Depression: An Insight into Heterocyclic and Cyclic Hydrocarbon Compounds Inspired from Natural Sources

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Abstract: Depression, a well-known mental disorder, has global prevalence, affecting nearly 17% of the population. Due to various limitations of the currently available drugs, people have been adopting traditional herbal medicines to alleviate the symptoms of depression. It is notable to mention that natural products, their derivatives, and their analogs are the main sources for new drug candidates of depression. The mechanisms include interplay with γ-aminobutyric acid (GABA) receptors, serotonergic, dopaminergic noradrenergic systems, and elevation of BDNF levels. The focus of this article is to review the role of signalling molecules in depression and highlight the use of plant-derived natural compounds to counter CNS depression.

Keywords: Antidepressants, plant-derived natural compounds, CNS, neurotransmitters, BDNF, monoamines.

1. INTRODUCTION

Depression is a multifactorial mental disorder [1], affecting more than 350 million people globally [2]. It is concomitant with substantial deficits of psychosocial activities and quality of life [3, 4]. Due to the heterogeneous nature of this disease, large disparities in clinical evaluation exist [5], making treatment more challenging. Its aetiology and pathophysiology are still relatively poorly elucidated [6]. Depressive disorders (mainly represented by major depressive disorder) are well-known causes of disability worldwide [7]. According to the Global Burden of Disease study, depression is counted at 4th position in causing disability worldwide, and it is projected to be the 2nd by 2020 [8]. Though there are well-acknowledged chemotherapeutic agents available for mental disorders, a considerable percentage of patients from underdeveloped and developing nations receive no treatment for their disorders due to cost burden, improper counselling, and social stigma regarding depression [9].

Multiple research investigations have revealed imperative insights on various levels of depression, linking it with genetic abnormalities [10], imbalance in levels of neurotransmitters [11], defects in brain anatomy [12], and cognitive deficits [13], so pharmaceutical industries consider high-risk in developing therapeutic agents for depressive disorders. Thus it becomes imperative to look for novel therapies based on natural products [14]. Before considering any novel therapeutic compounds, treatment-resistant depression, slower onset of action, risk of adverse effects, and substance abuse of these compounds must be ascertained, which are major limitations with the use of current pharmacotherapy [15]. Regardless of the fact that drug design and discovery have a high reliance on synthetic chemistry, the contribution of natural products cannot be ignored. Natural products are a potential source of drugs for nervous system-related disorders, cancer, endocrine disorders, etc. [16-25]. WHO list of essential drugs consists of 252 drugs, of which 11% are of plant origin [26]. So there is an absolute chance of finding a natural molecule having desired antidepressant activity. The natural heterocycles and cyclic hydrocarbons (sources include flavonoids, glycosides, alkaloids, terpenes, and saponins from plant sources may instill positive change which researchers are looking for, as they possess unique chemical diversity, even some of these cannot be synthesized by currently known methods. As a result, these natural compounds as novel drug molecules for depression remain untapped. Different scientific reports have focused on validating the supposedly psychoactive phytoconstituents from various medicinal plants, facilitating isolation of bioactive phytoconstituents acting on CNS as an antidepressant. Scientific investigations claiming various phytochemicals as ameliorative agents in depression are limited. However, some key findings have demonstrated that flavonoids, alkaloids, glycosides, terpenes, and saponins isolated from various medicinal...
plants exhibit antidepressant activity. In this review, we have discussed the potential of various heterocycles and cyclic compounds of plant origin to treat depression. This review will try to understand the research gap in depression, the mechanism of action of selected cyclic and heterocyclic molecules, and in vivo and in vitro activities of these phytoconstituents will also be covered.

2. NEUROTRANSMITTERS AND INTRACELLULAR SIGNALLING MOLECULES OF DEPRESSION

Among the signalling molecules related to depression, significant variation is well established, which can clarify the complexity of the condition. Much evidence has been gained from experiments in animal studies at the cellular and molecular levels regarding depressive conditions.

