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Indonesian Medicine Plants for Mental Health Disorders: Anxiety and Depression

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ABSTRACT

Mental health disorders are widely discussed, specifically anxiety and depression. The number of people living with these disorders in 2020 increased significantly due to the COVID-19 pandemic. Mental health disorders are quite serious and need to be addressed. Indonesian people have used medicinal plants in everyday life to treat symptoms of mental health disorders such as increasing mood and motivation, calming, overcoming depression, stress, anxiety, and sleep disorders. However, there has been no comprehensive review on the ethnopharmacology of medicinal plants. Therefore, this review aimed to analyze Indonesian medicinal plants used to treat mental health disorders and reviews the associated scientific evidence. Literature studies of scientific articles, research journals, and books were carried out at national and international levels. The search results identified 39 Indonesian medicinal plants used to treat symptoms of mental health disorders. The results showed that Fabaceae family had types of medicinal plants widely used and possess the potential to treat depression and anxiety. Several plants were proven in preclinical research, but many were not studied. Therefore, further analyses must be conducted to provide knowledge and develop drugs for mental health disorders.

Keywords: Antidepressant, Antianxiety, Ethnopharmacology, Indonesian Medicinal Plant

INTRODUCTION

Anxiety and depression are the most commonly discussed mental health disorders. The COVID-19 pandemic increased the number of people living with the disorders in 2020 (Kertzscher *et al*, 2022). Even though the pandemic is over, a mental health issue is still being discussed, affecting many people such as losing jobs and families. Anxiety and depression are two of the most common and highly comorbid psychiatric conditions worldwide. These negative emotions are associated with cognitive, biochemical, behavioral, and psychological changes (Saki *et al*, 2014). Anxiety is a state of resonant emotional arousal characterized by feelings of fear or worry. Excessive fear and worry, panic disorder, and related behavioral disorders are symptoms of anxiety. The symptoms are severe enough to cause significant pain or functional impairment (World Health Organization, 2022). Meanwhile, depression is a chronic mental illness that can be fatal. Depressive disorder is characterized by having a low mood for the majority of the day, practically every day, for at least two weeks (sad, irritable, or empty). This is also characterized by a loss of pleasure or interest in activities. Other signs could be trouble concentrating, excessive guilt or low self-esteem, hopelessness about the future, suicidal or death thoughts, sleep issues, changes in appetite, and extreme exhaustion (Dattani *et al*., 2021). Individuals experiencing depression are at an increased risk of suicide.

Indonesian Basic Health Research (Riskesdas) in 2018 reported that 19 and 12 million people experienced mental emotional disorders and depression, with an average

population of over 15 years old. The 2018 Riskesdas data experienced a significant increase, namely 5.3 per million from the 2013 Riskesdas data. According to Global Health Data Exchange (GHDx) (2022), approximately 301 and 280 million people lived with anxiety and depression disorders in 2019, including 58 and 23 million children and adolescents. Mental health disorders have been treated with psychological therapy and the use of antidepressants and antianxiety medications. However, long-term use of these drugs can result in unpleasant side effects. Headaches, nausea, drowsiness, diarrhea, insomnia, ejaculatory disorders, dry mouth, sweating, agitation, high blood pressure, constipation, nervousness, and loss of appetite are among the side effects (Chang *et al*., 2021; Cipriani *et al*., 2018). These medications are also expensive and are not recommended for children or adolescents. Alternative treatments that are safe, inexpensive, and easy to obtain are required, such as the use of medicinal plants. Medical plants in Indonesia are estimated to reach 30,000 species, and 7,500 are known to have medicinal and herbal properties (Salim and Munadi, 2017). For generations, Indonesian people have used medicinal plants in their daily lives. Some treat symptoms of mental health disorders, such as increasing mood and motivation, calming, and overcoming depression, stress, anxiety, and sleep disorders. Based on hereditary experience, medicinal plants are widely used for traditional medicine and must be proven. Proof can be carried out using scientific research in the form of preclinical and clinical trials. Traditional medicines have a historical track record of usage rather than relying solely on scientific research. After validation, these plants can be integrated into traditional and contemporary medical practices. This review considers plants extensively used for addressing mental health disorders in Indonesia. Furthermore, it explores the traditional utilization of these plants, their scientific scrutiny through screening methods, contemporary applications in healthcare, the corresponding scientific evidence, and the identification of active compounds.

METHODOLOGY

Search Strategy

The review article was prepared by conducting a literature study published until 2023. The literature used comprised scientific articles, research journals, and books on both the national and international levels, which contained the Indonesian ethnopharmacology, activities, and plants. The literature review was carried out by searching for articles using the keywords "antidepressant", "depressant", "antianxiety", "depressive disorder", "anxiolytic", "sedative", "insomnia", "forced swimming test", "tail suspension test" on Google Scholar, ScienceDirect, Springer, MDPI, PubMed and Researchgate. In addition, a search for several books and literature was carried out at the IPB University Library.

Study Selection

The search results obtained 361 literature which was then selected to obtain 157. The limited literature on the use of Indonesian medicinal plants in treating mental health disorders (depression and anxiety), both in the form of preclinical reports (in vivo and in vitro) and clinically. The selected studies discussed the pharmacology of antidepressants, antianxiety, and sedatives from extracts, fractions, or active compounds derived from medicinal plants in Indonesia. The selection process was based on search keywords in the title or abstract. The stages of selecting the appropriate article were first seen from the title, abstract, and analysis of the content, specifically for books from the table of contents.

Data extraction and processing

Data from books and literature were collected using previously determined tables containing information (plant names, parts of plants used, benefits, method of use, region or ethnicity, references) to support writing reviews of traditional uses. The construction of this review included four distincts. Traditional uses of medicinal plants were primarily sourced from books and literature while screening reviews, evidence, and information on active compounds were derived from articles and research journals. Data for evidence review was collected in a tabular form containing information on scientific and local plant names, extracts and active compounds, activity, dosage, test method, test animals, and references. An overview of active compounds was from data collected containing information on groups, active compounds, plants, activities, and mechanisms.

RESULTS AND DISCUSSION

Utilization of traditional Indonesian medicinal plants in overcoming mental health disorders

Indonesia is a multi-ethnic country, with around 300-700 ethnicities or tribes spread across various regions (Silalahi, 2016).

