International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319-6718, ISSN (Print): 2319- 670X
www.ijpsi.org Volume 12 Issue 4 ǁ Jul. –Aug. 2023 ǁ PP. 06-10

A Literature Review: The Potential of Natural Ingredients for Antidepressants

Ranatri Puruhita[1*], Arifah Sri Wahyuni[2], Andi Suhendi[3]
[1](*Master of Pharmacy, Postgraduated School, Muhammadiyah University of Surakarta, Surakarta, Indonesia)*
[2](*Faculty of Phramacy, Muhammadiyah University of Surakarta, Surakarta, Indonesia)*
[3](*Faculty of Phramacy, Muhammadiyah University of Surakarta, Surakarta, Indonesia)*

ABSTRACT: *Changes in mood, physical well-being, and behavior, such as sleep and hunger patterns, psychomotor skills, concentration, anhedonia, exhaustion, hopelessness and helplessness, and suicidal thoughts, define a mental illness known as depression. Alternative therapies that can use to avoid these side effects are herbal medicines from several types of plants. This literature review aims to determine the potential of natural ingredients that have activity as antidepressants 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 were eight research articles in the systematic review that met the inclusion criteria. Plants that have antidepressant potential are Viola odorata L, Impatiens glandulifera, Leptadenia hastata (Pers.), Alpinia zerumbet, Nigella sativa, Crocus sativus, Panax ginseng, and Achyranthes aspera.*

KEYWORDS - *Antidepressants, Literature Review, Natural Ingredients*

Date of Submission: 20-06-2023 Date of acceptance: 03-07-2023

I. INTRODUCTION

Changes in mood, physical well-being, and behavior, such as sleep and hunger patterns, psychomotor skills, concentration, anhedonia, exhaustion, hopelessness and helplessness, and suicidal thoughts, define a mental illness known as depression. Depression is a substantial problem worldwide. Only 10% of individuals experience severe depression, while 90% of patients experience mild to moderate depression [1]. *Depression* is a significant illness that affects around 13-20% of the world's population. Based on research, women are at greater risk of experiencing depressive disorders than men, with a percentage of 10-20% for women and 5-12% for men [2].

Depressive disorders cause a decrease in work productivity and disruption in social relations [3]. Neurotransmitters that can cause depressive disorders are norepinephrine, serotonin, and dopamine (Istriningsih, 2018). Several factors can trigger depression, including genetics, environment, biochemistry, and psychology, but sometimes they appear for no apparent reason or trigger.

Antidepressant medications help lessen the patient's 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, urine retention, impaired vision, constipation, and nausea. [5]. Drug side effects may impact the patient's quality of life. Patient non-adherence to treatment may result from them. An alternative to conventional antidepressant medication is herbal medicine made from various plants. According to WHO, natural goods represent the primary source of healthcare for 80% of people in underdeveloped countries [6]. Several preclinical studies have reported the antidepressant activity of various plants. Therefore a literature review was carried out to know the potential of natural ingredients that have 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.

II. RESEARCH METHOD

1.1 Tools and Materials

The literature search process using 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")

1.2 Article Selection Criteria

The inclusion criteria were restricted article searches in 2013-2022 with open-access articles. The articles used were Randomized Controlled Trials (RCT) with experimental designs that explained 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. Exclusion criteria in this study were non-open access articles, article year ≤ 2013, systematic review articles, literature review articles, and meta-analysis articles.

1.3 Research Procedure

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

III. RESULT AND DISCUSSION

Initial identification in database searches in 2013-2022 obtained 458 articles, and 407 articles were not selected because they did not meet the criteria, so 34 articles were obtained. Thirty-four articles were reviewed based on the availability of full text, title eligibility, and abstracts that met the inclusion criteria. The systematic review's final findings included eight research publications that satisfied the inclusion criteria. Figure 1 shows the flow chart of data acquisition results.