2.1. Glutamatergic Signaling in Depression

Mounting data indicate that MDD abnormally impacts the glutamatergic system. Among MDD patients, levels of glutamate are elevated in the cerebrospinal fluid, including brain tissue, so antidepressant therapy counters this mechanism [27]. In the post-mortem brain, the expression of receptors of glutamate is often atypical [27]. Significantly, NMDA receptor antagonists show strong therapeutic outcomes in patients suffering from depression [28]. Therefore, it can be outlined that in all experimental animals, atypical glutamate receptor expression and downstream signalling are correlated with depression. NMDA also prevents the development of microtubules [29], indicating that the stabilization of microtubule polymers leads to improvements in dendritic morphology and spine development/atrophy. Post-synaptic density protein 95 (PSD95) decreases in PFC in MDD patients [31, 32]. Various studies confirm that GSK-3b induces neuronal cell death responses [33, 34]. SSRI-dependent antidepressants block GSK-3 action through serine 9 phosphorylation. This occurs via 5-HT1A receptors [35]. Various investigations on different models of depression indicate that pharmacological regulation of GSK-3 expression produces antidepressant effects [36]. B-catenin, a GSK-3 substrate, undergoes proteasomal degradation of B-catenin following phosphorylation [37]. In comparison, cytosolic levels of β-catenin are raised due to inhibition of GSK-3, offering many advantages for cell survival and protection. GSK-3 also regulates neurogenesis in the hippocampal region. Thus it plays a role in depression as it prevents neurogenesis in the hippocampal region [38, 39]. Ironically, DISC-1 binds directly to GSK-3b, limiting its activity, which in turn can lead to modulation of different cellular processes. GSK-3b is blocked by DISC-1 directly. DISC-1 also reverses mice’s depressive actions, as did the GSK-3 pharmacological inhibition [40]. Importantly, GSK-3b SNPs were related to brain structural changes and human depression [41]. GSK-3 inhibition also generates its therapeutic results by deregulating the trafficking of AMPA receptors [42]. This is accomplished by GSK-3b light chain kinesin phosphorylation, which dissociates AMPA receptor cargo (GluR1) [43]. This research also found that a peptide caused antidepressant-like behaviour in mice. Lastly, as per various shreds of evidence, GSK-3 has been found to epigenetically regulate depression [44, 45].

2.2. GSK-3 Signaling and Depression

Various studies confirm that GSK-3b induces neuronal cell death responses [33, 34]. SSRI-dependent antidepressants block GSK-3 action through serine 9 phosphorylation. This occurs via 5-HT1A receptors [35]. Various investigations on different models of depression indicate that pharmacological regulation of GSK-3 expression produces antidepressant effects [36]. B-catenin, a GSK-3 substrate, undergoes proteasomal degradation of B-catenin following phosphorylation [37]. In comparison, cytosolic levels of β-catenin are raised due to inhibition of GSK-3, offering many advantages for cell survival and protection. GSK-3 also regulates neurogenesis in the hippocampal region. Thus it plays a role in depression as it prevents neurogenesis in the hippocampal region [38, 39]. Interestingly, DISC-1 binds directly to GSK-3b, limiting its activity, which in turn can lead to modulation of different cellular processes. GSK-3b is blocked by DISC-1 directly. DISC-1 also reverses mice’s depressive actions, as did the GSK-3 pharmacological inhibition [40]. Importantly, GSK-3b SNPs were related to brain structural changes and human depression [41]. GSK-3 inhibition also generates its therapeutic results by deregulating the trafficking of AMPA receptors [42]. This is accomplished by GSK-3b light chain kinesin phosphorylation, which dissociates AMPA receptor cargo (GluR1) [43]. This research also found that a peptide caused antidepressant-like behaviour in mice. Lastly, as per various shreds of evidence, GSK-3 has been found to epigenetically regulate depression [44, 45].

2.3. Wnt Signaling and Depression

Wnts are secreted glycoproteins that act to negatively regulate GSK-3 through the canonical Wnt pathway. Although Wnts play a vital role in growth, they also control neuroplasticity [46-48]. Wnts bind to Fzd receptors, inhibiting GSK-3 by stimulating dishevelled phosphoproteins [49, 50]. Wnt-2 is elevated in many antidepressant procedures, including continuous electroconvulsive treatment in animal models, and in the case of antidepressant treatment, Wnt-2 expression is increased in the hippocampus, and hippocampal induction of Wnt-2 also reduces antidepressant action [51]. Wnt3a expression is also improved in rats after SSRI therapy, in which adult hippocampal neurogenesis is stimulated [52]. Subtypes of Fzd have previously been used in addiction and psychiatric treatments. The viral-mediated hippocampal knock-down of Fzd6 reportedly evokes anhedonic behaviour and heightened fear [53]. Throughout a post-mortem analysis of suicidal cases and animal models of relevance, DLV2 mRNA expressions were substantially reduced in the mouse nucleus accumbens [54]. Such studies strongly link disrupted Wnt signalling with action that is close to depression.