Table I. The ethnopharmacology of Indonesian Medicinal Plants

No	Family	Scientific Name	Local Name	Material Part	Traditional Usage	How to Use (Oral/Topical etc.)	RA	Ethnic	References
1	Amaryllidaceae	*Zephyranthes candida*	Bawang brojol/ kembang cokelat	Herbs and tubers	To treat epilepsy, insomnia, and impaired liver function (liver)	The herb is boiled in 3 cups of water to make 1 cup. After cold, boiled water is taken twice a day each ½ cup.	Oral	Melayu dan Sunda	Hariana, 2007
2	Annonaceae	*Cananga odorata* (Lam.) Hook f.& Thomson	Kenanga/ kanthil	Leaf and flower	For traditional rituals, aphrodisiacs, and aromatherapy, reduces sleeping problems and tension, and overcome insomnia.	Soaked, and distilled to take the essential oil. Flowers are boiled with water for up to half. The boiled water is filtered and drunk regularly morning and evening.	Oral and inhalational	Osing	Hartati, 2011
3	Annonaceae	*Annona squamosa* L.	Srikaya	Root and leaf	Anti-inflammatory, antidepressant, calms hysterical sufferers and treats constipation	The leaves are washed and then pounded until smooth. Bring close to the nose of the hysterical and depressed sufferers and inhale the smell.	Inhalational	Sumatera, Jawa, Kalimantan	Dalimartha, 2005
4	Apiaceae	*Centella asiatica*	Pegagan	Leaf	Brain tonic, wound, antihypertension, hemorrhoid, aphrodisiac, relax, mental fatigue, and neuroprotective	Boiled, drunk, used as a salad	Oral		Ahmad *et al*., 2021
5	Apiaceae	*Foeniculum vulgare* Mill.	Adas	Leaf, fruit, and oil	Aphrodisiac, antianxiety, overcomes insomnia, abdominal pain, cough, lack of appetite, and menstrual pain	Brew fennel fruit powder with boiling water. After cold, filter and add honey, then drink.	Oral	Jawa, Osing, Madura	Hartati, 2011
6	Arecaceae	*Areca catechu* L	Jambe/siwu/ penang	Fruit	Energy, back pain, aphrodisiac, antidepressant	Potion	Oral	Jawa, Sunda	Adelina, 2013
7	Asteraceae	*Vernonia cinerea* (L) Less	Sawi langit/ buyung-buyung/ sembung kebo, leuleuncaan	Leaf	Fever medicine, body freshener, and overcomes insomnia	Fresh leaves are boiled in 2 cups of water to become 1 cup. After cooling, boiled water is taken one time a day, each 1 cup	Oral	Jawa, Sunda, Bali, Minang, Minahasa, Bugis, Makassar, Sasak, Ternate	Djauhariyah & Hernani, 2004
8	Asteraceae	*Artemisia vulgaris* Linn.	Sudamala/ lokot mala	Root	Treating epilepsy, pain during menstruation, and relaxing.	Fresh root plus fresh ginger and palm sugar to taste are boiled until slightly thick. After cooling, drink two times a day ½ cup.	Oral	Jawa, Sunda	Djauhariyah & Hernani, 2004
9	Calophyllaceae	*Mesua ferrea L.*	Dewadaru/ nagasari	Flower stalk	Overcomes mental illness, expectorant, antidepressant	The flower stalks are boiled in 3 cups of water until 1 cup remains. After chilling, the boiled water is filtered and drunk once daily.	Oral	Sunda, Jawa, Melayu	Andila *et al*., 2020; Hariana, 2007
10	Fabaceae	*Clitoria ternatea*	Bunga telang	Flower	Antioxidant, relaxation, and eye medicine	Brewed	Oral		Adelina, 2013
11	Fabaceae	*Mimosa pudica* L	Putri malu/ Si kejut/ Jukut riut	Leaf	Sedatives, overcome insomnia, antidepressant	Fresh leaves are washed, then boiled with 3 cups of water to 1 cup. After cold, boiled water is drunk at once in the afternoon	Oral	Jawa, Sunda	Hakim, 2015; Djauhariyah & Hernani, 2004
12	Fabaceae	*Mimosa invisa* Colla	Putri malu besar	Leaf	Sleep disorders, diabetes medications	Take a bath using boiled water consisting of 100 g of fresh leaves in 20 L of water for 30 minutes	Topical		Karyati & Adhi, 2018

13	Fabaceae	*Tamarindus indica* L.	Asam jawa	Fruit and leaf	Appetite enhancer, conditioning, insomnia	Brew fruit plus enough brown sugar with hot water, and drink while warm. A handful of fresh leaves or fruit and add one turmeric rhizome, boiled with 2 glasses of water to 1 glass, then drink the water	Oral	Jawa, Sunda, Bali, Aceh, Makasar	Hidayat & Napitupulu, 2015
14	Fabaceae	*Flemingia macrophylla* (Willd.) Merr.	Polita	Leaf and root	Reducing sleeping problems	Boiled and drink	Oral	Manui ethnic of Central Sulawesi	Rahmawati *et al*., 2020
15	Fabaceae	*Flemingia strobilifera* (L.) W.T.Aiton	Polita	Stem, bark, and root	Antidepressant	Scrape the stem, brew the bark with hot water, and drink a glass twice a day	Oral	Manui ethnic of Central Sulawesi	Rahmawati *et al*., 2020
16	Lamiaceae	*Leucas lavandulifolia*	Lenglengan	Leaf	Medicine for headaches, anxiety, heat cramps in children, insomnia	The leaves are boiled with 2 cups of water until 1.5 cups remain. The boiled water is filtered and added with honey to taste, then drink ¾ cup 2 times a day, morning and evening.	Oral	Padang, Jawa, Sunda, Madura, Ternate, Tidore	Djauhariyah & Hernani, 2004
17	Lamiaceae	*Clerodendrum japonicum* (Thunb.)	Pagoda	Root, flower, leaf	Anti-inflammatory relieves swelling, overcomes insomnia	Powdered flowers or roots are taken 1 teaspoon, then put into a shot of sweet wine. Next, stir well and drink all at once before going to sleep.	Oral		Hartati, 2011
18	Lauraceae	*Cinnamomum burmanii*	Kayu manis	Stem, bark	Aphrodisiac, increases energy, headache, and antihypertension, makes relaxation and calm	Cinnamon is boiled using boiling water to produce a cinnamon drink	Oral	Bajau and Jawa	Hakim, 2015
19	Melastomataceae	*Melastoma affine* D. Don	Senduduk/ benggani/ harendong	Root	Soothing and treating hangovers	The roots are washed, and finely ground, then add enough water. After that, the herb is squeezed, then drunk	Oral	Jawa and Sunda	Djauhariyah & Hernani, 2004
20	Moraceae	*Morus alba* L.	Murbei	Fruit	Hypertension overcomes insomnia	The fruit is boiled with water up to half. Then the boiled water is drunk	Oral	Sumatera dan Jawa	Dalimartha, 2005
21	Myristicaceae	*Myristica fragrans* Houtt	Pala	Seed	Overcomes insomnia, antidepressant, aphrodisiac	Made water infusion, distilled to take the oil, or made food. The seeds are boiled with lotus seeds and angco until half of the water remains. Drink while warm, once a day.	Oral		Istriningsih *et al*., 2018; Hariana, 2007
22	Myrtaceae	*Melaleuca leucadendra* L.	Kayu putih	Leaf, bark	Body warmer boosts spirit, improves sleep, and relaxation, overcomes weakness (neurasthenia), insomnia	Distil leaves to take the oil, smeared. The bark is boiled with 2 cups of water until 1 cup remains. Boiled water is filtered and added honey to taste, then drink two times ½ cup.	Oral and inhalational		Hariana, 2007
23	Nelumbonaceae	*Nelumbium nelumbo* Druce	Teratai	Seed, shoots	Insomnia, lethargy, lack of enthusiasm, treating fever, and restlessness	Lotus seeds and buds are boiled with water for up to half. Then the boiled water is drunk every day like tea.	Oral		Hartati, 2011

