glycosylated derivatives due to their lower molecular weight; however, cell metabolism and transporters can mediate their active absorption [171]. In this sense, Caco-2 cell assays showed that apigenin is more permeable than apigenin-7-*O*-glucoside; furthermore, in vivo rat studies reported higher absorption of apigenin. Moreover, due to the xenobiotic metabolism in the body, most flavones in plasma are reported in their conjugated form by sulfation, glucuronidation, or methylation.

Few reports assess the bioaccessibility of flavones from plants of the *Salvia*, *Thymus*, *Origanum*, *and Ocimum* genus. These reports are summarized in Table 5. All reports use an in vitro gastrointestinal digestion process that simulates the digestion in the mouth, stomach, and small intestine, mimicking their physiological and enzymatic conditions; only two reports that coupled the simulated digestion to cell-based assays were found. In this sense, Chohan et al. [172] evaluated the effect of cooking and an in vitro digestion process on the total phenolic content and bioactive properties of *Salvia officinalis* and *Thymus vulgaris*. The cooking process increased the bioaccessible phenolic compounds, which might be related to the improvement of the release of phenolics from the vacuoles due to the cell wall rupture during cooking. In addition, following this, the anti-inflammatory potential of these extracts increased after the cooking and digestion process, indicating a correlation between bioaccessibility and bioactivity. Gayoso et al. [173] evaluated the bioaccessibility, through an in vitro digestion, of *Origanum vulgare* where an HPLC analysis showed the presence of a luteolin glycoside derivative. After digestion, luteolin glycoside had a bioaccessibility of 41%; moreover, the antioxidant activity of *O. vulgare* remained stable with no significant changes after the digestion process, indicating that digested phenolics are potentially bioactive. Recently, de Torre et al. [114] also evaluated the bioaccessibility of *O. vulgare* in an improved oral pharmaceutical form; the authors encapsulated *O. vulgare* and subjected it to gastrointestinal digestion. Three flavones were identified in the samples, namely two luteolin glycosides and one apigenin glycoside. The encapsulation enhanced the bioaccessibility of *Origanum* flavones, based on initial values with a bioaccessibility of 82.52, 85.31, and 89.28%, for the two luteolin glycosides and the apigenin glycoside, respectively. The high bioaccessibility of the flavones in the encapsulated samples is related to a higher stability as they were protected from the gastrointestinal environment.

Rubió et al. [174] showed that a mixture of olive oil and *Thymus vulgaris* extracts increased the bioaccessibility of luteolin as compared to thyme extract alone, with values of 16.7% and 14.6%, respectively. Moreover, a Caco-2 and Caco-2/HepG2 co-cultured assay showed that luteolin was one of the flavonoids detected after the incubation and that luteolin conjugated with sulfate and glucuronide were the main metabolites identified in

the apical and basolateral sides of the cell cultures. On the other hand, incubation with HepG-2 cells only showed the presence of luteolin glucuronide.

Similarly, Villalva et al. [175] evaluated ethanol extracts of *O. majorana* subjected to a combination of simulated gastrointestinal digestion and a Caco-2 permeability assay. The authors identified several apigenin and luteolin derivates in the samples. The in vitro digestion process showed that the flavones with higher bioaccessibility were diosmin, luteolin-7-*O*-glucuronide, and luteolin-7-*O*-glucoside, with high stability values of nearly 99.7, 94.55, and 94.19% of the initial content. Furthermore, the contents of apigenin-7-*O*-glucoside and apigenin-7-glucuronide increased by 31.42 and 57.7%. The Caco-2 assay showed that luteolin and apigenin derivatives have low bioaccessibility, showing poor permeability capacity through the enterocytes. The increased levels of apigenin-7-*O*-glucoside and apigenin-7-glucuronide suggested cellular reflux of metabolized flavones, which are usually excreted at a physiological level. Additionally, the authors showed that rosmarinic acid enrichment of *O. majorana* extracts increases the content of its phenolic acids and flavonoids by 1.5–1.8 times, with luteolin and its glycosides being the main flavones detected in the enriched sample. In addition, it was suggested that the flavones luteolin and apigenin showed a synergistic effect with rosmarinic acid, protecting it from degradation during the digestion process. Furthermore, the aglycone forms of luteolin and apigenin were the main metabolites detected in the apical side of the Caco-2 monolayer culture, which might be attributed to the action of the metabolic enzyme lactase-phlorizin hydrolase. Due to the overall low bioaccessibility of phenolic compounds, it is sometimes suggested that after ingestion, their health-promoting properties could decrease. Nonetheless, in this study, the authors found that digested extracts displayed anti-inflammatory activity through inhibition of the secretion of the cytokines TNF-α, IL-1β, and IL-6 in a THP-1 cell line.