2.4. CREB and Depression

CREB has a role in controlling transcription that activates many signalling events that are important in depression pathology. A review of 26 suicidal victims showed a drop in the expression of CREB in the hippocampal region [55]. Likewise, the CREB function was found to decrease in animal distress experiments [56, 57]. In line with this, CREB rates in the hippocampus are increased after the administration of fluoxetine, which contributes to augmented BDNF production [58-60]. In comparison, CREB gets triggered by protein kinase A, which activates in reaction to persistent antidepressant therapy [61], although other kinases activate CREB in a stimulus-reliant manner [61-63]. The antidepressant activity at CREB is therefore hardly unexpected. CREB binds gene targets in the nucleus for controlling neuroplasticity, cell viability, and cognition [60]. Importantly, BDNF is one of such targets, which might prove beneficial in depressive disorders. Thus disruptions of signalling processes that arise due to depression are distinctly complex. Targeting such signalling proteins provides a vision to develop newer therapies.

2.5. BDNF and Depression

Various neurotrophic factors, particularly researched in association with BDNF, have revealed its extensive connection with depressive disorders. Depressive patients have reduced serum BDNF levels [64, 65]. BDNF mRNA in rodents declines in the hippocampus subjected to stress [66, 67] and PFC [68]. BDNF is also down-regulated after corticosterone therapy [69]. On the other side, BDNF has also been reported to increase after induction of stress [70, 71] and is hypothesized to act as a tool to defend against the consequences of potential stressful incidents. Similarly, the systematic deple-
tion of BDNF in the dentate gyrus decreased the effectiveness of antidepressants [72], and the hippocampal knockdown of BDNF caused anhedonia in rodents [73]. Studies have also confirmed that BDNF also modulates the production of numerous important synaptic proteins [74]. A single variation in the nucleotide sequence of BDNF imparts the vulnerability of humans and rodents towards depressive disorders [75]. Due to compromised dendritic transport [75, 76], this modification results in decreased levels of BDNF. BDNF post-synaptic release triggers presynaptic Rab3a expression [77], which has been found to be downregulated in patients suffering from depression [78]. Impaired BDNF control is inextricably linked to depression. As mentioned in this segment, BDNF activates many main signaling mechanisms that have been shown to be important in animal models for antidepressant responses.

3. UNDERSTANDING RESEARCH GAP TO UNVEIL FUTURE ANTIDEPRESSANTS

The current antidepressant medications are far away from being ideal. The development of newer antidepressant therapeutic compounds has trickled down in the recent past due to the high failure rate of drug development for psychiatric illnesses, so it is important to understand incompetency in antidepressant research. Although it is apparent that antidepressants have significant short- and long-term effects, it is often obvious that complications exist, such as addiction, toxicity, reduced effectiveness over time, relapse, and recurrence concerns. In depression, various neuroscientific abnormalities oscillate from low or high levels of neurotransmitter molecules, impaired brain cells, and cognitive decline. Three theoretical lines of future research investigation may be considered: creating a comprehensive neuroscience depression model that offers mechanistic linkages between symptoms and the outcomes of antidepressant interventions. The continuation of the search for aetiological and pathophysiological factors involved in depression development. A greater emphasis on translational initiatives to strengthen clinical practice and work utilizing proven fundamental neuroscientific insights. Another relevant aspect is the theoretical problem as to why antidepressants have reduced effectiveness; it is because they work through raising monoamine levels, whereas lower concentrations of these neurotransmitters are not always encountered by individuals with depression. Following the ingestion of antidepressants, monoamine levels improve significantly; however, a therapeutic delay is common. Eventual neurophysiological improvements such as differential activation of monoaminergic receptor rates and downstream intracellular impact on metabotropic enzyme cascades and eventual adjustments to the nuclear transcription of proteins may tend to modulate the therapeutic results.

It is now obvious that other neuromodulators have a role in depression, so there are pretty close chances that current therapeutic targets may be insufficient in producing therapeutic efficacy. So it is thought that an in-depth understanding of molecular targets may culminate the problems like delayed onset, habituation, and adverse drug reactions. Hence depression is considered a multifactorial disease, which requires a multidimensional treatment approach, including psychopharmacological intervention.

Better results can be achieved with faster-acting effective antidepressants. To achieve this reality, different approaches can be applied with the help of advanced tools of genetic and neuroscience. Still, again, it is difficult to predict the outcome of modern health technologies. So the present drug design essentially needs to be faster acting, much efficacious, least complex for physicians to conduct, tolerable by patients, cheap for healthcare providers, otherwise future antidepressants will have a partial impact. All such qualities may be fulfilled by plant-derived drug molecules subjected to experimentation on animal and human subjects.