24	Oleaceae	*Jasminum sambac* L.	Melati	Flower and Root	Calms the mind, treats madness, and epilepsy, relieves itching, fever, and nausea, Aromatherapy, makes happy, relaxed, love, playful, insomnia, antistress, and analgesic	Used as an essential oil or brewed in tea, burned with candles, inhaled, or distilled. Jasmine root 10 g and a little water, crushed, taken 2 times a day @ 1 tablespoon	Oral and inhalational	Jawa and Sunda	Hakim, 2015; Andila *et al*., 2020
25	Piperaceae	*Piper nigrum* Linn.	Lada	Fruit	Stimulates endorphins' production, antidepressants, aphrodisiac		Oral		Hakim, 2015
26	Piperaceae	*Peperomia pellucida* (L.) Kunth	Evo mongura	Herbs	Antidepressant	Clean herbs, boil with 3 cups of water until 1.5 cups remaining, cool, and drink 3 times a day.	Oral	Manui ethnic of Central Sulawesi	Rahmawati *et al*., 2020
27	Poaceae	*Cymbopogon citratus* (DC) Stapf	Sereh	Stem, oil	Aromatherapy, revitalizes the body and reduces the symptoms of headaches and stress-related ailments.	Lemongrass oil is used extensively by therapists in massage, muscle therapy, and skin toner. Boiled stem, and drink	Oral, topical, and inhalational		Hakim, 2015
28	Polygalaceae	*Polygala paniculata* L.	Evo bokori	Herbs	Antidepressant	Clean herbs, boil with enough water, chill, and drink 2 times a glass a day. Effects begin to appear on the second day. You can also take *P. paniculata*, and *C. longa* rhizomes 3 segments or more, then grated. Each plant is then cleaned and brewed with hot water.	Oral	Manui ethnic of Central Sulawesi	Rahmawati *et al*., 2020
29	Rosaceae	*Rosa hybrid*	Mawar	Flower	For expressions of love, essential oil producers, beauty, mood enhancers, for traditional rituals	Flowers distilled by distillation, dried rose petals, then brewed into tea, rose water, can also be made by infusion of rose petals with water, then left for a day	Oral and inhalational		Hakim, 2015
30	Rubiaceae	*Morinda citrifolia* L.	Mengkudu	Fruit	Increase stamina and vitality, immunomodulator, pain reliever, sedative/calming, antidepressant	Boiled	Oral		Adelina, 2013
31	Rubiaceae	*Gardenia jasminoides* J. Ellis	Kacapiring	Fruit and flower	Calms emotions, hypnotic/calm effect, anti-seizure	The fruit and flowers are dried and made into tea. The flower essential oil is used as aromatherapy	Oral and inhalational		Andila *et al*., 2020
32	Rutaceae	*Citrus hystrix* D. C.	Jeruk purut	Fruit, leaf, and fruit skin	Overcoming influenza, stimulant, refresher, and sedative	Squeezed, the juice is brewed with hot water and drunk while warm. Lime leaves are boiled with water. The boiled water is poured into a bucket of warm water and then used for bathing.	Oral, topical, and inhalational	Batak, Lampung, Jawa, Sunda, Bali, Bugis, Nias, Flores, Ambon	Dalimartha, 2005
33	Rutaceae	*Ruta graviolens*	Daun inggu	Leaf	Treating seizures in children, soothing and hepatitis	Fresh leaves are cut into pieces, then boiled in 2 cups of water down to 1 cup. After chilling, the boiled water is filtered and drunk 2 times a day every morning and evening.	Oral		Subagja, 2013
34	Rutaceae	*Citrus aurantifolia* (Christm.) Swingle	Jeruk nipis	Oil and fruit	Antidepressant, fever, cough, sore, anticholesterol, aphrodisiac, overcome insomnia	Squeezed, drunk	Oral	Sunda and Priangan	Hakim, 2015
35	Solanaceae	*Datura metel* L.	Kecubung	Flower	Treats asthma, cough, fear-induced epilepsy, mental illness, and drugs	Flowers are dried, then brewed/ boiled, and steeped/ boiled water is drunk. Dried flowers are rolled up and burned, and the smoke is inhaled.	Oral and inhalational	Nias, Melayu, Madura, Manado, Bugis, Bali, Makassar	Dalimartha, 2005

36	Zingiberaceae	*Curcuma aeruginosa*	Temu hitam	Rhizome	Treat epilepsy, calm, and increase appetite.	The rhizome is sliced, plus *K. galanga* L, *C. asiatica* leaves, *M. arvensis* leaves, and *B. polystachyon* leaves, then all boiled with 6 cups until half is left. Boiled water is taken 3 times a day after eating ½ cup.	Oral		Duryatmo, 2004
37	Zingiberaceae	*Curcuma longa*	Kunyit, kunir, konyek	Rhizome	Antidepressants and for neurological disorders	Grated and brewed	Oral	Osing, Jawa	Ahmad *et al*., 2021
38	Zingiberaceae	*Curcuma xanthorrhiza*	Temulawak	Rhizome	Treats loss of appetite, convulsions, Parkinson's disease, nervous system, and relieves fatigue	Grated then squeezed, the juice is drunk, or boiled, brewed, or made into powder	Oral	Jawa, Sunda, and Riau	Syamsudin *et al*., 2019
39	Zingiberaceae	*Zingiber officinale* Roscoe	Jahe	Rhizome	Herbal medicine (jamu), body warmer, treats headaches, and loss of appetite, neuroprotective and as a stimulant	The rhizomes are cleaned, chopped, or grated, then brewed with hot water, add honey, then drink	Oral		Ahmad *et al*., 2021