Our literature search found two recent studies that included an in vivo evaluation of the bioavailability of flavones from the *Ocimum*, *Origanum*, *Salvia*, and *Thymus* genus. Briefly, Rubió et al. [176] evaluated the effect of the combination of olive oil and *Thymus vulgaris* on the bioavailability and antioxidant capacity of the mixture using Wistar rats administered a dose of 1.5 mg/kg BW. The study showed that this type of extract modulated plasmatic antioxidant activity. Thyme extract and an olive oil/thyme mixture decreased the levels of the antioxidant enzymes superoxide dismutase and glutathione peroxidase, but catalase activity was increased. In addition, the pharmacokinetic data showed that the presence of thyme extracts enhances olive oil phenolics; for instance, luteolin and apigenin were the main flavones identified in the sample, and the metabolites found in plasma were hydroxyphenylpropionic acid sulfate and dihydroxyphenylpropionic acid sulfate. The other study was reported by Zhang et al. [177], who evaluated the pharmacokinetics of danshen and huangquin (dried root of *Scutellaria baicalensis* Georgi), administered to Sprague-Dawley rats, which were prepared using a 1:1 ratio of weight in the mixture. Four main flavones were identified in the administered samples: baicalein, baicalin, wogonin, and wogonoside; these were found at concentrations of 13.606, 447.983 8.901, and 122.236 mg/kg, respectively. In plasma, the content of aglycone and glycoside flavones decreased significantly. Moreover, the T_{max} values ranged from 1 to 8 h, and the C_{max} values were 306.92, 2465.0, 373.17, and 1779.17 mg/L for baicalein, baicalin, wogonin, and wogonoside, respectively.

Table 5. Bioaccessibility and bioavailability studies of flavones from Lamiaceae species.

Plant Species	Description of Sample	Bioaccessibility Method	Flavones in Sample	Results	Reference
Salvia officinalis	1 g of sage was infused in water (25 mL, 37 °C, 10 min). Cooking treatment consisted of heating sage in a frying pan for 10 min.	Static simulated digestion (mouth, stomach, small intestine)	Not identified	Cooked and digested sage had higher levels of phenolic compounds. Cooked and digested sage inhibited IL-8	[172]
Thymus vulgaris	1 g of thyme was infused in water (25 mL, 37 °C, 10 min). The cooking treatment consisted of heating thyme in a frying pan for 10 min.	Static simulated digestion (mouth, stomach, small intestine)	Not identified	Cooked and digested thyme had higher levels of phenolic compounds, and inhibited IL-8	[172]
Origanum vulgare	Methanol extracts (10 g/250 mL) were boiled by refluxing for 30 min.	Static simulated digestion (stomach, small intestine)	Luteolin glycoside	Luteolin glycoside had a bioaccessibility of 41%. The simulated digestion did not affect the antioxidant capacity of the *O. vulgare* extract by chemical methods (ABTS, DPPH, TPC, FRAP)	[173]
Origanum vulgare	Hydroalcoholic extracts were obtained (10 g sample, 250 mL ethanol 50%). The extracts were used lyophilized in oral pharmaceutical forms.	Static simulated digestion (stomach, small intestine)	Luteolin glycosides Apigenin glycoside	Two luteolin glycosides with higher bioaccessibility, of around 83%, were identified in encapsulated form, and the apigenin glycoside was identified, with nearly 90% bioaccessibility	[114]
Thymus vulgaris	Freeze-dried olive cake and dried thyme were used for extracts by means of an accelerated solvent extractor.	Static simulated digestion (stomach, small intestine) coupled to a Caco-2 permeability assay and Caco-2 cells co-cultured with HepG-2 cells.	Luteolin	The bioaccessibility of luteolin from thyme and in thyme and olive oil during the simulated digestion was 14.6% and 16.7%, respectively. Luteolin and its sulfate and glucuronide metabolites were detected after the incubation of Caco-2 cells. The flavone luteolin and its metabolites were the most bioaccessible.	[174]
Origanum majorana	100 mg of oregano dissolved in 50% ethanol were used	Static simulated digestion (stomach, small intestine) coupled to a Caco-2 permeability assay	6-Hydroxyluteolin-7-*O*-glucoside Luteolin-*O*-glucoside Luteolin-7-Oglucoside Luteolin-7-*O*-glucuronide Diosmin Apigenin-7-*O*-glucoside Apigenin-7-*O*-glucuronide Luteolin Apigenin	The highest bioaccessibility was shown for diosmin, luteolin-7-*O*-glucuronide, and luteolin-7-*O*-glucoside, with 99.70, 94.55 and 94.19%, respectively. The process decreased the content of the flavones and their derivatives. Luteolin-7-*O*-glucoside and luteolin-7-*O*-glucuronide were the most stable. Luteolin and apigenin derivatives had low permeability in the Caco-2 assay.	[175]

