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A LITERATURE REVIEW: THE POTENTIAL OF NATURAL INGREDIENTS AS ANTIDEPRESSANTS

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ABSTRACT

Changes in mood, physical well-being, and behavior, such as sleep and hunger patterns, psychomotor abilities, concentration, anhedonia, exhaustion, hopelessness, helplessness, and suicidal thoughts, define a mental illness known as depression. Alternative therapies that can be used to avoid these side effects include herbal medicines from several types of plants. This literature review aims to determine the potential of natural ingredients that have antidepressant activity in plant biomarkers, methods of obtaining biomarkers, effective dose, and their mechanisms of action. Article searches use keywords ("Herbal plant" OR "Medicinal plant" OR "Herbal" OR "Plant Extract" OR "Plant Extracts") AND ("Antidepressant" OR "Antidepressive") AND ("Mechanism of antidepressant") using the Science Direct, PubMed, and Google Scholar databases. The final results included eight research articles in the systematic review that met the inclusion criteria. Plants that have antidepressant potential include flowers of Viola odorata L, Crocus sativus, Impatiens glandulifera, and Leptadenia hastata (Pers.) and Alpinia zerumbet, seeds of Nigella sativa, root of Panax ginseng, and Achyranthes aspera.

***Keywords**: Antidepressants, Natural Ingredients, Literature Review*

INTRODUCTION

Changes in mood, physical well-being, and behavior, such as sleep and hunger patterns, psychomotor skills, concentration, anhedonia, exhaustion, hopelessness, helplessness, and suicidal thoughts, define a mental illness known as depression. Depression is a major global problem. Only 10% of individuals experience severe depression, whereas 90% of patients experience mild to moderate depression (Hellion *et al.*, 2016). Depression is a significant illness that affects approximately 13-20% of the world's population. Research has shown that women are at a greater risk of experiencing depressive disorders than men, with a percentage of 10-20% for women and 5-12% for men (Dubey *et al.*, 2020).

Depressive disorders cause a decrease in work productivity and disruptions in social relationships (Puspitasari, 2017). The neurotransmitters that can cause depressive disorders include norepinephrine, serotonin, and dopamine (Istriningsih, 2018). Several factors can trigger depression, including genetics, the environment, biochemistry, and psychology, but sometimes they appear for no apparent reason or trigger.

Antidepressant medications help reduce the symptoms of suffering. Selective Serotonin Reuptake Inhibitors (SSRI), Serotonin Norepinephrine Reuptake Inhibitors (SNRI), Tricyclic Antidepressants (TCA), and Monoamine Oxidase Inhibitors (MAOI) are common antidepressant medications. These medications can cause nausea, vomiting, tachycardia, dry mouth, orthostatic hypotension, urinary retention, impaired vision, constipation, and nausea. (Dipiro, 2015). Drug side effects may affect the patient's

quality of life. Patients' non-adherence to treatment may have resulted from these factors. Herbal medicines made from various plants are alternatives to conventional antidepressant medications. According to the WHO, natural goods represent the primary source of health care for 80% of people in underdeveloped countries (Ekor, 2014). Several preclinical studies have reported the antidepressant activity of various plants. Therefore, a literature review was conducted to determine the potential of natural ingredients with biomarker activity as antidepressants, the acquisition of biomarkers, the mechanisms of plant action, the effective doses of plants as antidepressants, and the antidepressant methods used.

RESEARCH METHOD

Tools and Materials

The literature search process used scientific databases, such as PubMed, ScienceDirect, and Google Scholar, from 2013 to 2022. Data searches used keywords ("Herbal plant" OR "Medicinal plant" OR "Herbal" OR "Plant Extracts" OR "Plant Extracts") AND ("Antidepressant" OR "Antidepressive") AND ("Mechanism of antidepressant")

Article Selection Criteria

The inclusion criterion was restricted article searches in 2013-2022 with open-access articles. The articles used were Randomized Controlled Trials (RCT) with experimental designs that explain biomarkers that have potential as antidepressants, biomarker acquisition, plant mechanism of action, the effective dose of the plant as an antidepressant, and the antidepressant method used. The exclusion criteria were non-open access articles, articles published in 2013, systematic review articles, literature review articles, and meta-analysis articles.

Research Procedure

Two authors reviewed the articles selected based on their title and abstract. An article search of the PubMed database yielded 1 article, 16 articles on the ScienceDirect database, and 441 articles on the Google Scholar database with exact keyword searches. The output of this study was 407. Article duplication in Microsoft Office Excel 2016 resulted in no duplications among the three databases. The following process was used to re-select the eligibility of the title and abstract for each article, and the final results included eight articles that met the inclusion criteria. The Mendeley Citation Manager is used to compile and export articles.

