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A dive into natural leads against depression from family Lamiaceae

Pargat Singh[1,2], Ujjwal Kaushik[1*]
[1]Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, India.
[2]University College of Pharmacy, Guru Kashi University, Bathinda, Punjab, India.

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ABSTRACT

One of the most significant herbal families, the Lamiaceae, has a vast range of plants having biological and therapeutic uses. Due to its curative and preventative qualities, species of the Lamiaceae family have a long history of usage in flavoring, food preservation, and medicine. The family comprising around 236 genera is known for the herbaceous plant species enriched in aromatic compounds. The review focuses on the potential antidepressant properties, active ingredients, and potential mechanisms of action of plant species found in the selected unexplored genus of the Lamiaceae family. The insights emphasized in this review will contribute to the body of knowledge on the unique effects of Lamiaceae plants on depression. It is possible to do more research on the plant species covered under each genus to identify and isolate potentially active substances that may have commercial application in medicinal industry.

INTRODUCTION

Depression is a serious medical disorder that impairs mood, energy, sleep, and individual's capacity to enjoy life. Stress state often disrupts homeostasis, wellbeing, and physiological balance, leading to neurodegenerative disorders and susceptibility to neuro-damage due to activation of the HPA axis, glucocorticoids, oxidative stress, and inflammation [1]. The vivid stress-operated mechanisms leading to depression have been depicted in Figure 1. Clinical research has shown that treating depression has poor therapeutic results [2]. Active ingredients in medicinal plants are crucial for clinical therapeutics due to their multi-pharmacological activities [3]. With regard to the adverse effects, plant-based bioactive compounds hold promise as an alternative to the current pharmaceutical therapies for depression. These molecules also have antioxidant and neuroprotective capabilities. The current review focuses on species from five selected genera (viz. *Salvia*, *Mentha*, *Rosmarinus*, *Sideritis*, and *Scutellaria*) of a vast yet unexplored family Lamiaceae in depressive disorders. The reports on antidepressant effects of reported plant species from these genera over the past 10 years of research have been presented.

*Corresponding Author
Ujjwal Kaushik, Chitkara College of Pharmacy, Chitkara University, Rajpura, India. E-mail: ujjwal.kaushik @ chitkara.edu.in

MATERIALS AND METHODS

Using specific keywords for both whole plant products and plant extracts, such as "antidepressant plants lamiaceae," "antidepressant extract lamiaceae," and "antidepressant herbs lamiaceae," the authors of this review searched internationally recognized databases, including Science Direct, PubMed, and Google scholar. Regarding a targeted search on antidepressant reports of particular plant species beneath each genus, a combination of keywords was employed. A graphical representation of the availability of articles on research done in the past 10 years has been represented in Figure 2.

SPECIES OF THE LAMIACEAE FAMILY WITH ANTIDEPRESSANTS EFFECTS

Salvia genus

Salvia, which means "to save," is a Latin word that was used to name the genus in reference to its purported medical powers. With 1,000 species, *Salvia* is a rather varied genus [4]. *Salvia* genus belongs to the subfamily Nepetoideae in the Lamiaceae family. The existence of more than 100 active chemicals underlies the pharmacological actions of *Salvia* essential oils.

Salvia officinalis

In terms of active main contents, the species holds the highest value among other species. The aqueous leaf extract