This figure shows the diversity of the country and each tribe has its cultural wealth and local wisdom, including using plants for traditional medicine. Therefore, it is critical to understand how an ethnic group uses plants for treatment to advance both traditional and modern medicine. Many new medicines have been developed from plants that are more efficacious, effective, and safe using this knowledge approach (Süntar, 2020). As a result of the knowledge collection, 1000 materials for treatment were obtained. Based on their application, 193 different types of materials with relaxing properties were reported. However, there are no comprehensive reviews of the ethnopharmacology of mental health disorders such as depression and anxiety. In this review, a comprehensive overview and up-to-date information are provided on the ethnopharmacology of mental health disorders. According to literature review, a total of 39 Indonesian medicinal plants are traditionally used to treat mental disorder symptoms. The selected plants have the potential to treat sleep disorders (insomnia), anxiety disorders (antianxiety), epilepsy, calming, relaxing, elevating mood, treating mental illness, overcoming stress (anti-stress), and treating depression (antidepressant).

Medicinal plants with the potential to treat mental disorders consist of 23 families (Table I). The family with the most widely used plants and the potential to treat disorders is the Fabaceae family (16%), followed by Zingiberaceae (11%) and Rutaceae (8%) (Figure 1a). Fabaceae is widely used because this family is the third-largest flowering plant in the world with more than 19,400 species and almost 770 genera (Azani *et al*., 2017) in tropical areas. Most Fabaceae plants possess medicinal properties and have long been used as traditional medicines. Results of ethnopharmaco-logical studies in several regions such as in South Tambun District, Bekasi Regency (Anugrah *et al*., 2022), Sejahtera Village, Sukadana District, North Kayong Regency (Aminah *et al*., 2016), and around the Ake Tajawe Lolobata National Park, Maluku Province Utara (Nurrani *et al*., 2015) shows that the family is most widely used as medicine by local people. Besides being a medicine, it has many benefits for human life, including food, animal feed, ornamental plants, natural dyes, tannin producers, craft materials, furniture, and building materials (Hariri *et al*., 2021).

Zingiberaceae is the second family widely used and found in abundance in Indonesia with a tropical climate (Zahara, 2019). This family is used as spices, medicines, ornamental plants, cosmetics, drinks, and hair tonics. Zingiberaceae has also been used as a raw material in the industry of "jamu" and herbal medicine (Pitopang *et al*., 2018).

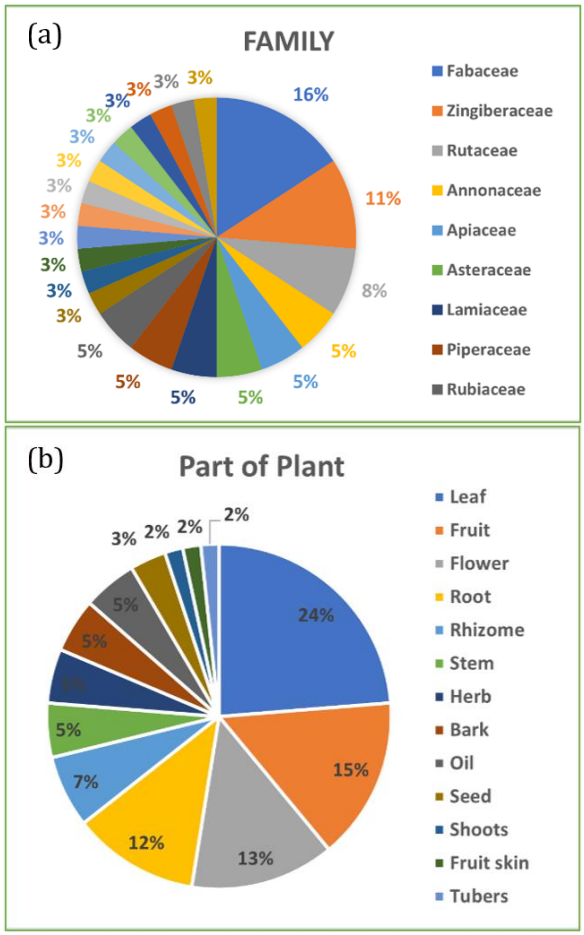

Figure 1. Frequency distribution of plant part (a), dan plant families (b)

The part of the plant often used is the leaf (24%) (Figure 1b). The leaves are easy to use and obtained in large quantities compared to other plant parts (Tugume *et al*., 2016). This is because the fruit and flower need enough time to grow. The most widely used route for administering medicinal plants to treat mental health disorders is oral administration, totaling 14 species (Figure 2). Traditionally, many plants have been used orally and inhaled. Aroma comes from essential oils contained in plants and plays a role in lowering the level of the stress hormone cortisol. Therefore, essential oils are often used in aromatherapy to enhance calm feelings and avoid anxiety (Hakim, 2015). The results also show that some plants have the same use in various regions, such as kaffir lime

and mustard greens. This shows that the plant has been widely known for its usefulness in various regions.

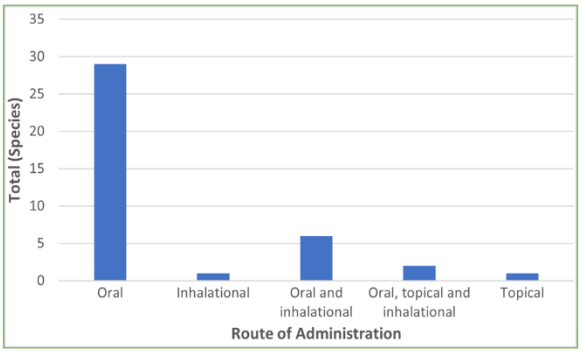

Figure 2. Frequency distribution of general administration routes

Screening and drug development of mental disorders

Knowledge of the use of plants for treatment by an ethnic group can be adopted to develop traditional and modern medicines. Potential plants based on ethnopharmacological knowledge are proven by conducting scientific research in the form of preclinical and clinical trials. Regarding mental disorders, preclinical scientific research has mostly used animal models to uncover the mechanisms included in anxiety and depression disorders. Animal models are also used to assist in screening plants and developing new drugs (Parle *et al*., 2010). This model is also known as the in vivo method. Furthermore, there are also in vitro methods for plant screening and drug development. Plant screening and drug development that play a role in treating mental disorders such as depression and anxiety will be reviewed.