RESULT AND DISCUSSION

Literature Study Search Results

Initial identification in database searches in 2013-2022 obtained 458 articles, and 407 articles were not selected because they did not meet the criteria; thus, 34 articles were obtained. Thirty-four articles were reviewed based on the availability of the full text, title eligibility, and abstracts that met the relevance of the methodology and the results on animals. The final findings of the systematic review included eight research publications that satisfied the inclusion criteria. The names of the journals and publishers of each article include the International Phytotherapy and Neurochemistry Journals published by Elsevier, Dutse Journal of Pure and Applied Sciences published by African Journals, Pharmaceutical Biology Journal published by Taylor and Francis Group, Pharmacognosy and Natural Product Journal published by Pharmacognosy magazine, Drug Research Journal published by Thieme, Journal of Ginseng Research, and Journal of Traditional and Complementary Medicine published by Crossmark. **Figure 1** shows the scope of the selected journal, and **Figure 2** shows a flow chart of the data acquisition results.

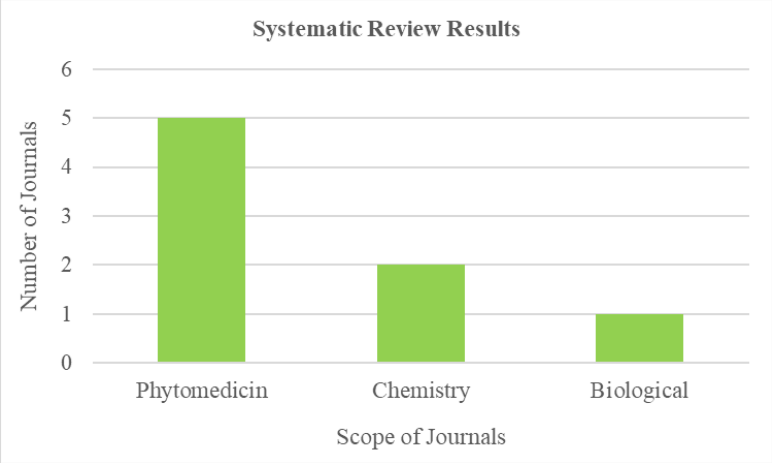

Figure 1. The Scope of Journals Selected as Reference

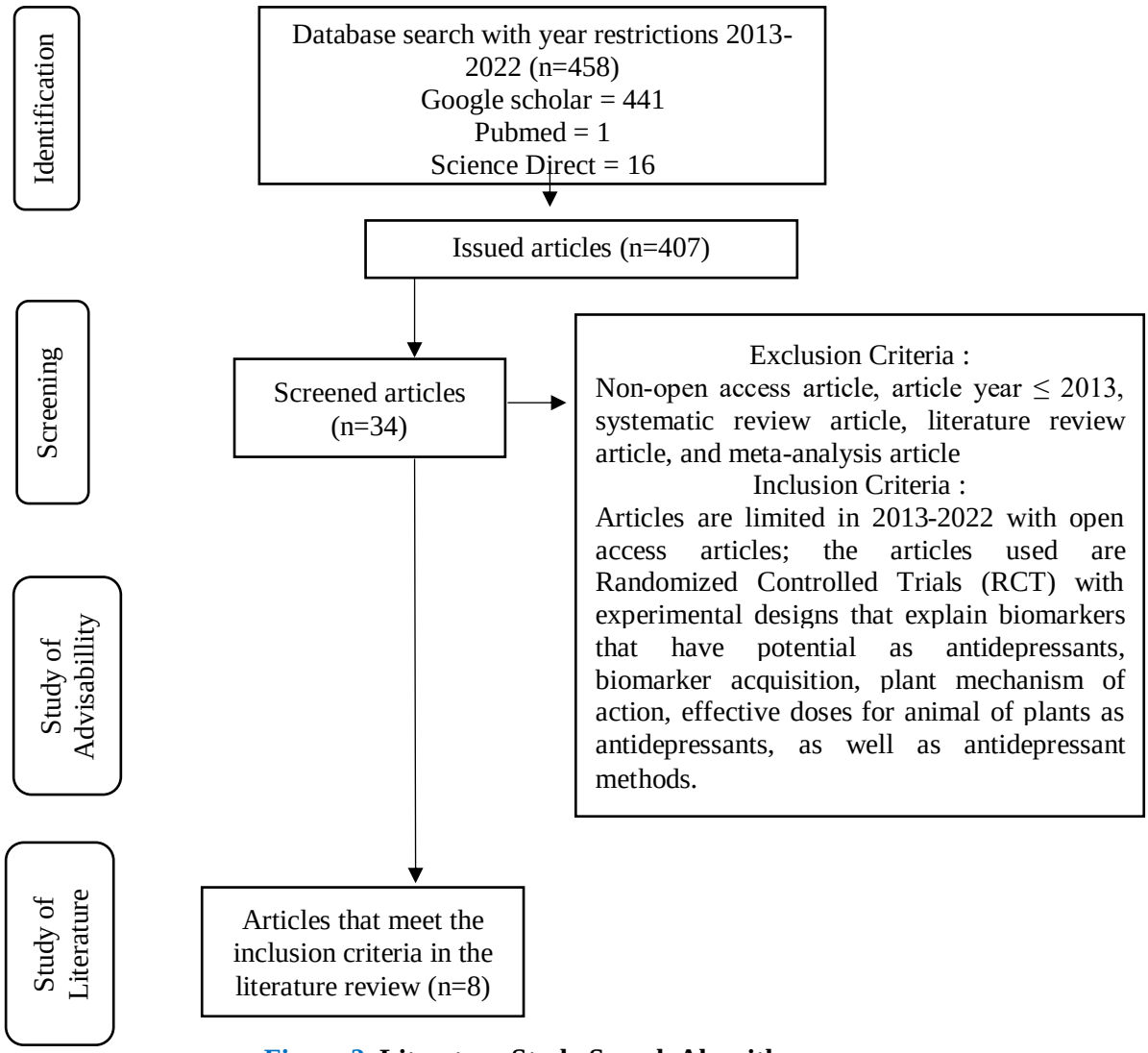

Figure 2. Literature Study Search Algorithm

The Potential of Plants as Antidepressants

Based on research results from the library, several plants have the potential as antidepressants, namely *Viola odorata* L, *Impatiens glandulifera*, *Leptadenia hastata* (Pers.), *Alpinia zerumbet*, *Nigella sativa*, *Crocus sativus*, *Panax ginseng*, and *Achyranthes aspera*.**Table I** shows plants that have antidepressant activity.

***Viola odorata* L.**

The Violaceae family includes *Viola odorata* L. In continental regions, the plant produces tiny fragrant flowers in late winter or early spring (March–April) (Fazeenah and Quamri, 2020). The plant leaves are crenate-bordered, robust, cordate, or approximately ovate in form. There are 930 species of *Viola odorata* L., also known as Sweet Violet, Gule-Banafsh, and English Violet. Areas that have these plants are South Asia, including Pakistan, India, China, Sri Lanka, Nepal, and Australia. *Viola odorata* L. is a member of the Plantae phylum, Violaceae family, Magnoliophyta division, Magnoliopsida class, Order: Violates, and the Genus: *Viola* (Singh and Dhariwal, 2018).