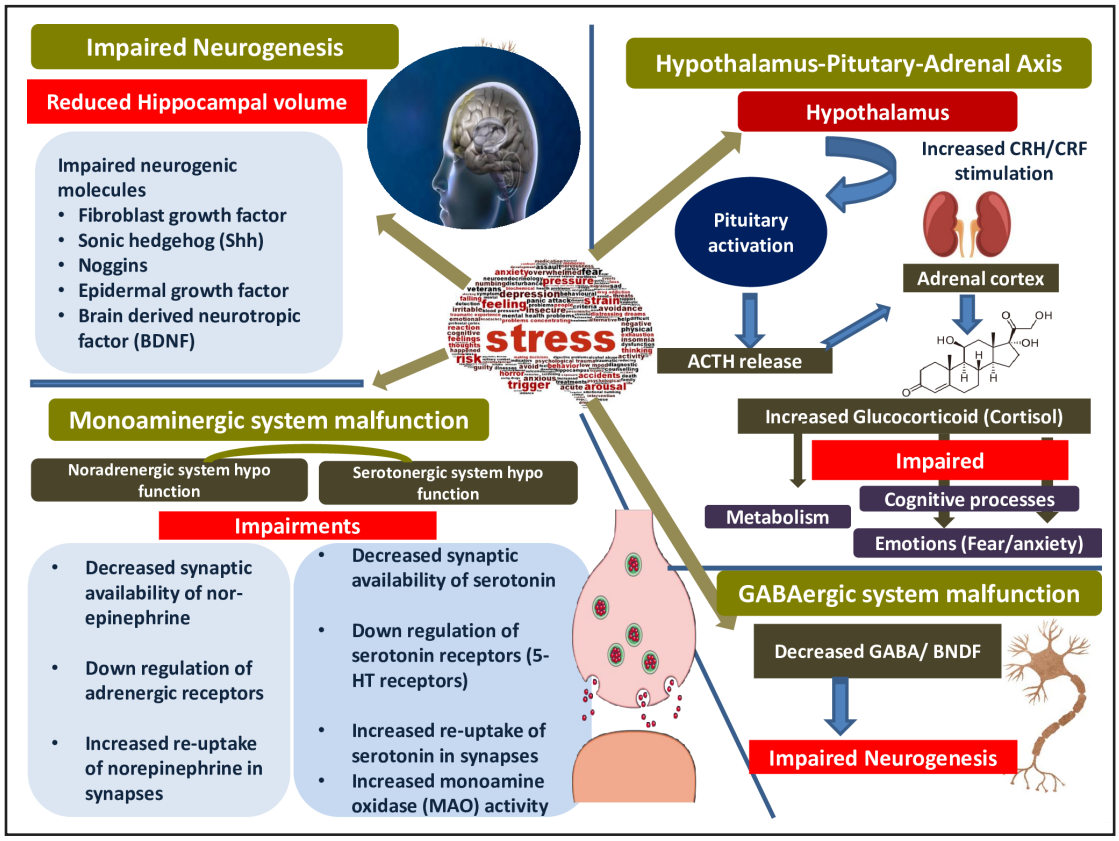


Figure 1. Basic mechanisms of stress-induced impairments leading to depression.

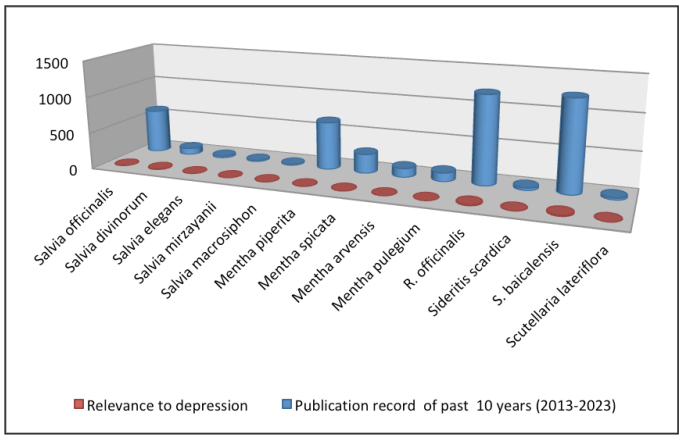


Figure 2. Number of publications according to PubMed.

at an escalating dosage level of up to 1,000 mg/kg has been reported to dramatically lower the duration of mice immobility [5]. The methanolic extract of *S. officinalis* extract had effects against depression, exhibited anxiolytic action, and may have bioactive components (phenolic, flavonoid, and tannin) that boosted rat learning [6]. Apigenin, Hispidulin, and Cirsimaritin, as well as the diterpenes 7-methoxyrosmanol and galdosol, are among the components of *S. officinalis* that have been shown to affect benzodiazepine receptor activation [7]. At 300 mg/kg, both alcoholic and aqueous extracts delayed the start of sleep, and has been suggested that *S. officinalis* can be used to treat insomnia and anxiety [8].