The development of medicinal plants into ingredients that can be medically justified can be started with preclinical trials. Preclinical tests used for plant screening can be *in vivo* or *in vitro*. In mental health disorders, specifically anxiety and depression, many in vivo methods are used. Animal models widely used for screening for antianxiety agents are elevated plus maze (EPM) and Y, X, T, radial, and zero mazes. Furthermore, there are also Light-dark models (LDT), Open field/Closed field (OFT/CFT), Staircase tests, Hole board tests (HBT), Mirror chamber tests (MCT), and Marble burying tests (MBT). All models except the MBT are based on the spontaneous behavior of test animal responses without learning/memory and hunger/thirst impairments. Meanwhile, MBT is a model based on conditioned tasks (Parle *et al*., 2010). A model based on spontaneity is widely used in EPM to identify anxiolytic (anxiety-reducing) and anxiogenic (anxiety-increasing) drugs. The EPM test is performed with a 'plus sign' maze apparatus with two closed arms surrounded by a wall facing each other and separated by a square in the middle with two open arms. The labyrinth is raised from the ground to high, with open arms incorporating the elements of ignorance, fear, openness, and height. EPM is based on animals' natural aversion to exploring high open spaces. A sample with anxiolytic activity increases the animal's exploration time in open arms, and vice versa for anxiogenic (Parle *et al*., 2010).

Using animal models is also an important tool in antidepressant drug screening. Depression-induced animals can mimic depressive symptoms exhibited by behavioral changes such as cognitive dysfunction. Depression animal models that are widely used for screening antidepressant agents are the forced swimming test (FST), tail suspension test (TST), open field test (OFT), chronic unpredictable mild stress (CUMS), and sugar preference. A sample with antidepressant activity can decrease immobilization time in TST and FST, as well as decrease the number of crossings, rearing, grooming in OFT, and sugar preference (Zhang *et al*., 2021). FST is the most widely used model in antidepressant research. In the test, rodents are forced to swim in a narrow cylindrical transparent container. Animals were put into a container filled with water for 15 minutes for a desensitization session and were returned to the cage. After 24 hours, the animal will be given the extract and put back into the cylindrical container. The originally active animal will become immobile, and removed from the container after a certain time. The antidepressant activity was assessed when the animals were active. The duration of immobility is documented and is anticipated to diminish with the administration of antidepressant agents (Sewell *et al*., 2021).

Several preclinical tests of antidepressant agents also used the in vitro method, including tests for monoamine oxidase (MAO) inhibition, citalopram-binding, serotonin transporter (SERT), norepinephrine transporter (NET) and dopamine transporter (DAT) uptake inhibition, brain-derived neurotrophic factor (BDNF) for antidepressants, neuroprotective on PC12 cells injured by corticosterone and GABA (Ferraz *et al*., 2019; Pedersen *et al*. al., 2008; Zheng *et al*., 2012).

The most widely performed in vitro test is MAO inhibition. MAO is a family of enzymes that catalyze monoamine oxidation and cause a decrease in the synaptic cleft, reducing the activation of monoamine receptors. The family consists of two isoforms, namely MAO-A and MAO-B. MAO-A causes oxidative deamination of serotonin, melatonin, and noradrenaline, while MAO-B degrades phenethylamine and benzylamine (Martins & Brijesh, 2018). Plant extracts with antidepressant activity will be able to inhibit MAO enzyme activity thereby increases synaptic availability and restores monoamine receptor levels.

Clinical trials follow the results of preclinical tests of plants that have been proven by testing directly on patients with mental health disorders such as MDD to determine their effects. Tests were conducted, extending beyond crude extracts, to identify the active substances in medicinal plants effective against mental health disorders. After the active substances are identified, the development of both modern and traditional medicines is carried out. The content of active plant substances that are quite large (> 2%) was developed by conducting isolation and purification. This purified isolate is developed into a modern drug ready to be prescribed by a doctor whose quality is similar to the active ingredients. The levels of active ingredients are large, and medicinal plants are said to be a source of ingredients/precursors (single component) (Parwata, 2016). Standardization is carried out to develop traditional medicines containing small active substances. This process is conducted starting from the raw materials to becoming preparations of natural medicines.

Scientific Evidence Indonesian Medicinal Plants overcome mental health disorders

Several Indonesian plants (Table I) lack scientific validation, with some not featured in the literature showing research on their potential in treating mental health disorders, including depression and anxiety, through clinical or preclinical trials. However, there are quite a few plants whose potential has been proven using preclinical tests. The following is scientific evidence for several medicinal plants which are differentiated based on their families. A total of 13 plant families have the potential to overcome mental health disorders, including the Annonaceae, Apiaceae, Arecaceae, Lauraceae, Asteraceae, Fabaceae, Lamiaceae, Myrtaceae, Piperaceae, Poaceae, Rubiaceae, Solanaceae, and Zingiberaceae families. These plants are divided into three bioactivities, namely, antidepressants, antianxiety, and sedatives. The part of the plant used for the bioactivity test can be essential oil or extract. Families extensively researched and proven to be able to overcome mental health disorders are the Fabeaceae and Lemiaceae.

Fabaceae is known as the Leguminosae and leguminous family. In this family, 14 plants have the potential to overcome mental health disorders, specifically depression and anxiety, as shown in Table II. Antidepressant activity is possessed by the plants *Ceratonia siliqua* L., *Trigonella foenum-graecum*, *Prosopis cineraria*, *Glycine max* L. Merr., *Mimosa pudica* L., *Vicia faba*, *Tamarindus indica* L., and *Vigna unguiculata*. Plants with antianxiety activity include *Sesbania grandiflora* (L.) Pers, *Caesalpinia pulcherrima* (L.) Swartz., and *Clitoria ternatea* L.. Meanwhile, the plants that had both activities were *Mucuna pruriens* (L.) DC., *Erythrina variegata*, and *Cassia singueana*. *C. siliqua* L fruit acetone extract had the highest antidepressant activity when viewed from the dose at 25 and 50 mg/kg (Agrawal *et al*. 2011). Furthermore, the highest antianxiety activity was possessed by the benzene ethyl acetate fraction of *Sesbania grandiflora*, with a dose of 100 mg/kg and the EPM test method (Kasture *et al*. 2002).