Furthermore, *Viola odorata* L. showed evidence of a reduction in body weight and an antidyslipidemic effect, possibly by blocking lipid metabolism and exhibiting antioxidant properties. This study also showed that the plant leaf extract exhibited antihypertensive characteristics by preventing the release of Ca^{2+} from intracellular storage, restricting the input of Ca^{2+} through membranous Ca^{2+} channels, and interfering with NO-mediated pathways. Furthermore, the injection of ethanolic and chloroform extracts of V. odorata prolongs sleep duration and produces pre-anesthetic effects that are considerably different from those of diazepam (Monadi and Rezaie, 2013). It has been demonstrated that intranasal administration of Viola odorata L. before bed for a month helps induce sleep and effectively treats insomnia.

Viola odorata syrup dosages of 15 mL·kg−1 have been shown to have dose-dependent inhibitory effects on the progression of dysplasia induced by the tongue (Helli *et al.*, 2016). In addition, Azari et al. investigated the antidiabetic properties of *Viola odorata* L. and found that in streptozotocin-induced diabetic rats, 400 mg·kg−1 doses of the aqueous extract and 100, 200, and 400 mg·kg−1 doses of the hydro-alcoholic extract may lower serum glucose levels (Azari *et al*., 2020). Shafei *et al*. (2018) found that the hydroalcoholic extract of *Viola odorata* L. exhibited antidepressant effects akin to those of fluoxetine, maybe due to an elevation in serotonergic activity.

A part of the plant used as an antidepressant is the flower (**Figure 3**). Dried flowers were ground and extracted using 70% methanol within 3 × 24 hours. The methanol extract was evaporated by rotary vacuum evaporation. The methanol extract was dissolved in methanol and water (1:1), and chloroform and water were added at a 1:1 ratio. The resulting chloroform was separated by silica gel column chromatography with elution starting from chloroform. The polarity was gradually increased with methanol until the eluent was 100% methanol, producing 5 fractions. The fraction was then separated again using silica column chromatography with 20% ethyl acetate-hexane solvent to produce the compounds 5,7-Dihydroxy-3,6-dimethoxyflavone 5,7,4'-trihydroxy-3',5'dimethoxyflavone and 5,7,4′-trihydroxy-3′-methoxy flavone (Karim, *et al*, 2018).