Salvia divinorum

Recreational users of *S. divinorum* may experience subjective sensations partly due to Salvinorin A's anxiolytic and antidepressant-like actions, mediated by both k-opioid and endocannabinoid systems [9]. In a study, anhedonia, which is frequent in depression, was reportedly reversed with SalvA [10].

Salvia elegans

Salvia elegans Vahl (Lamiaceae), sometimes referred to as "mirto" is a plant whose leaves and blooms are used to make an infusion that is used to treat CNS disorders in traditional Mexican medicine including insomnia, depression, and anxiety. Aerial fractions of *S. elegans* containing oleanolic acid (OA), rosifoliol, and agaraspirol have been reported to exhibit anxiolytic and antidepressant effects [11]. *Salvia elegans* leaf hydroalcoholic extract (60% ethanol) has been shown to provide sedative and antidepressant effects on mice [12,13]. According to a study ursolic acid and 5-O-(6-rhamnosylglucoside)-7-hydroxy-4'-methoxyflavanone extracted from *S. elegans* leaves, have antidepressant effects [14].

Salvia mirzayanii and Salvia macrosiphon

Salvia mirzayanii and *Salvia macrosiphon* extracts showed similar antidepressant efficacy, with the hydroalcoholic extract being more efficient than the aqueous extract [15].

Mentha genus

The genus *Mentha* contains between 13 and 18 species of plants. The genus is widely distributed in North America,

Europe, Africa, Asia, and Australia. *Mentha piperita*, *Mentha spicata*, *Mentha rotundifolia*, *Mentha arvensis*, and *Mentha suaveolens* are the most popular and widely grown mints for commercial cultivation.

Mentha piperita

Mentha piperita sometimes known as peppermint, is a hybrid species of *Mentha aquatica* and *Mentha spicata* L. The plant is one of the most extensively dispersed species in the Lamiaceae family and is found in Europe, Turkey, and a few areas of West Asia. Leaves contain phenolic acids, triterpenes, luteolin, rutin, hesperidin, and fatty acids, with menthol and menthone being the main components of essential oil [16]. Due to *M. piperita's* potential as a monoamine oxidase inhibitor, peppermint may have antidepressant properties. The interactions between the dopaminergic, noradrenergic, and serotonergic receptors may be responsible for this effect [17,18]. Researchers suggest that the fraction containing polyphenols and its primary ingredients, rosmarinic acid, eriocitrin, and luteolin-7-O-rutinoside, may contribute to its biological activity [19].

Mentha spicata

The decoction of spearmint leaves is used to treat biliary diseases, menstrual cramps, stomach discomfort, constipation, gingivitis, and ondotalgies. *Mentha spicata* teas are commonly used by Colombian communities to alleviate stress and insomnia [20]. The Elevated Plus-Maze test showed increased open arm time and longer sleep time in mice treated with *M. spicata* extract and sodium pentobarbital [21]. The carvone moiety in the essential oil of *M. spicata* has been considered to contribute toward this activity through a serotonergic mechanism [22]. Recent research evaluated the impact of fresh peppermint leaves and infusions on university students' mental health. The therapy group's students reported improved memory, higher sleep quality, and less anxiety [23].

Mentha arvensis

The use of *M. arvensis* in traditional Korean medicine has been reported to have significant antidepressant potential [24]. Intraperitoneal injections of Japanese mint oil emulsion at dosages of 78, 1,56, and 2,25 l/kg of body weight increased struggle time and also reduced immobility in the Forced swim technique depicting considerable antidepressant and cytotoxic effects [25]. Citronellal, nerol, and linarin are the three primary essential oils extracted from the leaves and flowers of this species. According to *in vitro* experiments, the α-citronellal has been reported to possess inhibitive activities against the MAO-A enzyme [26].

Mentha pulegium

It is a fragrant plant that is native to America, a member of the Lamiaceae family, and grows in Asia, Ethiopia, Iran, and Western, Southern, and Central Europe. The bulk of the essential oil in this species is composed of a complex mixture of monoterpenes in oxygenated form (76.8%), including menthone, pulegone, neo-menthol, and 8-hydroxy-4(5)-p-menthen-3-one. The species has reportedly been effective in treating anxiety and anxiety symptoms [27]. The length of BALB/c mice immobility in the fast swim test was significantly reduced in a study after *M. pulegium* administration. The antidepressant effect, however, was not dose-dependent [28].