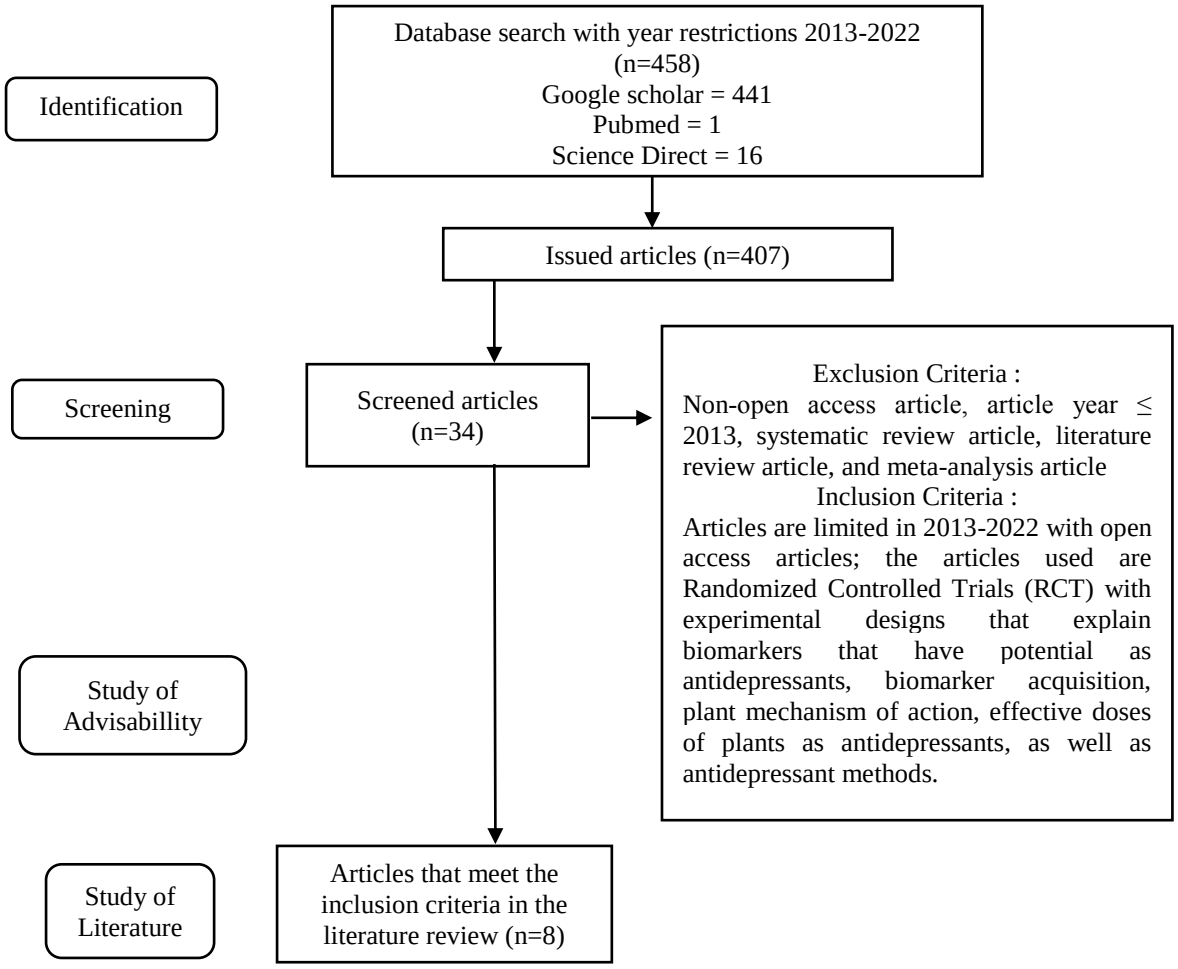

Figure 1. Literature Study Search Results

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, Saffron, Nigella sativa, Crocus sativus, Panax ginseng, and Achyranthes aspera. Table 1. shows plants that have antidepressant activity.

Table 1. Search Results of Several Libraries on the Potential of Plants as Antidepressants

No	Plant Name	Plant Section	Test Material	Animal Test	Antidepressant Test Method	Effective Dose	References
1.	*Viola odorata* L	Flower	Isolate	Swiss strain male mice	TST, OFT, dan FST	10 mg and 30 mg/KgBW i.p	[7]
2.	*Impatiens glandulifera*	Flower	Isolate	Swiss strain male mice	SLA, FST, dan TST	1.875 and 15 mg/KgBW i.p	[8]
3.	*Leptadenia hastata (Pers.)*	Leaf	Methanol Extract	Swiss strain male mice	TST dan OFT	250 mg/KgBW i.p	[9]
4.	*Alpinia zerumbet*	Leaf	Methanol Extract	Swiss strain male mice	TST	800 mg/KgBW p.o	[10]
5.	*Nigella sativa*	Seed	Isolate	Swiss strain male mice	OFT, TST, dan FST	100 mg/KgBW p.o	[11]
6.	*Crocus sativus*	Flower	Aquous Extract	Wistar strain male rat	FST	40 mg/KgBW i.p	[12]
7.	*Panax ginseng*	Root	Aquous Extract	Swiss strain male mice	FST dan TST	150 mg/KgBW p.o	[13]
8.	*Achyranthes aspera*	Root	Methanol Extract	Swiss strain male mice	FST, OFT, dan Splash Test	2.5 mg/KgBW i.p	[14]