The isolate from the flower of *Viola odorata* L. has antidepressant potential, as demonstrated by the decrease in immobility time in male Swiss strain mice administered doses of 10 and 30 mg/kg BW (i.p.) compared with the positive control. The FST and TST results were not significantly affected by fluoxetine at 20 mg/kg BW (i.p.). In comparison, the standard control displayed outcomes that were noticeably different from those of the negative controls. Additionally, the Open Field Test (OFT) is a technique for assessing antidepressant action. In the criteria of lack of influence on ambulation and frequency of rearing, the results of the OFT demonstrated a significant decrease in motor stimulation. The OFT evaluates exploratory behavior, anxiety levels, and motor activity (Karim *et al*., 2018).

Table I. Search Results of Several Libraries on the Potential of Plants as Antidepressants

No	Plants Name	Used part(s)	Chemical Compound	Animal Test	Antidepressant Test Method	Effective Dose	References
1.	*Viola odorata* L	Flower	5,7-Dihydroxy-3,6-dimethoxyflavone 5,7,4′-trihydroxy-3′,5’dimethoxyflavone and 5,7,4′-trihydroxy-3′-methoxyflavone	Swiss strain male mice	TST, OFT, FST	10 mg and 30 mg/kgBW i.p	(Karim *et al.*, 2018)
2.	*Impatiens glandulifera*	Flower	Hyperoside (HYP), Protocatechuic acid (PCA)	Swiss strain male mice	FST, TST	1.875 and 15 mg/kgBW i.p	(Orzelska-Gorka *et al.*, 2019)
3.	*Leptadenia hastata (Pers.)*	Leaf	Alkaloids, flavonoids	Swiss strain male mice	TST, OFT	250 mg/kgBW i.p	(Sani *et al.*, 2022)
4.	*Alpinia zerumbet*	Leaf	Rutin, kaempferol-3-O-glucoronide	Swiss strain male mice	TST	800 mg/kgBW p.o	(Bevilaqua *et al.*, 2016)
5.	*Nigella sativa*	Seed	Tauroside E, Sapindoside B, Quercetin-3-O-L-rhamnopyranoside, Quercetin-7-O-b-D-glucopyaranoside	Swiss strain male mice	OFT, TST, FST	100 mg/kgBW p.o	(Elkhayat *et al.*, 2016)
6.	*Crocus sativus*	Flower	Crocin	Wistar strain male rat	FST	40 mg/kgBW i.p	(Ghasemi *et al.*, 2015)
7.	*Panax ginseng*	Root	Resveratrol, Ginseng total saponins, Ginsenoside	Swiss strain male mice	FST, TST	150 mg/kgBW p.o	(Choi *et al.*, 2018)
8.	*Achyranthes aspera*	Root	Phenols, Alkaloids, Flavonoids, Glycosides, Amino Acids	Swiss strain male mice	FST, OFT, dan Splash Test	2.5 mg/kgBW i.p	(Gawande *et al.*, 2022)

TST : Tail Suspension Test; FST : Forced Swimming Test; OFT : Open Field Test
i.p. : intraperitonial; p.o : per oral

Figure 3. *Viola odorata L's* Flower (Dhimana, S., et al, 2023)

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***Impatiens* sp.**

In the Old World, primarily in tropical Africa, India, the southwestern region of Asia, and southern China, *Impatiens* L. species are found in tropical and subtropical climate zones. North America, Russia, Northern Europe, and Japan are also home to a few species (Szewczyk *et al.*, 2018). Several plants in the genus *Impatiens* L. have long been utilized in Asian and American medicine. *Impatiens glandulifera* is a species of balsam belonging to the family Balsaminaceae, specifically in the genus Impatiens. There are only two genera in this family: Hydrocera Blume (one species) and *Impatiens* L. (approximately 900 species). Formerly, the family Balsaminaceae was either categorized as a member of Geraniales or recognized as a separate order, Balsaminales. According to recent molecular phylogenetic investigations, Balsaminaceae is a sister group to all other Balsaminoid species, and presently encompasses 22 families in the APG IV classification. There are now five resolved synonyms of *Impatiens glandulifera* mentioned in the Plant List: *Impatiens macrochila* L., *Impatiens roylei*, *Balsamina glandulifera* (Royle) Ser., *Balsamina macrochila* (Lindl.) Ser., and *Balsamina roylei* (Walp.) Ser (Helsen *et al.*, 2021).