Rosmarinus genus

The Lamiaceae family's woody, perennial *Rosmarinus* plant is native to the Mediterranean Basin and features fragrant, needle-like evergreen leaves.

Rosmarinus officinalis

Rosmarinus officinalis, L., a Mediterranean-native Lamiaceae plant, has a polyphenolic profile consisting of carnosic acid, carnosol, rosmarinic acid, and hesperidin [29]. The chronic administration of hydro-alcoholic extract has been proven to reduce hyperactivity and behavior in olfactory bulbectomized mice [30]. A pentacyclic triterpenoid named ursolic acid from this species has been reported to decrease mice's immobility in the forced swimming and tail suspension method. In anxiety and depression models, it has been observed that the ethyl acetate, hexane, ethanolic, and essential oil-free fractions, as well as essential oil and the isolated chemicals Saligenin, rosmanol, cirsimaritin, carnosol, and betulinic acid, exhibit CNS effect [31–33]. The extract (distillation residue of essential oil) of *R. officinalis*, significantly improved depressive and anxiety-like behavior in mice, reversing the alterations in gene expressions caused due to stress [34]. Tyrosine hydroxylase (TH) and pyruvate carboxylase (PC), two important genes were significantly upregulated in PC12 cells treated with *R. officinalis* polyphenols [35].

*Sideritis*genus

More than 150 plant species make up the *Sideritis* genus, which is mostly found in the Mediterranean region but also occurs in the Atlantic areas, North Africa, and even Norway.

Sideritis scardica

Other names for *S. scardica* include "Greek tea" and "mountain tea." The high concentration of flavonoid and phenolic chemicals in *S. scardica* is thought to be responsible for its pharmacological effects. According to research, *Sideritis* extract total phenolic content showed potential cognitive, anxiolytic, and antidepressant benefits [36]. Four flavonoids associated with genus *Sideritis*, include xanthomicrol and isoscutellarein 7-O-[6‴-O-acetyl--D-allopyranosyl-(12)]. Isoscutellarein 7-O-[6‴-O-acetyl--D-allopyranosyl-(12)]--D-glucopyranosideSaligenin and -6″-O-acetyl-D-glucopyranoside have been shown to specifically and permanently block hMAO-A [37]. *Sideritis scardica* extracts, known for triple monoamine reuptake inhibitors, have the potential for phytochemical therapy in treating mental disorders such as anxiety, depression, attention-deficit hyperactivity disorder, and neurodegenerative diseases [38].

Genus *Scutellaria*

Scutellaria, has between 360 and 469 recognized species. This genus is responsible for the identification of more

than 295 compounds, including flavonoids and diterpenes. Flavonoids and neo-clerodane diterpenoids can be credited with the majority of the bioactivities [39]. Scutellaria is used in various therapeutic settings; however, there has not been much study done on this genus [40].

Scutellaria baicalensis

Flavonoid baicalein from dried roots of this species (*Scutellariae radix*) inhibits the inflammatory process through peripheral immunological response [41]. Baicalin and baicalein, two of *S. baicalensis* bioactive ingredients, block MAO A/B and facilitate the release of monoamines, particularly dopamine associated with neurological and psychiatric disorders [42]. Baicalein was found to have effective antidepressant effects which are probably attributed to the suppression of the HMGB1/TLR4/NF-B pathways [43]. It also significantly reduced TLR4 expression, decreased IL-1, IL-6, and TNF- levels in the hippocampus, and improved chronic mild stress-induced depressive-like symptoms [44]. In addition, baicalein has been shown to have antidepressant properties by promoting the differentiation of neurons, their maturation into mature neurons, and their survival [45]. Baicalin treatment significantly enhances hippocampus apoptosis which is thought to contribute to its potent antidepressant effects [46].