Table 5. *Cont.*

Plant Species	Description of Sample	Animal Model Used	Flavones in Sample	Bioavailability Assay Results	Reference
Thymus vulgaris	Phenolic extracts were obtained using 80% ethanol. After that, thyme extracts and a combination of freeze-dried olive cake and dried thyme extract (1:1) were used	Male Wistar rats were treated intragastrically and gavaged with 1.5 g/kg BW in water of the extracts	Apigenin Luteolin	Sulfate conjugated forms of phenolics were the main identified metabolites after dosing. The C_{max} in thyme extracts showed a two-phase mode kinetic pattern. The identified metabolites in rat plasma were hydroxyphenylpropionic acid sulphate, dihydroxyphenylpropionic acid sulfate, and caffeic acid sulfate.	[176]
Danshen (dried roots and rhizomes of *Salvia miltiorrhiza* Bunge)	Danshen and huangquin (dried root of *Scutellaria baicalensis* Georgi) were used to obtain water extracts. Pure extract of danshen and a combination with huangqin was used at a 1:1 ratio	Sprague-Dawley rats (12 weeks old, 200–220 g). Rats were orally administered with a single dose of danshen and the combination of danshen and huangqin at concentrations of 12.5 g/kg	Baicalein (5,6,7-trihydroxyflavone) Baicalin (Baicalein-7-*O*-glucuronide) Wogonin (5,7-dihydroxy-8-methoxyflavone) Wogonoside (Wogonin-7-*O*-β-D-glucuronide)	The pharmacokinetic parameters of baicalein, baicalin, wogonin, and wogonoside in the combined extracts of Danshen and Huangqin were Cmax values of 306.92, 2465, 373.17, and 1779.17, respectively.	[177]

Furthermore, some chemical characteristics can aid in predicting the bioavailability of flavones and other phenolics, and these characteristics are known as the rule of five (or Lipinski's rule of five) [178]. These rules predict the drug-likeness of the passive absorption of a molecule. For instance, a molecule can permeate cells by passive absorption if the following conditions are met:

- Molecular weight $\leq$500;
- The molecule has no more than 5 hydrogen bond donors;
- The molecule has no more than 10 hydrogen bond acceptors;
- The partition coefficient (Log p) is $\leq$5.

Following these characteristics, conjugated flavones will often have lower cell permeability due to their higher molecular weight and numbers of H bond donors and acceptors. Nonetheless, cell transporters can metabolize these molecules via active means of absorption. The predicted passive absorption of some flavones mentioned in this study is shown in Table 6.

Table 6. Predicted passive absorption of some flavones found in plants of the *Ocimum*, *Origanum*, *Salvia*, and *Thymus* genus.

Molecule	Molecular Weight [1]	H Bond Donors [1]	H Bond Acceptors [1]	Log p * [1]	Predicted Bioavailability
Apigenin	270.2369	3	5	3.07	Yes
Luteolin	286.2363	4	6	2.73	Yes
Diosmetin	300.2629	3	6	3.06	Yes
Cirsimaritin	314.29	2	6	3.21	Yes
Scutellarein	286.24	4	6	2.74	Yes
Hispidulin	300.26	3	6	3.09	Yes
Luteolin-7-glucoside	448.3769	7	11	0.58	No
Apigenin-7-glucoside	432.381	6	10	0.68	No
Luteolin-7-glucuronide	462.3604	7	12	1.22	No
Apigenin-7-glucuronide	446.361	6	11	1.03	No
Baicalein	270.2369	3	5	3.19	Yes
Baicalin	446.361	6	11	1.27	No
Wogonin	284.26	2	5	2.092	Yes
Wogonoside	460.4	5	11	1.44	No

* Log p is defined as the partition coefficient. [1] Chemical data obtained from Kim et al. [179], Wishart et al. [180], Wishart et al. [181], Wishart et al. [182], and Wishart et al. [183].

6. Conclusions

Plants of the Lamiaceae family, such as *Ocimum*, *Origanum*, *Salvia*, and *Thymus*, are rich sources of flavones. Flavones are flavonoids with antioxidant, anti-inflammatory, anticancer, and anti-diabetic potential. Some of the most abundant flavones in these species are apigenin and luteolin (and their derivates), cirsimaritin, and scutellarein. Thus, the development of methods to enhance their extraction is of interest to human health. For this, conventional techniques involving maceration, Soxhlet extraction, hydrodistillation, and boiling have been used for many years. It has been reported that the bioactive properties of flavones are highly dependent on their chemical structure, which is in turn highly dependent on the method of extraction and its further metabolism after ingestion. The factors mentioned above, plus an effort to diminish the environmental impact of conventional techniques, have led to the development of more environmentally friendly techniques such as ultrasound-assisted extraction, microwave-assisted extraction, pressurized liquid extraction, and supercritical fluid extraction. These techniques usually involve a higher initial investment expense but offer a higher yield, purity, and bioactivity of flavones. Moreover, after ingestion, flavones are highly metabolized in the gastrointestinal system by pH changes, digestive enzymes, and xenobiotic metabolic enzymes in the enterocytes and liver. In this sense, most flavones identified in plasma are conjugated derivatives rather than parental molecules. This can affect their bioactive effect and prevent their delivery at target sites in the body. Moreover, we suggest a systematic approach when evaluating the properties of flavones, including the appropriate extraction methods coupled with bioaccessibility/bioavailability studies concomitant to the evaluation of their bioactive properties.

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