This plant can be used as an antibacterial, antioxidant, analgesic, anticytotoxic, antidepressant, antinoceptive, and anxiolytic agent (Pires *et al.*, 2021). Its polyphenol family, hyperoside (HYP), and Protocatechuic Acid (PCA), are obtained from *Impatiens glandulifera* flowers (**Figure 4**). Using Spontaneous Locomotor effect (SLA), FST, and TST techniques, it has been demonstrated that this isolate possesses antidepressant properties. Swiss strain mice were used in the FST to examine the effects of antidepressants on the monoaminergic system. Significantly less time spent immobile was observed in the FST test on HYP and PCA at a dose of 1.875 mg/kg BW (i.p.) compared to normal saline controls (p 0.05). In comparison to fluoxetine, 15 mg/kg BW (i.p.) in the TST, HYP, and PCA at a dose of 1.875 mg/kg BW (i.p.) substantially shortened the immobility period (p 0.05). The SLA test revealed that, compared to the saline group, HYP and PCA at a dose of 15 mg/kg BW (i.p.) considerably reduced the distance walked (p 0.001) (Orzelska-Gorka *et al.*, 2019). The SLA test measures the distance walked by mice to confirm changes in the immobility time in the FST and TST (Fiorino *et al.*, 2017).

Figure 4. *Impatiens glandulifera* Flowers (Helsen et al, 2021)

Hyperoside (HYP) and protocatechuic acid (PCA) compounds were obtained by extracting *Impatiens glandulifera* with 50% ethanol by the reflux method for 3 hours, followed by sonication with a mixture of ethanol-acetone-water (3:1:1, v/v/v) at a controlled temperature (40 ± 2°C) for 30 minutes. The extract was evaporated and redissolved in hot distilled water (1000 mL) and partitioned with chloroform-ethyl acetate-n-butanol (2:2:1). Thus, a fraction was produced. The methanol–water fraction (40:60, v/v) was rechromatographed on a Sephadex LH-20 column eluted with a mixture of MeOH–H2O (60:40 to 100:0, v/v in 4 steps). The methanol-water (50:50, v/v) fraction (3.08 g) was subjected to preparative HPLC (A: 0.1% HCOOH in H2O, B: 0.1% HCOOH in MeCN, flow 20 ml/min, temperature column 25 °C, detection 280 nm, gradient 0 min–6%B, 50 min−23%B) to produce protocatechuic acid and hyperoside.

***Leptadenia hastata* (Pers.)**

Plants of the *Asclepiadaceae* family include *Leptadenia hastata* (Pers.). *Leptadenia hastata* can be found in African countries. It has been empirically demonstrated that *L. hastata* leaf extract can be used to treat onchocerciasis, hypertension, catarrh, skin conditions and wounds, trypanosomiasis, and other skin illnesses. Additionally, *L. hastata* (**Figure 5**) possesses an antibacterial pharmacological action (Haruna *et al.*, 2017). Male Swiss strain mice were tested for antidepressant efficacy using the TST and OFT techniques on a methanol extract of *Leptadenia hastata* (Pers.) leaves. The findings of a reduction in immobility time at a dose of 250 mg/kg BW (i.p.) with imipramine at 10 mg/kg BW in the TST test were not substantially different ($p>0.05$). The number of squares crossed parameter did not substantially differ between the control group and the OFT test dose of 250 mg/kgBW (i.p.) Phytochemical compounds that have antidepressant activity in this plant are flavonoids and alkaloids.The method used to make methanol extract of *Leptania hastata* leaves is soxhletation. Simplicia is dried and crushed using a mortar and pestle. Approximately 1000 g of crushed leaves was extracted with 3.5 L of methanol. The resulting extract was then dried in a water bath at 45°C (Sani *et al.*, 2022).

Figure 5. ***Leptania hastata*** **Leaves**

Alpinia zerumbet

Alpinia zerumbet (**Figure 6**) is a traditional plant in Brazil that has potential as an antidepressant, antipsychotic, and anxiolytic agent. This plant is used worldwide to treat rheumatism and digestive disorders and has carminative, diuretic, stomachic, sedative, and antihypertensive properties (Cruz *et al.*, 2020). The ethanol extract of *Alpinia zerumbet* leaves contained secondary metabolites in the form of rutin and kaempferol-3-O-glucoronide. According to the TST test, this substance displayed antidepressant efficacy at 800 mg/kg BW (p.o.) when administered to male Swiss strain mice. According to the TST test procedure, the reduction in immobility time caused by the *Alpinia zerumbet* extract was significant at p 0.01 compared to the conventional saline control (Bevilaqua *et al.*, 2016).

Figure 6. ***Alpinia zerumbet*** **Plant (Chan et al, 2017)**

A. zerumbet leaves were powdered (425 mm; 35 Tyler/Mesh) and dried at room temperature. Powdered leaves (500 g) were extracted by percolation with 70% (v/v) EtOH (17 L), followed by evaporation under low pressure and lyophilization (38.2% yield). The Foline-Ciocalteu method was used to quantify the total phenolic content.17, 18 Briefly, 1 ml of 10-fold-diluted FolineCiocalteu reagent was mixed with 100 mL of extract HEA (hydroethanolic extract of *Alpinia zerumbet*) solution. The mixture was stirred and then left to stand at room temperature for 5 minutes. After adding 1 ml of 10% (w/v) Na2CO3, the mixture was left in the dark for 90 minutes. At 725 nm, the absorbance of the blue product was determined and compared to that the of blank sample. This revealed the ability of phenolic compounds to diminish Folin-Ciocalteu in an alkaline medium. Gallic acid equivalents (mg GAE/g dry weight) were used to determine the total phenolic content. Values were computed using the means of three separate trials (Roman *et al.*, 2013).