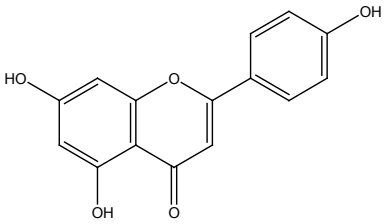
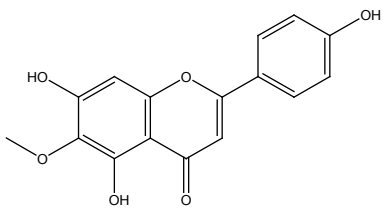
Scutellaria lateriflora

The extract of *S. lateriflora* has been reported to significantly improve global mood without affecting energy or cognition [47]. Baicalin and its aglycone baicalein among flavonoids are known to have anxiolytic activity because of their attachment to the benzodiazepine site of the GABA-A receptor [48].

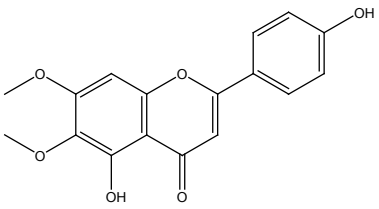
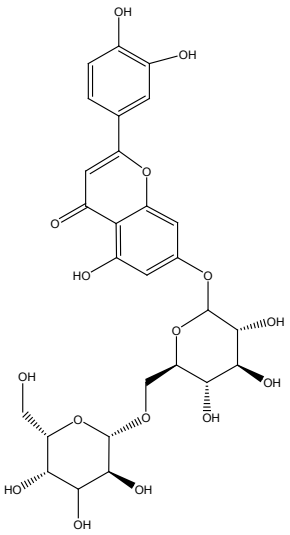
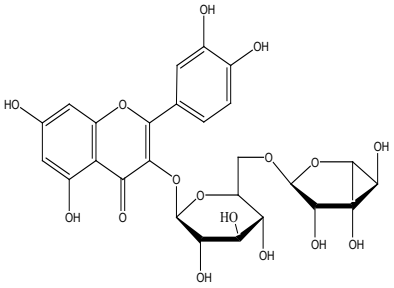
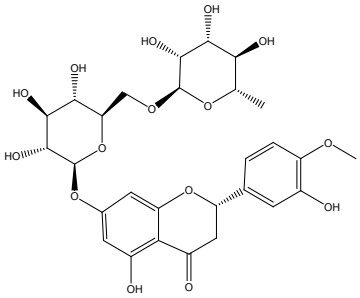
EVALUATION OF ISOLATED COMPOUNDS *IN-VIVO* AGAINST DEPRESSION

Except for a few explored genera, there have been very less studies to explore a link between the antidepressant lead moieties and phytoconstituents in different species of the family Lamiaceae. The details of isolated moieties with recent reports on their molecular-level mechanisms against depression have been discussed in Table 1. The published literature from the studied genera indicates that most of the plant-based isolated components as potential candidates against depression fall under the categories of flavones, terpens, terpenoids, polyphenols, or their derivatives. Many of these components mentioned either in the whole plant extracts or in their essential oils have not been evaluated extensively in depression models and present a potential area for further research. For instance, linarin (a glycosylated flavonoid) and Carvone (terpene) were found to

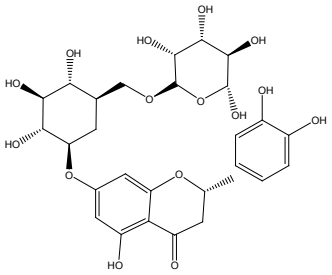
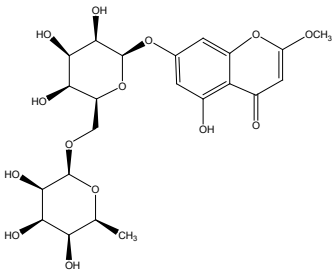
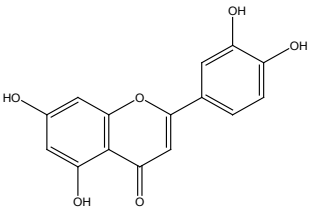
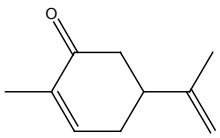
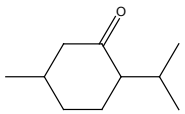
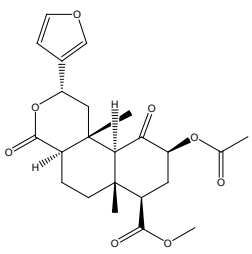
Table 1. Details on isolated components from different plant species with proposed mechanism of action in depression.