A total of 13 plants in the Lamiaceae family have the potential to treat mental health (Table III). This family is known for its distinctive aroma widely used to treat mental health disorders by calming, relaxing, elevating mood, improving sleep quality, and overcoming anxiety. Plants with antidepressant activity are *Mentha arvensis* L., *Mentha piperita*, *Pogostemon cablin* Benth, *Perilla frutescens*, *Ocimum sanctum* L., *Ocimum basillicum* L., *Nepeta cataria*, *Lavandula angustifolia* Mill. *Plectranthus scutellarioides* have antianxiety activity, while *Rosmarinus officinalis* L., *Melissa officinalis* L., and *Leucas lavandulifolia* J.E. Smith have both antidepressant and antianxiety activities. Some plants have a sedative effect, namely *Ocimum americanum* L. and *Perilla frutescens* and the highest antidepressant activity based on dose is Perilla essential oil at 3 mg/kg (Ji *et al*. 2014).

Based on Table S1, two plants of the Annonaceae family can overcome anxiety, namely *Annona muricata* and *Cananga odorata* (Lam.) Hook f. & Thomson) (Samuel *et al*., 2018; Ohemeng *et al*., 2020; Borgonetti *et al*., 2022). Part used is in the form of leaves, bark, and flowers.

Table II. Fabaceae Family

Scientific/Local Name	Extraction	Activity	Dose	Test Method (Animal)	Reference
Cassia singueana/ cassia	Methanol leaf extract	Anxiolytic and antidepressant	100 and 200 mg/kg	HBT, EPM, OFT (A), FST and TST (B)	Alkali *et al*., 2019
Ceratonia siliqua L./ Pohon carob	Acetone extract of Fruits	Antidepressant	25 and 50 mg/kg	FST dan TST (C)	Agrawal *et al*., 2011
Clitoria ternatea L./ Bunga telang	Methanol extract of aerial parts	Antianxiety	100 and 200 mg/kg	EPM (D)	D. Kumar & Dhobi, 2017
Clitoria ternatea L./ Bunga telang	Methanol extract from roots	Antianxiety	100 mg/kg	EPM (D)	D. Kumar & Dhobi, 2017
Tamarindus indica L./ Asam jawa	Methanol stem bark extract	Antidepressant	75 and 150 mg/kg	FST and TST (D)	Yunusa *et al*., 2021
Trigonella foenum-graecum/ kelaba/ fenugreek	Seed fraction	Antidepressant	140 mg/kg	FST, TST, SPT, MAO-A and B inhibition assay (E)	J. Wang *et al*., 2019
Prosopis cineraria/ Pohon shami	Aqueous extract of leaves	Antidepressant	200 mg/kg	FST (F)	George *et al*., 2012
Caesalpinia pulcherrima (L.) Swartz./ Kembang Merak, jambul merak	Methanol extract from leaves	Anxiolytic	200 and 400mg/kg	EPM (B)	Vuyyala *et al*., 2021
Erythrina variegata/ Dadap ayam	Ethanol extract from the bark	Anxiolytic and antidepressant	50, 100, and 200 mg/kg	EPM, LDT, OFT, FST and TST (E)	Chu *et al*., 2019
Glycine max L. Merr./ Kedelai	Methanol extract from the seed	Antidepressant	500 mg/kg BW	FST (G)	Burdah *et al*., 2021
Mimosa pudica L./ Putri malu	Ethanol extract of leaves	Antidepressant	100 and 400 mg/kg	FST and TST (F)	Udyavar *et al*., 2021
Mucuna pruriens (L.) DC.,/ Kacang kara benguk	Ethanol 50% extract of seeds	Antidepressant	100 and 200 mg/kg	FST, TST, and CUMS (H)	Galani & Rana, 2014
Mucuna pruriens (L.) DC.,/ Kacang kara benguk	Methanol extract from seeds	Anxiolytic and antidepressant	200 and 300 mg/kg	EPM, LDT, MBT, HBT, FST, and TST (F)	R. A. Patil & Ahmad, 2021
Sesbania grandiflora (L.) Pers/ Turi	Benzene ethyl acetate fraction	Anxiolytic	100 mg/kg	EPM (I)	Kasture *et al*., 2002
Vicia faba/ Kacang babi	Methanol extract from hulls	Antidepressant	1200 mg/kg	FST and TST (H)	Alam *et al*., 2016
Vigna unguiculata/ Kacang Tunggak	Aqueous extract of aerial part (leaf and stem)	Antidepressant	600 and 800 mg/kg	FST, TST, LC, and OFT (C)	Akinpelu *et al*., 2017

(A) Wistar rats, (B) Albino mice, (C) Male albino mice, (D) Mice, (E) Male kunming mice, (F) Swiss albino mice, (G) Male *Mus musculus* mice, (H) Male Swiss mice, (I) Male mice