Nigella sativa

Nigella sativa (**Figure 7**), also known as black cumin, originates from Asia. As an annual herbaceous plant, *N. sativa* is a member of the Ranunculaceae family and is primarily found in southern Europe and in certain regions of Asia, such as Syria, Turkey, Saudi Arabia, Pakistan, and India. With five–ten petals, the flowers are exquisite and mostly white, yellow, pink, light blue, or lavender. This plant produces large, inflated capsule-shaped fruits that are filled with many black seeds that taste bitter and fragrant. The best season for cultivating *N. sativa* is often from November to April, and the germination process takes approximately 10 to 15 days. Plants typically flower and fruit between January and April (Kooti *et al.*, 2016).

Many studies have been conducted on the biological activities and restorative potential of *Nigella sativa*, and the plant has been shown to possess a variety of properties, including calming, spasmolytic, bronchodilator, anti-inflammatory, anti-tussive, gastroprotective, hepatoprotective, low-density lipoprotein cholesterol decreasing, renal-protective, antioxidant, immunomodulatory, antimicrobial, and analgesic properties. *Nigella sativa* seeds are commonly used in traditional medicine to treat various ailments, including obesity, rheumatoid arthritis, back pain, hypertension, gastrointestinal issues, bronchitis, asthma, heart diseases, sexually transmitted infections, diarrhea, and respiratory conditions (Beheshti, 2016).

Figure 7. *Nigella sativa* Plant (Kooti et al, 2016)

Nigella sativa seeds were used to separate and characterize possible antidepressant components. To obtain the polar extract, 300 g of N. sativa seeds was crushed into a fine powder, extracted using chloroform, dried, and then extracted again using 70% MeOH (3 L × 1 L) at room temperature until exhaustion. After filtering and evaporating the combined methanol extract under reduced pressure, a dark brown oily residue of the polar extract was obtained. The antidepressant-like properties of the extract were validated by tail suspension test (TST) and forced swimming test (FST) preliminary experiments. Subsequently, the dried extract was separated using an RP-18 column by eluting it successively with H2O, H2O/MeOH (8:2, 1:1, 3:7), and then 100% MeOH. This resulted in five fractions, N1–5. TLC analysis showed that the compositions of N1 and 2 were similar; therefore, N1 and 2 were combined into one fraction, called N-1. Initial FST and TST antidepressant assays showed that only fractions N-3 and N-4 exhibited antidepressant-like effects. Two types of isolates were obtained: tauroside E, sapindoside B, and Quercetin-7-O-b-D-glucopyranoside (Elkhayat *et al.*, 2016).

Identification of isolates from *Nigella sativa* seeds using the NMR-Analysis instrument and the results indicated that the isolates contained Quercetin-7-O-b-D-glucopyranoside, Tauroside E, and Sapindoside B, which are all forms of quercetin that acts as an antidepressant. This was demonstrated by the OFT, TST, and FST methods. TST and FST tests showed that black cumin isolates at 100 mg/kg BW (p. o.) had an antidepressant effect on male Swiss strain mice. The reduced immobility time compared with sertraline 5 mg/kg

BW (p. o.) indicates that this approach is practical. The immobility time was decreased by 28.3%, 33.8%, 22.5 %, and 31.3%, respectively, in the TST and FST tests. The effect of the OFT method on the number of crossings and rearing characteristics on changes in locomotor activity was unaffected by administration of 100 mg/kg BW (p.o) (Elkhayat *et al.*, 2016).

***Crocus sativus* L**

The most significant plant in the genus *Crocus* is *Crocus sativus* L., and much research has been conducted on its various pharmacological properties. This plant is widely grown throughout Iran, Morocco, Afghanistan, India, Greece, Italy, and Spain, and its annual global production is estimated to be 418 tons (Cardone *et al.*, 2020). The genus *Crocus*, particularly *C. sativus*, has therapeutic properties that are used to treat gastrointestinal, ophthalmic, cardiovascular, and respiratory disorders as well as cancer (Mohtashami *et al.*, 2021).