4. NATURE-INSPIRED COMPOUNDS AS AN EMERGING SOURCE FOR THE TREATMENT OF DEPRESSION

The existence of a wide variety of phytochemicals in medicinal plants is known for their therapeutic potential in the ministration of several diseases, including brain-associated disorders [79-84]. Herbal medicines including saffron, Rhodiola, lavender as well as Echium are used for the treatment of depression. From the last decade, various phytochemical entities with strong anti-depressant activity have been disclosed from various herbal medicines. Constituents that have been well characterized and are under focus on animal models followed by other studies are reviewed here.

4.1. Flavonoids

Polyphenols represent a class of compounds that are found ubiquitously in nature [85]. Due to their significant antioxidant potential, they are widely used as alternative medicine in the assistance of various CNS-related disorders [86]. The basic structure of Phenolic compounds consists of an aromatic ring with various hydroxyl groups. Based on the structure, they are categorized into flavonoids, stilbenes, lignans, phenolic acids, and coumarins [87, 88]. Among all, flavonoids represent an important class of phenolic, which is further categorized into isoflavones, anthocyanins, 4-isoflavonoids, and flavan-3-0f derivatives [89]. To date, more than 6000 flavonoids have been reported exhibiting diverse pharmacological activities [90-92]. The antidepressant activity of flavonoids isolated from various natural sources has been confirmed in various in-vitro and in-vivo animal studies involving attenuating the levels of various neurotransmitters like 5-HT, NA and DA, and (5-HIAA) besides the balancing of various receptors [93-95]. There are several flavonoids isolated from plants (Fig. 1) which are having outstanding preclinical effects against depression, supporting evaluation of their clinical profile as well [96]. Moreover, various epidemiological evidence support that a diet containing an adequate amount of flavonoids helps in augmenting depression [97-101]. The various plant-derived flavonoids [102], along with their diversified mechanistic cognizance to exhibit antidepressant-like effects, are shown in Table 1.
## Table 1. Plant-derived flavonoids against depression.

| Constituent | Type of Study | Cellular/Animal/Clinical | Description of Study along with Doses | Mechanism | Refs. |
|-------------|---------------|--------------------------|--------------------------------------|-----------|-------|
| Astilbin | CUMS model of depression in mice | Immobility time is significantly reduced at doses 10, 20, and 40 mg/kg (i.p.) without affecting locomotor activity | Activates BDNF signalling pathway | [103] |
| Apigenin | FST in mice | Duration of immobility time is greatly reduced at doses 12.5 and 25 mg/kg (i.p.). | Inhibitory activation on Monoamine oxidase | [104-106] |
| Kaempferol | FST and TST model | Reduces the immobility time at doses 30 mg/kg (o.p) in the FST and TST | Inhibitory activity on Monoamine oxidase | [104, 107] |
| Quercetin | FST model | A decrease in immobility time in comparison to imipramine (15 mg/kg, i.p) | MAO-A inhibition | [108] |
| Chrysin | Brain cells of rats | Suppressing MAO-A relating to an antidepressant-like effect | Inhibitory activity on Monoamine oxidase | [104] |
| Quercetin-3-O-apiosyl(1 → 2)-rhamnosyl(1 → 6) glucoside | PC12 nerve cells | Prevents nerve damage to rat adrenal medulla | Nerve cell protection | [109] |
| Isoquercetin | FST in rats | Decreases the immobility time at doses 30, 60, and 125 mg/kg similar to imipramine (20 mg/kg) | Inhibition of MAO-B | [110] |
| Icariin | CUMS model of depression in rats | Enhances antioxidant and anti-inflammatory activity at doses (20 or 40 mg/kg) | Acting on (HPA) axis and (HPT) axis | [111] |
| Isoflavone | Postmenopausal women | Reduces depressive symptoms in postmenopausal women | Inhibitory activity on Monoamine oxidase | [112] |
| Baicalin | Murine models | Reduces immobility time | MAO-A and B inhibition | [113] |
| Naringenin | Behavioural models of depression | Reduces immobility time at doses 10, 20, and 50 mg/kg | Elevating NA, 5-HT, and GR levels in the hippocampus region | [114] |
| Nobiletin | FST, TST | Signifying its potential for the treatment of depression by reducing the immobility time of mice | Acting via interplay with the 5-HT1A receptors | [115] |
| Amentoflavone | FST, TST | Reductions in the duration of immobility time | Interplay with 5-HT2 receptors | [116] |
| Hyperoside | FST | Shortened the immobility time at doses of 30, 60, and 125 mg/kg, in male rats | Interplay with the 5-HT (1A) receptors | [117] |
| Hesperidin | FST | Duration of immobility time gets reduced at doses 0.1, 0.3 and 1 mg/kg (i.p) | Interplay with the 5-HT (1A) receptors | [118, 119] |
| Luteolin | FST, TST | A dose of 50 mg/kg/ reduces immobility time | Enhance GABA A Receptor Cl ion channel complex. | [120] |
| Curcumin | FST, TST, and various other animal models | Curcumin was active in mouse FST and TST at doses 5 and 10 mg/kg | Inhibition of MAO | [121, 122] |
| Chlorogenic acid | TST and FST | When tested in mouse FST and TST, it exhibits antidepressant-like activity | Unclear | [123] |
| Ellagic acid | FST, TST | Ellagic acid reduces immobility period in both FST and TST comparable with fluoxetine at doses 25-100 mg/kg | Acting on adrenergic, serotonergic, and NO system | [124] |
| Fisetin | FST, TST | Immobility time in FST and TST gets reduced at doses (10 and 20 mg/kg, p.o.) | Inhibition of MAO-A only | [125] |
| Rutin | FST, TST | Immobility time in TST gets reduced at doses (0.3-3.0 mg/kg, p.o.) | Acting via Serotonergic, noradrenergic pathways | [126] |
| Ferulic acid | FST, TST | (0.01,10 mg/kg, p.o.) | Acting through the Serotonergic pathway | [127] |
| Resveratrol | FST, TST | Reduces the immobility period in mouse models of FST and TST at doses (20-80 mg/kg, p.o) | Inhibition of MAO-A | [128] |
| Isoliquiritin | FST, TST | Immobility time in FST and TST gets reduced at doses 10, 20, and 40 mg/kg | Raising 5-HT and NE levels | [129] |
| Baicalein | FST, TST | 1, 2 and 4 mg/kg (i.p.) | Increase in BDNF level | [130] |
(Fig. 1) Contd...
4.2. Glycosides