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. 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 given doses of 10 and 30 mg/kg BW (i.p.) compared to the positive control.. The FST and TST test methods were not significantly affected by fluoxetine 20 mg/Kg BW (i.p.). The standard control, in comparison, displayed outcomes that were noticeably different from the negative control. Additionally, the Open Field Test (OFT) is a technique for antidepressant action. In the criteria of lack of influence on ambulation and frequency of rearing, the results of the OFT demonstrate a significant decrease in motor stimulation. The OFT test evaluates exploratory behavior, anxiety levels, and motor activity [7].

Its polyphenol family, Hyperoside (HYP) and Protocatechuic Acid (PCA), they are taken from *Impatiens glandulifera* flowers. Using the 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 approach to examine how antidepressants affected the monoaminergic system. Significantly less time spent immobile was seen in the FST test on HYP and PCA at a dose of 1.875 mg/kgBW (i.p.) compared to normal saline controls (p 0.05). In comparison to fluoxetine, 15 mg/KgBW (i.p.) in the TST test, HYP and PCA at a dose of 1.875 mg/KgBW (i.p.) substantially shorter immobility period (p 0.05). The SLA test revealed that compared to the saline group, HYP and PCA at a dose of 15 mg/KgBB (i.p.) considerably reduced the distance walked (p 0.001) [8]. The SLA test measures the distance walked by mice to confirm changes in immobility time in FST and TST [15].

Plants in the *Asclepiadaceae* family include *Leptadenia hastata* (Pers.). It finds in there. 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/kgBW (i.p.) with imipramine 10 mg/kgBW 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/KgBB (i.p.) [9].

Alpinia zerumbet is a traditional plant in Brazil that has the potential as an antidepressant, antipsychotic, and anxiolytic empirically. The ethanol extract of *Alpinia zerumbet* leaves contains secondary metabolites in the form of flavonoids. According to the TST test, this substance displays antidepressant efficacy at 800 mg/KgBW (p.o.) 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 [10].

Nigella sativa, also known as black cumin, is a plant that originates from Asia. Identification of isolates from *Nigella sativa* seeds using the NMR-Analysis instrument and the results stated that the isolates contained Quercetin-7-O-b-D-glucopyranoside, Tauroside E, and Sapindoside B are all forms of quercetin which has acted as an antidepressant. The OFT, TST, and FST methods have proved this. TST and FST tests showed that black cumin isolates at 100 mg/kgBW (p.o) had an antidepressant effect on male Swiss strain mice. Reduced immobility time compared to Sertraline 5 mg/KgBW (p.o) indicates this approach is practical. The immobility time was decreased by 28.3%, 33.8%, and 22.5%, 31.3%, respectively, on the TST and FST tests. The OFT

method's effect on the number of crossings and rearing characteristics on changes in locomotor activity was unaffected by isolating the dosage of 100 mg/KgBW (p.o) [11].

Saffron, or *Crocus sativus*, is a widely used spice. Saffron is a plant that belongs to the Iridaceae tribe. Traditional treatment of depression can use the saffron plant on the flower parts. Saffron water extract at a dose of 40 mg/KgBW (i.p.) has been shown in the study by Ghasemi et al. (2015) to considerably shorten immobility time in the FST test when compared to imipramine at a dose of 10 mg/KgBW (i.p.). FST results showed that saffron extract could reduce immobility time, thereby significantly increasing BDNF, CREB, and p-CREB protein levels in male Wistar rats. Saffron extract showed that the VGF protein levels increased not significantly.

In East Asia, including Korea, China, and Japan, the plant Panax ginseng has been used for more than 2,000 years as a traditional herbal remedy. The *Panax ginseng* plant, especially its roots, has 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/KgBB (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 [13].

A typical plant used in herbal medicine in India is *Achyranthes aspera*. The FST, OFT, and Splast Tests on Swiss strain mice demonstrated the antidepressant effect of the methanol extract of *Achyranthes aspera* root. The findings demonstrated that in comparison to fluoxetine at a dose of 10 mg/KgBB (i.p.), the extract considerably decreased the time that mice remained immobile during the FST test at an adequate amount of 2.5 mg/KgBB (i.p.). The antidepressant activity uses the OFT and Splast Test procedures. In studies using the OFT technique, *Achyranthes aspera* extract administer at a dose of 2.5 mg/KgBB (i.p.). Neither the ambulation nor rearing parameters showed any change in locomotor activity. *A. aspera* extract 2.5 mg/KgBB, and Fluoxetine 10 mg/KgBB 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 shows the number of activities carried out by mice as an indication of concern for personal hygiene (self-care) [14].