Table III. Lamiaceae Family

Scientific/Local Name	Extraction	Activity	Dose	Test Method (Animal)	Reference
Lavandula angustifolia Mill./ Lavender	Essential oil of Flower	Antidepressant-Like	30 mg/kg BW 10 mg/kg BW	FST (A) PC12 cells	Friedland *et al*., 2021
Leucas lavandulifolia J.E.Smith/ Lenglengan	Methanol extract	Anxiolytic and CNS depressant	200 dan 400 mg/kg BW	EPM, HBT, OFT and FST (B)	Islamie *et al*., 2021
Nepeta cataria/ Catnip	*n*-hexane and ethanol extract from leaves	Antidepressant	10 %	Behavioral despair test, EPM, and OFT (C)	Bernardi *et al*., 2010
Ocimum americanum L./ Kemangi	Essential oil	Sedative Effect		OFT (D)	Shanaida *et al*., 2021
Ocimum basillicum L/ Selasih	Fractions of the Basil Leaves	Antidepressant	50 mg/kg BW	FST dan TST (E)	Suhendy *et al*., 2018
Ocimum basillicum L/ Selasih	leaves essential oil	Antidepressant	0,025 ml/kg BW/day	TST (B)	Suryani *et al*., 2019
Ocimum sanctum L/ Kemangi/ Lampes	*n*-butanol fractions of leaves	Antidepressant	50 mg/kg BW	SPT, TST, FST, OFT (F)	Nguyen *et al*., 2021
Ocimum sanctum L/ Kemangi/ Lampes	Methanol extract	Antistress	-	Blocking CRHR1 receptor and inhibiting 11β-HSD1 and COMT activities (G)	Jothie Richard *et al*., 2016
Plectranthus scutellarioides/ Miana/ jawer kotok	Hydroalcoholic extract of leaves	Anxiolytic-like effects	100 and 200 mg/kg BW	The Staircase Model (SCM) and Light and Dark Chamber (LDM) (H)	Shanbhag *et al*., 2022
Perilla frutescens/ Perilla	Leaves essential oil	Antidepressant	3 mg/kg	SPT, TST, FST, OFT (I)	Ji *et al*., 2014
Perilla frutescens/ Perilla	Essential oil	Sedative effect		Inhalation administration and GABAergic system pathways (I)	Zhong *et al*., 2021
Pogostemon cablin Benth/ Nilam	Essential oil of Leaves and stems	Antidepressant		TST (J)	Astuti *et al*., 2022
Rosmarinus officinalis L./ Rosmarin	Ethanol extract	Antidepressant and antianxiety		TST and EPMT post-LPS injection (I)	Sasaki *et al*., 2021
Melissa officinalis L./ Lemon balm	Ethanol extract from leaves	Anxiolytic and antidepressant	300 mg/kg	EPM, OFT, FST (K)	Taiwo *et al*., 2012
Mentha piperita/ Papermint	Ethanol extract	Antidepressant	200 and 400 mg/kg	FST (L)	(Abbasi-Maleki *et al*., 2017)
Mentha arvensis L./ daun poko	Essential oil	Antidepressant	781/kg MW	FST (F)	Yousuf *et al*., 2021

(A) Male Sprague-Dawley rats, (B) Male Balb-c mice, (C) Male mice, (D) Male albino rats, (E) Male Swiss Webster mice, (F) Male Swiss albino mice, (G) Male and female albino Wistar rats, (H) Albino rats, (I) Male ICR mice, (J) Male rats, (K) Male and female Wistar rats, (L) Male Naval Medical Research Institute (NMRI) mice

The essential oil from ylang flowers has a relatively high anxiolytic activity compared to others at a dose of 30 mg/kg (Borgonetti *et al*. 2022). In Table S2, the Apiaceae family has three plants that have the potential to overcome mental health problems, namely *Apium graveolens*, *Centella asiatica*, and *Foeniculum vulgare* Mill. (Shayani Rad *et al.* 2022; S. Kumar & Singh, 2019; A. Abbas *et al*., 2020). These plants have the potential as antidepressants and antianxiety drugs, while *A. graveolens* has a sedative effect. *A. graveolens* and *F*. *vulgare* Mill. use the seeds while *C. asiatica* uses the leaves. The essential oil from *F*. *vulgare* Mill. seeds have antidepressant activity at around 100-400 mg/kg (Abbasi-Maleki and Maleki 2021).

The Arecaceae family in Table S3 also contains three plants with the potential to overcome mental health disorders, *Areca catechu* L., *Salacca zalacca*, and *Cocos nucifera* L. (Mansour *et al*., 2021; Fahrudin & Haribowo, 2021; Azis & Rinding Lawan, 2020). *A. catechu* and *S. zalacca* seeds have antidepressant activity. Extract of *A. catechu* nuts or seeds has the potential as an antidepressant with a dose of 50 mg/kg to decrease immobilization time in the forced swimming test (FST) (Abbas *et al*. 2013). Extracts from several parts of *C. nucifera* L. also have the potential to address mental health problems, namely antidepressants and antianxiety.

The search results obtained 6 plants of the Asteraceae family (Table S4) with the potential to overcome mental health disorders, namely *Gynura procumbens* L. Merr., *Lactuca sativa*, *Matricaria chamomilla*, *Pluchea indica*, *Erigeron liinfolius*, *Tagetes erecta* L. (Akter *et al*., 2019; Rajaram *et al*., 2020; Ioniță *et al*., 2019; Thongpraditchote *et al*., 1996; Pandey & Tripathi, 2014). Hydromethanol extract from *T. erecta* L. flower has the highest antidepressant activity of the others with a dose of 25 mg/kg. *T. erecta* L. flower can decrease immobility time in the FST test (Khulbe *et al*. 2013). Antianxiety activity of the ethanol extract of chamomile flowers has the highest value compared to the others at a dose of 10-50 mg/kg (Kesmati *et al*. 2014). Meanwhile, *G. procumbens* L. Merr. and *P. indica* plants possess a sedative effect.

Cinnamomum burmanii and kilemo *Litsea cubeba* (Lour.) Pers. from Lauraceae family (Parisa *et al*., 2020; Chen *et al*., 2012) have sedative effects. *L. cubeba* (Lour.) Pers. also has antianxiety. *C. burmanii* contains essential oils such as eugenol, which provide a calming feeling/psychological effect. The plant is widely used to treat neurodegenerative diseases (Judge 2015) and the ethanol extract has antidepressant activity at 25-100 mg/kg (Parisa *et al*. 2020).

In Table S6 and S7 families, there are two plants with the potential to overcome health disorders, namely *Syzygium aromaticum* and *Syzygium cumini* (Myrtaceae), as well as *Piper methysticum* L. and *Piper nigrum* Linn. (Piperaceae) (Rehman *et al*., 2020; P. Tiwari *et al*., 2014; Emon *et al*., 2021). *S. aromaticum* has antianxiety activity, while *S. cumini* possesses antidepressant, antianxiety, and sedative effects (Galal and Abdellatief 2015; Rehman *et al*. 2020). *P. nigrum* Linn. and *S. aromaticum* are used as extracts or essential oils. The two plants with the best activity are essential oils. Considering the dose, the activity of the essential oil is higher than the extract. For example, Galal and Abdellatief (2015) showed that essential oil from *S. aromaticum* has antianxiety activity at a dose of 0.05-0.1 mg/kg.