Glycosides are a class of compounds containing a sugar molecule (glycone) attached via a glycosidic linkage to an anomeric carbon of a non-sugar moiety (aglycone). Glycosides as such are various types in nature based on aglycone moiety, including alcoholic, cardiac, steviol, chromone, flavonoid, anthraquinone, coumarin, cyanogenic, iridoid, phenolic, saponins, etc. Glycosides are known for their various pharmacological activities, including antidiabetic, anticancer, antithrombotic, antifungal, analgesic, antiviral, antioxidant, and cardioprotective activity. It has been reported that glycosides isolated from various plant extracts (Fig. 2) exhibit anti-depressant activity mainly by upregulating the level of BDNF in the hippocampus region, which results in promoting synaptic efficacy connectivity of neurons and neuroplasticity. The various plant-derived glycosides along with their diversified mechanistic cognizance to exhibit antidepressant-like effects are shown in Table 2.

4.3. Alkaloids

Alkaloids, which are plant secondary metabolites that contain nitrogen in the heterocyclic ring, are known for their wide array of pharmacological activities, including anti-inflammatory, tranquillizer, and antiarthritic. Alkaloids such as harmine, nonharmine, and harmane are reported to exhibit anti-depressant activity (Fig. 3). Besides, harmine also reduces the serum level of ACTH. It has been reported that in animal models of depression, diterpene alkaloids isolated from Aconitum baicalense enhance serotonergic activity. Berberine, a vital plant alkaloid, has been reported to reduce the various symptoms of depression by acting on multiple pathways, including serotonergic, noradrenergic, dopaminergic, L-arginine-NO-cGMP, as well as δ opioid receptor pathway. Piperine isolated from piper longum has been reported to exhibit anti-depressant activity via repression of MAO enzymes, elevating brain 5-HT and BDNF levels, and regulating the HPA axis. The various plant-derived alkaloids along with their diversified mechanistic cognizance to exhibit antidepressant-like effects are shown in Table 3.

4.4. Terpenes

Terpenes are a class of phytochemicals that contain an isoprene unit as their basic unit and are widely known for their pharmacological activity, including antibacterial, antifungal, antiviral, anticancer, antimalarial, and anti-inflammatory. Some of the terpenes exhibit antidepressant activity involving dopamine D1 and D2 receptors without interacting with noradrenergic receptors. Some terpenes are known to show anti-depressant activity (Fig. 4) by raising the level of 5-HT and norepinephrine levels in the brain. Moreover, the BDNF/TrkB signalling pathway in the cortex region, κ-opioid and endocannabinoid receptors, and elevation of brain monoamine levels are other possible pathways by which terpenes are reported to exhibit anti-depressant activity. The various plant-derived terpenes, along with their diversified mechanistic cognizance to exhibit antidepressant-like effects, are shown in Table 4.
Table 2. Plant-derived glycosides against depression.