Isolated compound	Structural class	Chemical structure	Plant species(s) from family Lamiaceae	Proposed mechanism of action reported in depression in different plant species	Reference
Flavone(s)/flavanone					
Apigenin	Flavone		*Perilla frutescens*	• Enhancement of autophagy through the AMPK/mTOR pathway • via α-adrenergic, dopaminergic, and 5-HT3 serotonergic receptors mediated action • The upregulation neurotrophic factor brain derived neurotrophic factor (BDNF) present in hippocampus region of brain is believed to have effect against depression. • Reduced production of interleukin-1 and activation of inflammasome in the brain leading to halt of depression due to stress • serve as a specific, reversible inhibitor of monoamine oxidase A (MAOA), thereby reducing MAOA enzyme activity.	[45,52–57]
Hispidulin	Flavone		*S. officinalis*	• Via inhibiting catechol-O-methyltransferase and indirectly activating D1 receptors by increasing dopamine levels in the prefrontal cortex. • Involvement of GABAergic and glutamatergic mechanisms	[58]

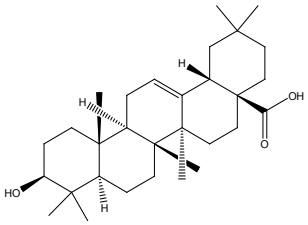
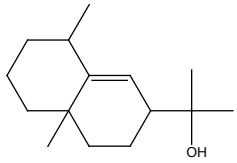
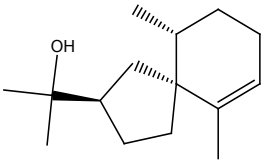
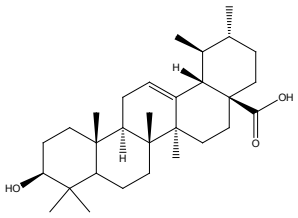
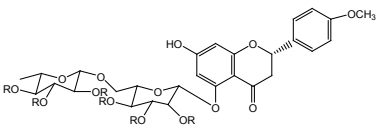
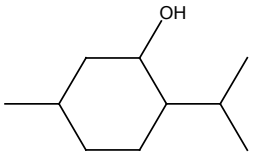
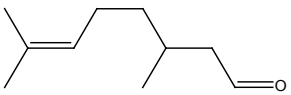
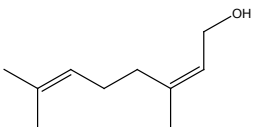
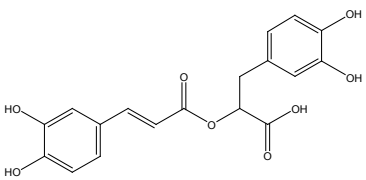
(Continued)

Isolated compound	Structural class	Chemical structure	Plant species(s) from family Lamiaceae	Proposed mechanism of action reported in depression in different plant species	Reference
Cirsimaritin	Flavone		*S. officinalis*	• Acts via biphasic modulation of GABAA receptors • It prevents the synthesis of inflammation mediating moieties (TNF-, IL-6, and inducible nitric oxide synthase) and prevents IB, Akt, c-fos, and STAT3 from being phosphorylated.	[32,59]
Luteolin-7-O-rutinoside	Flavone		*P. frutescens*	• Enhances the hippocampus BDNF mRNA and protein levels, which are decreased under the stress of sleep deprivation • Acts via axon guidance pathway, which through axon guidance molecules affects the therapeutic effects of late onset depression.	[60,61]
Rutin	Flavone		*M. piperita*	• Acts by increasing serotonin, norepinephrine, and dopamine levels inside hippocampal and cortical regions	[62]
Hesperidin	Flavanone		*R. officinalis* *M. piperita*	• inhibits the levo arginine nitric oxide cyclic Guanosine 3',5'-cyclic monophosphate pathway and enhancement in brain derived neurotopic factor levels in the hippocampus. • Hesperetin improve anxiety and depression-like behaviors in rats due to its activation of the Nrf2/ ARE pathway. • Acts via controlling NLRP3-mediated pyroptosis. • Reduces neuroinflammation and oxidative damage, and boosts the synthesis of neurotrophic factor BDNF in the hippocampus of brain.	[63–66]