Figure 8. *Crocus sativus* Plant (Mollazadeh, 2015)

Saffron and *Crocus sativus* are two widely used spices. Saffron is a plant that belongs to the Iridaceae tribe. The traditional treatment for depression can use saffron plants on the flower parts. The maceration process produced aqueous extracts of C. sativus. Briefly, 8 g of stigma powder was continuously shaken for 72 hours and macerated in 300 mL of distilled water in a refrigerator. Centrifugation was followed by a 24-hour freeze-drying of the supernatant. Saffron water extract at a dose of 40 mg/kg BW (i.p.) was shown in a study by Ghasemi et al. (2015) to considerably shorten immobility time in the FST compared to imipramine at a dose of 10 mg/kg BW (i.p.). The FST results showed that saffron extract reduced immobility time, thereby significantly increasing BDNF, CREB, and p-CREB protein levels in male Wistar rats. Western blot analysis showed that the VGF protein levels in the hippocampus were not significantly increased.

Panax ginseng

In East Asia, including Korea, China, and Japan, *Panax ginseng* (**Figure 9**) has been used for more than 2,000 years as a traditional herbal remedy. The primary ginsenoside metabolite produced by gut bacteria, a ginsenoside compound, possesses a variety of pharmacological properties, including anti-inflammatory, hepatoprotective, antidiabetic, anticancer, and possibly health-promoting effects. Apart from the previously mentioned role, the neuronal functions of ginsenoside metabolite compound K, including enhancement of cognition, neuroprotection, and neurotransmission modulation, have garnered increasing attention in recent times. Despite the powerful neuroprotective effects of the ginsenoside metabolite compound K, there is relatively limited data suggesting an antidepressant effect in menopausal mice (Song *et al.*, 2018).

Figure 9. *Panax ginseng* Plant (Lee et al., 2020)

The *Panax ginseng* plant, especially its roots, exhibits antidepressant activity. Giving *Panax ginseng* aqueous extract for 14 days can improve the condition of mice induced by chronic stress by minimizing the amount of time spent stationary in the FST and TST tests. *Panax ginseng* extract dose of 150 mg/kgBW (p.o) can significantly reduce immobility time in the FST test within 50.3 ± 9.1 seconds compared to the negative control at 29.9 ± 5.8 seconds. In contrast, the TST test can reduce immobility time by 97.5 ± 7.1 seconds compared to the negative control at 76.2 ± 4.9 seconds (Choi *et al.*, 2018).

Three hours were spent extracting 5 grams of ginseng powder at 100 °C and 60 °C using 150 mL of extraction solvents and ginseng powder, respectively. The solid residue was extracted again under identical conditions after the slurry was filtered. A rotating evaporator was used to gather, extract, and evaporate each extract after extraction. The extracted samples were weighed and stored at -20 °C. Finally, the extracts were transferred to tubes for freeze-drying and lyophilization (Zhang *et al.*, 2018).

Achyranthes aspera

Achyranthes aspera is a typical plant used in herbal medicine in India (**Figure 10**). The FST, OFT, and Splast Tests on Swiss strain mice demonstrated the antidepressant effect of the methanol extract of *Achyranthes aspera* root. Additionally, antibacterial, antifungal, thyroid-stimulating, antiperoxidative, anti-inflammatory, anti-arthritic, immunomodulatory, wound-healing, anti-obesity, anticonvulsant, anticancer, and hepatoprotective properties have been found in *A. aspera* through biological investigations. Numerous phytochemicals have been identified in this plant, including terpenoids, alkaloids, flavonoids, phenolic compounds, and saponins (Sinan *et al.*, 2020).

The findings demonstrated that, in comparison to fluoxetine at a dose of 10 mg/kg BW (i.p.), the extract considerably decreased the time that mice remained immobile during the FST at an adequate amount of 2.5 mg/kgBW (i.p.). Antidepressant activity was assessed using the OFT and Splast Test. In studies using the OFT technique, *Achyranthes aspera* extract was administered at a dose of 2.5 mg/kgBW (i.p.). Neither ambulation nor rearing parameters showed any change in locomotor activity. *A. aspera* extract 2.5 mg/kgBW, and fluoxetine (10 mg/kg BW) significantly differed in the grooming latency parameter for 14 days based on antidepressant effectiveness in the Splash Test. Grooming behavior, as an indicator of depressive symptoms in mice, was measured using two methods. Grooming refers to the number of activities carried out by mice as an indication of concern for personal hygiene (self-care) (Gawande *et al.*, 2022).

Figure 10. *Achyranthes aspera* Plant (Somagari et al., 2014)

Using a grinder, the roots were ground into a fine powder after cleaning with tap water, shade-dried at room temperature, and sieved through a mesh number of 40. In addition, 2000 ml of methanol was macerated with 200 g of powdered *A. aspera* roots for three days with periodic shaking. A consistent time interval was maintained while collecting the menstruum in nine identical batches. Using a rotating vacuum evaporator set to low pressure and 60 °C, it was mixed and filtered, and the solvent was evaporated. A refrigerator was used to maintain the concentrated extract after it had been lyophilized (Gawande *et al.*, 2022).