| Constituents                          | Type of Study | Cellular/Animal/Clinical | Description of Study along with Doses                                                                 | Mechanism                          | Refs. |
|---------------------------------------|---------------|--------------------------|-----------------------------------------------------------------------------------------------------|-----------------------------------|-------|
| Rotunduside G                         | FST, TST      |                          | At a dose of 50 mg/kg (i.g.), Rotunduside G shows the antidepressant effect                           | -                                 | [131] |
| Rotunduside H                         | FST, TST      |                          | At the dosage of 50 mg/kg (i.g)                                                                     | -                                 | [131] |
| Cyprotusides B                        | *In-vivo* depression models |          | Cyprotusides B displayed marked antidepressant activity in the despair mice models                 | -                                 | [132] |
| Cynanauriculoside C                   | *In-vivo* depression models |          | Exhibits antidepressant activity at the doses of 50 mg/kg (i.g)                                    | -                                 | [133] |
| Cynanauriculoside D                   | *In-vivo* depression models |          | Showed antidepressant activity at doses of 50 mg/kg (i.g) in comparison to fluoxetine (20 mg/kg)    | -                                 | [133] |
| Cynanauriculoside E                   | FST, TST      |                          | Exhibits significant antidepressant activity at the doses of 50 mg/kg (i.g)                         | -                                 | [133] |
| Otophylloside L                       | FST, TST      |                          | At 50 mg/kg doses, It shows its effect in FST and TST                                              | -                                 | [133] |
| Cynauricuoside C                      | FST, TST      |                          | At 50 mg/kg doses, it shows its effect in FST and TST                                              | -                                 | [133] |
| 3,4,5,6-tetrahydroxy-2-O-α-L-arabinosyl benzophenone | MOA Inhibition assay |       | The MAO-A inhibition by these compounds was 111.2 mM, which is comparable with clorgyline 0.5 mM. | Inhibition of MAO-A               | [134] |
| 3,4,5/-trihydroxy-6-methoxy-2-O-α-L-arabinosyl benzophenone | MOA Inhibition assay |       | The MAO-A inhibition by these compounds was 310.3 mM, which is comparable with clorgyline 0.5 mM. | Inhibition of MAO-A               | [134] |
| 3,4-dihydroxy-5-methoxy-2-O-α-L-arabinosyl-6-O-β-D-xylosyl benzophenone | MOA Inhibition assay |       | The MAO-A inhibition by these compounds was 726.0 mM, which is comparable with clorgyline 0.5 mM. | Inhibition of MAO-A               | [134] |
| Quercetin-3-O-α-L-arabinofuranoside   | MOA Inhibition assay |       | The MAO-A inhibition by these compounds was 534.1 mM, which is comparable with clorgyline 0.5 mM. | Inhibition of MAO-A               | [134] |
| Albiflorin                            | FST, TST      |                          | Reduction in immobility time in FST and TST at doses 3.5, 7.0 and 14.0 mg/kg                       | Upregulation of hippocampal BDNF expression | [135] |
| Paeoniflorin                          | CUMS          |                          | Decreased ACTH levels in the CUS-treated rats.                                                     | Upregulating Noradrenergic receptors | [136] |
| Rotunduside F                         | Despair mice models |          | At a dosage of 50 mg/kg, it shows antidepressant activity comparable to fluoxetine (20 mg/kg)      | Similar to fluoxetine (20 mg/kg)   | [137] |

(Fig. 2) Contd....
Fig. (2). Plant-derived glycosides against depression (26) Rotunduside G (27) Rotunduside H (28) Cyprotusides B (29) Cynanauriculoside C (30) Cynanauriculoside D (31) Cynanauriculoside E (32) Otophylloside L (33) Cynauricuoside C (34) 3',4,5',6-tetrahydroxy-2-O-α-L-arabinosyl benzophenone (35) 3',4,5'-trihydroxy-6-methoxy-2-O-α-L-arabinosyl benzophenone (36) 3,4-dihydroxy-5-methoxy-2-O-α-L-arabinosyl-6-O-β-D-xylosyl benzophenone (37) Quercetin-3-O-α-L-arabino furanoside (38) Albiflorin (39) paoniflorin.
Table 3. Plant-derived alkaloids against depression.