Chemical Compounds and 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 comes from plant parts such as flowers, leaves, roots, and seeds and can even be found in all parts of the plant. Table 2 shows plants suspected of having chemical compounds and mechanisms of antidepressant activity.

Table 2. Chemical Compounds and Mechanism of Action of Antidepressants

No	Plant Name	Chemical Compounds	Mechanism of Action	References
1.	*Viola odorata* L	5,7-Dihydroxy-3,6-dimethoxyflavone; 5,7,4′-trihydroxy-3′,5′-dimethoxyflavone; 5,7,4′-trihydroxy-3′-methoxy flavone	5-HT receptor antagonists	[7]
2.	*Impatiens glandulifera*	Hyperoside (HYP) dan Protocatechuic acid (PCA)	Modulate monoamine levels in the brain via hydroxylase or monoamine oxidase (MAO) inhibition.	[8]
3.	*Leptadenia hastata (Pers.)*	Alkaloids and flavonoids	Antagonists of the opioidergic, muscarinic, serotonergic, dopaminergic, and adrenergic receptors.	[9]
4.	*Alpinia zerumbet*	Rutin and kaempferol-3-O-glucoronide	Monoamine oxidase (MAO) inhibition	[10]
5.	*Nigella sativa*	Tauroside E, Sapindoside B, Quercetin-3-O-L-rhamnopyranoside, and Quercetin-7-O-b-D-glucopyaranoside	It raises 5-hydroxytryptamine and norepinephrine levels in the brain while decreasing norepinephrine, serotonin, and dopamine absorption.	[11]
6.	*Crocus sativus*	Crocin	MAO-A and MAO-B non-competitive inhibitors	[12]
7.	*Panax ginseng*	Resveratrol, Ginseng total saponins, and Ginsenoside	Increases Nrf2 and HO-1 activity and increases BDNF activity	[13]
8.	*Achyranthes aspera*	Phenols, Alkaloids, Flavonoids, Glycosides, and Amino Acids	Increases BDNF in the prefrontal cortex and hippocampus.	[14]

Compounds of flavonoids, alkaloids, polyphenols, saponins, amino acids, and glycosides have been suspected of having antidepressant activity. The flavonoid group is known to affect 5-HT receptors BDNF levels, increase nerve growth, inhibit certain enzyme activities, modulate calcium and potassium ion channels, maintain brain plasticity, and prevent dissipation of mitochondrial membrane potential [7]. 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 by activating D2 receptors. In vitro, screening tests showed that PCA significantly inhibited MAO-A, MAO-B, and dopamine-β hydroxylase (DBH) [8]. Rutin compounds, kaempferol-3-O-glucoronide, and crocin also have the exact antidepressant mechanism of action as the polyphenols, which work by inhibiting monoamine oxidase (MAO) [9]. The quercetin substance's antidepressant action involves preventing norepinephrine, serotonin, and dopamine receptors from being absorbed while raising levels of norepinephrine and 5-hydroxytryptamine (S-HT) in the brain [11].

Resveratrol, Ginseng total saponins, and Ginsenoside 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 [13]. BDNF is a neurotrophin type with Tropomyosin Receptor Kinase B (TrkB). The hippocampus, hypothalamus, and cortex are three regions of the brain that express BDNF due to their high level of plasticity. Another function of BDNF is to modulate changes in neuronal activity-driven expression and synaptic transmission. BDNF helps support the development of new neurons in the central nervous system, promotes synaptogenesis, aids in neurogenesis, and can protect neural stem cells (NSC) and neural precursor cells (NPC). It also aids in the growth and differentiation of existing neurons. If stress and the stress hormone corticosterone are continuously present, BDNF expression will decline, and if this process is allowed to continue, hippocampus shrinkage will result [16].

IV. CONCLUSION

Considering the outcomes of a literature search, the conclusion is that the plant *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, so further research is needed.

Acknowledgements

The author would like to thank the Faculty of Pharmacy, Surakarta Muhmmadiyah University, Dr. apt. Arifah Sri Wahyuni, M.Sc and apt. Andi Suhendi, M.Sc guided in compiling a literature review research.

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