(Continued)

Isolated compound	Structural class	Chemical structure	Plant species(s) from family Lamiaceae	Proposed mechanism of action reported in depression in different plant species	Reference
Eriocitrin	Flavanone		*M. piperita*	• Serve as competitive and reversible human monoamine oxidase (MAO) inhibitors.	[67]
Linarin	Glycosylated flavone		*M. arvensis*	• Unknown mechanism	[49]
Luteolin	Tetrahydroxyflavone		*P. frutescens*	• regulate autophagy disorders by affecting glycerophospholipid metabolism in various brain regions, thereby alleviating depression-like behavior. • Via inhibition of vasopressin, dopamine, and monoamine oxidase receptors (hMAO-A, hD4R, and hV1AR) • acts by increasing the potency of the GABAA receptor-Cl(-) ion channel complex. • Lowers serotonin levels while raising norepinephrine levels in the hippocampus and medial prefrontal cortex	[68–71]
Terpene(s)					
Carvone	Monoterpene		*M. spicata*	• Unknown mechanism	[50]
Menthone	Monoterpene		*M. piperita* *M. pulegium*	• By regulating inflammasome (NLRP3) and arbitrating inflammation-causing cytokines and central neurotransmitters	[72]
Terpenoid(s)					
Salvinorin A	Oxygenated cyclic diterpenoid		*S. divinorum*	• Acts via biphasic modulation of GABA-A receptors • Highly selective kappa-opioid receptor agonist	[9,32,73,74]

(Continued)

Isolated compound	Structural class	Chemical structure	Plant species(s) from family Lamiaceae	Proposed mechanism of action reported in depression in different plant species	Reference
OA	Pentacyclic triterpenoid		*S. elegans*	• Acts through the involvement of 5-HT1A receptor and BDNF • Acts through down-regulation of serine/threonine-protein Kinase 1 (SGK)	[75–77]
Rosifoliol	Eudesmane sesquiterpenoid		*S. elegans*	• Acts through involvement of 5-HT1A receptor	[11]
Agarospirol	Sesquiterpenoid			• Inhibit D2 receptor binding and 5-HT2A receptor binding.	[78,79]
Ursolic acid	Pentacyclic triterpenoid		*S. elegans* *R. officinalis*	• Acts through modulation of Bcl-2 (anti-apoptosis marker)/Bax expression (pro-apoptosis marker) in hippocampus • Enhancing stress resistance by acting through serotonin receptors.	[80,81]
Isosakuranetin-5-O-rutinoside	Flavanone			• Unknown mechanism	[14]
Menthol	Monoterpenoid		*M. piperita* *M. pulegium*	• Acts by BDNF/TrkB signaling pathway stimulation and reduction of neuroinflammation • modification of 5-HTergic, GABAergic, and DAergic systems	[82,83]
Citronellal	Monoterpenoid aldehyde		*M. arvensis*	• inhibitory effects on MAO-A enzyme	[26,84]
Nerol	Monoterpenoid alcohol		*M. arvensis*	• increase the level of serotonin	[85,86]
Polyphenol(s)					
Rosmarinic acid	Polyphenol		*P. frutescens*	• Acts via cannabinoid receptors/ PPAR-γ signaling pathways • via upregulation of the key genes controlling the dopaminergic, serotonergic, and GABAergic pathways, TH and PC.	[35,87]

be an effective antidepressant principle but their antidepressant mechanism still remains unclear [49,50]. Hispidulin (flavonoid) reported to improve social withdrawal behavior in mice can be further explored for its efficacy and related mechanisms in depressive disorders [51].

FUTURE PERSPECTIVES AND CONCLUSION

This review explores the potential role of medicinal plants in depressive disorders, revealing promising therapeutic agents. Most extracts were nontoxic and comparable to synthetic drugs. However, the data is preliminary and lacks clear cellular and molecular mechanisms. Future studies should focus on detailed molecular mechanisms, dosages, clinical efficacy, and safety of these extracts and isolated compounds.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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