| Constituents       | Type of Study Cellular/Animal/ Clinical | Description of Study along with Doses | Mechanism                                                   | Refs. |
|--------------------|----------------------------------------|---------------------------------------|------------------------------------------------------------|-------|
| Antiepilepsirine   | FST, TST                               | Reduces the immobility time in both FST and TST, at doses 10-20 mg/kg | A decline in DA and 5-HT only                               | [138] |
| Berberine          | FST, TST                               | Berberine at a dose of (20 mg/kg, p.o.) elevates 5-HT levels in the frontal cortex and hippocampus | Suppression of MAO-A and B activity                        | [139] |
| Harmane            | FST                                    | Harmane reduces the time of immobility at doses 5-15 mg/kg, i.p. | Acting as Bzd inverse agonist                              | [140] |
| Harmine            | FST, UCMS                              | Harmane for seven days reverse anhedonia at doses 15 mg/kg | Acting as Bzd inverse agonist                              | [141] |
| Mitragynine        | FST, TST                               | Significantly reduce the immobility time at doses 10 mg/kg and 30 mg/kg i.p in FST and TST | Acting on HPA axis                                         | [142] |
| Neferine           | FST                                    | Compared to imipramine, elicited anti-immobility effects in mice at doses 25 to 100 mg/kg i.p | Acting on HT1a receptor                                    | [143] |
| Palmatine          | TST                                    | Compared to fluoxetine (10 mg/kg), it decreases immobility time in unstressed tail suspension test at doses 0.5 and 1 mg/kg | A decrease in MAO-A activity                               | [144] |
| Piperine           | FST, TST SCP                           | At doses 2.5, 5, and 10 mg/kg, it reverses plasma corticosterone level and open field activity | Elevating 5-HT but not NE and DA                           | [145] |
| Punarnavine        | FST                                    | At doses 20 and 40 mg/kg, it decreases immobility periods in a forced swim test | A decrease in MAO-A activity                               | [146] |
| Sanguinarine       | FST                                    | SA (2.5, 5, or 10 μg/0.5 μl per side) reduces immobility time in a dose-dependent manner | A decrease in expression of Mkp-1                          | [147] |
| Tetrandrine        | FST, TST SPT                           | Reduces immobility time in both the FST and TST | Increase in 5-HT and NE                                   | [148] |

Fig. (3). Plant-derived alkaloids against depression (41) Antiepilepsirine (42) Berberine (43) Harmane (44) Harmine (45) Mitragynine (46) Neferine (47) Palmatine (48) Piperine (49) Punarnavine (50) Sanguinarine (51) Tetrandrine.
### Table 4. Plant-derived terpenes against depression.

| Constituents   | Type of Study Cellular/Animal/Clinical | Description of Study along with Doses | Mechanism                                                                 | Refs. |
|----------------|---------------------------------------|--------------------------------------|---------------------------------------------------------------------------|-------|
| Podoandin      | TST and FST                           | Reduces the immobility time in FST at doses 10 mg/kg | Acting on HT₁a, 5-HT₁a, dopamine D₂ receptors                              | [149] |
| Cannabidiol    | TST and FST                           | At a dose of 30 mg.kg⁻¹, it induces dose-dependent antidepressant-like effects | Acting on 5-HT₁a receptor activation                                      | [150, 151] |
| Carvacrol      | FST                                   | Elevate dopamine and serotonin levels at doses 12.5 mg/kg | Action on dopamine D₁ and D₂ receptors                                     | [152, 153] |
| β-Caryophyllene| TST and FST                           | Mitigates the stress-related changes in the hippocampus region at doses 25, 50, 100 mg/kg | Action on cannabinoid receptor subtype 2                                   | [154, 155] |
| Genipin        | CUMS model                            | Elevates the levels of 5-HT, NE in CUMS-induced depressive rats | Elevates 5-HT and NE level                                                | [156] |
| Hyperforin     | *In-vivo* and *in-vitro* methods were employed | Enhancing BDNF expression in the frontal cortex | Acting on the BDNF/TrkB pathway in the cortex                            | [157] |
| Salvinorin A   | Chronic mild stress (CMS)             | Animals treated with Salv A 1 mg /kg reversed anhedonia | Involvement of κ-opioid and endocannabinoid receptors                    | [158] |
| Ursolic acid   | TST and FST in mice                   | Immobility time gets reduced in FST (10 mg/kg) and in TST (0.01 and 0.1 mg/kg) in comparison to fluoxetine 10 mg/kg | Dopamine D₁ and D₂ receptors                                              | [159, 160] |

![Fig. (4). Plant-derived terpenes against depression](image-url)

Table 5. Plant-derived saponins against depression.