Mechanisms of Action of Plant Antidepressants

Antidepressant traditional medicine, derived from several plants, is an alternative therapy to avoid side effects. Allegedly, the content of secondary metabolites or single compounds originates from plant parts such as flowers, leaves, roots, and seeds, and can even be found in all parts of the plant. **Table II** shows the plants suspected of having chemical compounds and the mechanisms of antidepressant activity.

The main chemical constituents with potential antidepressant effects are depicted in the structures. The flavonoid group is known to affect 5-HT receptor BDNF levels, increase nerve growth, inhibit certain enzyme activities, modulate calcium and potassium ion channels, maintain brain plasticity, and prevent the dissipation of mitochondrial membrane potential (Karim *et al.*, 2018). Polyphenols can modulate monoamine levels in the brain by inhibiting neurons, stimulating hydroxylase or tyrosine hydroxylase, and inhibiting monoamine oxidase (MAO). PCA and HYP are single compounds from the polyphenol group with antidepressant activity that activates the D2 receptors. In vitro screening tests have shown that PCA significantly inhibits MAO-A, MAO-B, and dopamine-β hydroxylase (DBH) (Orzelska-Gorka *et al.*, 2019). Rutin compounds, kaempferol-3-O-glucoronide, and crocin also have the exact antidepressant mechanism of action of polyphenols, which work by inhibiting monoamine oxidase (MAO) (Sani *et al.*, 2022). The antidepressant action of quercetin involves preventing the absorption of norepinephrine, serotonin, and dopamine receptors, while raising the levels of norepinephrine and 5-hydroxytryptamine (S-HT) in the brain (Elkhayat *et al.*, 2016).

Resveratrol, Ginseng total saponins, and ginsenosides in *Panax ginseng* extract have a mechanism of action that can block increased serum ACTH and corticosterone concentrations, increase Nrf2 and HO-1 activity, and inhibit inflammatory activity (COX-2) in the amygdala, thereby increasing BDNF activity (Choi *et al.*, 2018). BDNF is a neurotrophin with Tropomyosin Receptor Kinase B (TrkB). The hippocampus, hypothalamus, and cortex are the three brain regions that express BDNF because of their high levels of plasticity. Another function of BDNF is to modulate the changes in neuronal activity-driven expression and synaptic transmission. BDNF supports the development of new neurons in the central nervous system, promotes synaptogenesis, aids neurogenesis, and protects neural stem cells (NSC) and neural precursor cells (NPC). It also aids in the growth and differentiation of neurons. If stress and the stress hormone corticosterone are continuously present, BDNF expression will decline, and if this process continues, hippocampus shrinkage will result (Pansri *et al.*, 2021).

Table II. Chemical Compounds and Mechanism of Action of Antidepressants

No	Plant Name	Mechanism of Action	Reference(s)
1.	*Viola odorata* L	5-HT receptor antagonists	(Karim *et al.*, 2018)
2.	*Impatiens glandulifera*	Modulate monoamine levels in the brain via hydroxylase or monoamine oxidase (MAO) inhibition.	(Orzelska-Gorka *et al.*, 2019)
3.	*Leptadenia hastata (Pers.)*	Antagonists of the opioidergic, muscarinic, serotonergic, dopaminergic, and adrenergic receptors.	(Sani *et al.*, 2022)
4.	*Alpinia zerumbet*	Monoamine oxidase (MAO) inhibition	(Bevilaqua *et al.*, 2016)
5.	*Nigella sativa*	It raises 5-hydroxytryptamine and norepinephrine levels in the brain while decreasing norepinephrine, serotonin, and dopamine absorption.	(Elkhayat *et al.*, 2016)
6.	*Crocus sativus*	MAO-A and MAO-B non-competitive inhibitors	(Ghasemi *et al.*, 2015)
7.	*Panax ginseng*	Increases Nrf2 and HO-1 activity and increases BDNF activity	(Choi *et al.*, 2018)
8.	*Achyranthes aspera*	Increases BDNF in the prefrontal cortex and hippocampus.	(Gawande *et al.*, 2022)

CONCLUSION

Considering the outcomes of a literature search, the plants *Viola odorata* L, *Impatiens glandulifera*, *Leptadenia hastata* (Pers.), *Alpinia zerumbet*, *Nigella sativa*, *Crocus sativus*, *Panax ginseng*, and *Achyranthes aspera* have antidepressant activity. The alleged compounds that have antidepressant activity are compounds belonging to the class of flavonoids, alkaloids, polyphenols, saponins, amino acids, and glycosides. *Leptadenia hastata* (Pers.) and *Achyranthes aspera* have no known active compounds that act as antidepressants; therefore, further research is required.

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