| Constituents   | Type of Study Cellular/Animal/Clinical | Description of Study along with Doses | Mechanism                                                                 | Refs. |
|----------------|---------------------------------------|--------------------------------------|---------------------------------------------------------------------------|-------|
| Protopanaxadiol| CSDS-induced depression model         | PPD ameliorated behavioural alterations associated with CSDS-induced depression | Elevating 5-HT and NE levels                                              | [161, 162] |
| Hederagenin    | By *in-vitro* method in corticosterone-induced cytotoxicity on PC12 cells *In vivo* by TST and FST | Immobility time was reduced by HG (10 mg/kg) in TST after single administration after two consecutive weeks of administration | A decrease in Serum CRF and corticosterone                                  | [163, 164] |
| Sarsasapogenin | Evaluation of cholinergic signalling  | Treatment with sarsasapogenin alleviated abnormal cholinergic signalling | Decreases MAO-A and B activity                                              | [165, 166] |
| β-Amyrin palmitate| FST and TST                          | Reduction in immobility time of FST and TST model | Mechanisms involving MAO and GABA in the hippocampus.                     | [167] |

(Table 5) Contd....
### Constituents

| Constituents          | Type of Study Cellular/Animal/ Clinical | Description of Study along with Doses | Mechanism                                           | Refs.  |
|-----------------------|----------------------------------------|---------------------------------------|----------------------------------------------------|--------|
| Bacopaside I          | Shuttle-box escape test, FST, and TST  | Measuring the plasma level of corticosterone | MAO-A and MAO-B activity                           | [168]  |
| Ginsenoside RG I      | (CUMS)- model                          | Alleviation of the overexpression of proinflammatory cytokines | Suppression of Glial Activation                    | [169, 170] |
| Glycyrrhizin          | TST and FST                            | Reduce immobility time of mice in FST and TST model | Acting on α<sub>1</sub> adrenoceptor and dopamine D<sub>2</sub> receptor | [171]  |

### 4.5. Saponins

Saponins are a class of compounds known for their foaming ability due to their amphiphilic nature containing a hydrophilic glycone part (sugars/glycosides) and hydrophobic aglycone part (sapogenins). Based on structure, these are classified into steroidal and triterpenoid saponins exhibiting various pharmacological activities, including anti-inflammatory, antimicrobial, and cytotoxic activity. Recently, it has been reported that saponins (Fig. 5) impart a important role in the cure of clinical depression by modulating the various pathways involved in the onset of depression. The various plant-derived glycosides along with their diversified mechanistic cognizance to exhibit antidepressant-like effects are shown in Table 5.

### CONCLUSION

Depression is a growing psychiatric disorder globally and requires immediate medical attention. Though diverse phar-
macotherapeutics are used in treating depression, unfortunately, none of them seems to be felicitous. Strong evidence from different scientific studies support the idea of plant-derived phytochemicals that may offer newer therapeutic tools against depression due to multi-target effects, cost-effectiveness, easy availability, fewer side effects than synthetic prescription drugs. However, to assess the safety and potency of phytochemical with prospective antidepressant activities is also necessary. The current review discusses the available phytochemicals, including curcumin, Berberine, ginsenosides, and naringenin, amid the most studied isolated phytochemicals with antidepressant activity. Furthermore, clinical studies are also essential to confirm the efficacy and safety of these phytochemicals as natural antidepressants. Overall, these data underline the importance to test the tolerability and efficacy of natural products to ameliorate the symptoms or disease progression in depression in the context of controlled clinical trials.

LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|--------------|------------|
| UCMS         | Unpredictable Chronic Mild Stress |
| TST          | Tail Suspension Test |
| Wnt          | Wingless-related Integration Site |
| NMDA         | N-methyl-D-aspartate |
| PFC          | Prefrontal Cortex |
| SPT          | Sucrose Preference Test |
| mRNA         | Messenger RNA |
| NA           | Noradrenaline |
| MDD          | Major Depressive Disorder |
| 5-HIAA       | 5-Hydroxyindoleacetic Acid |
| H    | Propionic Acid Receptor |
| BDNF         | Brain-derived Neurotrophic Factor |
| CREB         | cAMP Response Element-binding protein |
| CSDD         | Chronic Social Defeat Stress |
| DISC1        | Disrupted in Schizophrenia 1 |
| DLV2         | Disheveled-2 |
| FST          | Forcet Swim Test |
| Fzd          | Frizzled Receptors |
| GSK          | Glycogen Synthase Kinase |
| 5HT          | 5-Hydroxytryptamine |
| MDD          | Major Depressive Disorder |
| mRNA         | Messenger RNA |
| NA           | Noradrenaline |
| NMDA         | N-methyl-D-aspartate |
| PFC          | Prefrontal Cortex |
| SPT          | Sucrose Preference Test |
| TST          | Tail Suspension Test |
| UCMS         | Unpredictable Chronic Mild Stress |
| Wnt          | Wingless-related Integration Site |

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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