A total of four plants has the potential to overcome mental health disorders from the Poaceae family, namely, *Cymbopogon citratus* (DC) Stapf, *Cymbopogon nardus* (L.) Rendle, *Sorghum halepense*, and *Vetiveria zizanioides* (Umukoro *et al*., 2020; Simorangkir *et al*., 2020; Rambabu and Rao Patnaik 2016; Nirwane *et al*., 2015). Based on the results of Table S8, *C*. *citratus* (DC) Stapf and *S. halepense* have antidepressant and anxiolytic activity, *C*. *nardus* (L.) Rendle possesses antidepressant and sedative activity, while *V. zizanioides* has anxiolytic activity. *C*. *citratus* (DC) Stapf has the highest activity when viewed from the dose. essential oil and extract of *C*. *citratus* (DC) Stapf have high activity at 10 mg/kg and decrease immobilization time in FST (Costa *et al*. 2011; (Dudhgaonkar *et al*. 2014).

The search results obtained 6 plants of the Rubiaceae family (Table S9) with the potential to overcome mental health disorders, namely, *Hamelia patens* Jacq., *Mitragyna speciosa* Korth., *Morinda citrifolia* L., *Nuclea latifolia* Smith, *Uncaria lanosa* Wallich var. Appendiculata Ridsd, *Uncaria rhynchophylla* (Miq.) Miq. Ex Havil (Surana & Wagh, 2017; Farah Idayu *et al*., 2011; Narasingam *et al*., 2017; Iliya *et al*., 2022; Hsu *et al*., 2012; Geng *et al*., 2019). *H. patens* Jacq., *M. speciosa* Korth., *U. lanosa*, *M. citrifolia* L., and *U. rhynchophylla* (Miq.) Miq. Ex Havil have antidepressant and *N. latifolia* has antianxiety activity, while mengkudu acts as both. Several previous studies have succeeded in isolating compounds with the potential as antidepressants. Farah Idayu *et al*. (2011) successfully isolated Mitragynine from *M. speciosa* Korth. (Rubiaceae), which has antidepressant

activity at a dose of 10-30 mg/kg and can decrease immobilization time in FST. Gang *et al*. (2019) also isolated catechin that acts as an antidepressant from *U. rhynchophylla* (Miq.) Miq. Ex Havil at a dose of 20-80 mg/kg decreases immobility time.

In the Solanaceae family (Table S10), 4 potential plants were obtained, namely *Datura stramomium* L., *Solanum torvum* Swartz, *Solanum nigrum* L., and *Withania somnifera* (Sobhanifar *et al*., 2021; Mohan *et al*., 2013; Momin & Mohan, 2011; Siswanti, 2016; Kaur *et al*., 2017). *D. stramomium* L. and *W. somnifera* have antianxiety and sedative activities, while *W. somnifera* acts as an antidepressant. *S. torvum* Swartz has antidepressant and antianxiety activity, while *S. nigrum* L. only possesses antidepressant activity. The sedative effect of water extract from short amethyst seeds is quite high at a dose of 20-80 mg/kg, which can induce sleep time in rats (Malami *et al*. 2014). The highest antidepressant activity is possessed by water extract of *W. somnifera* root with 20 mg/kg and can decrease the patient's immobility time in FST and TST (Jayanthi *et al*. 2012).

Zingiberaceae is known for its rhizome body widely used as herbal medicine in Indonesia. Several plants from this family also have the potential to overcome mental health disorders (Table S11) namely, *Alpinia galanga* L., *Curcuma longa*, *Curcuma xanthorrhiza*, *Kaempferia galanga* L., and *Zingiber officinale* Roscoe (Saha & Banerjee, 2013; Oyemitan *et al*., 2017; Kartikasari *et al*., 2019; Ali *et al*., 2015; Sharma *et al*., 2016). Extracts and essential oils from this family have activity in overcoming mental health disorders. The *n*-hexane *K. galanga* L. extract possessed the highest sedative effect at a dose of 1,5 and 10 mg (Huang *et al*. 2008). Gupta and Maheshwari (2017) also succeeded in isolating curcumin with antianxiety activity at a dose of 50 mg/kg capable of increasing animal exploration time in the EZM test.

The results of literature studies for scientific evidence of Indonesian medicinal plants with the potential to overcome mental health disorders are small. Screening of potential plants is still mostly carried out using in vivo methods, while in vitro are rarely used. The exploration of potential plants is still insufficient, with only a limited number studied to identify the active compounds with therapeutic effects. There is also limited research that has reached clinical trials. Therefore, this literature review serves as a valuable resource, offering insights into Indonesian medicinal plants with the potential to treat disorders. Further exploration and research are encouraged for the development of alternative medicines to address mental health challenges.

Active Compounds of Indonesian Medicinal Plants that have the potential to treat mental health disorders

Medicinal plants have activities that can overcome mental health disorders due to active compounds. Some of the above plants have been proven and studied to obtain active compounds such as flavonoids, terpenoids, alkaloids, aromatics, lactones, carboxylic acids, and lignans. The active compounds in several Indonesian medicinal plants that play a role in overcoming mental health disorders are shown in Table IV.

Flavonoids are active compounds found in many Indonesian medicinal plants that have the potential to treat mental health disorders. Based on the table, 12 these compounds are active, including curcumin, catechin, torvanol A, medicarpin-3-O-glucoside, gossypetin-3-O-glucoside, naringenin-7-O-glucoside, kaempferol 3-(p-coumaryl) glucoside, quercetin 4'-O-β-d-glucopyranoside, apigenin 4',7-diglucoside, schaftoside, isoschaftoside and apigenin 8-C-α-D-glucopyranoside. Flavonoids play a role in overcoming depressive disorders, except for curcumin and torvanol A used for anxiety disorders. Several previous studies have studied the effects of the compound on depression and anxiety disorders. The results show the presence of multiple mechanisms, including the activation of BDNF signaling pathway through the restoration of stress-induced BDNF regulation. Moreover, there is an observed elevation in BDNF expression and levels within the hippocampus. These mechanisms also comprise interactions with serotoninergic 5-HT1A, noradrenergic NA, and dopaminergic receptors (D1, D2, and D3). The intervention restores brain monoamine levels by augmenting serotonin and dopamine in the CNS, enhancing CREB expression with cytoprotective properties. Furthermore, there are interactions with opioid receptors, serving as a specific TrkB agonist, stimulating neurogenesis in the hippocampus, and reducing hyperglycemia. The intervention shows a neuroprotective effect by attenuating neuroinflammation with antioxidant properties, influencing iNOS transmission, modulating GABAA receptor regulation, and acting as a melatonin receptor agonist (MT1 and MT2). MAO-A expression and activity are also reported through the regulation of KLF 11-MAO-A and SIRT1-MAO-A

Tabel IV. Active compounds of Indonesian medicinal plants overcome mental health disorders

	Active Compound	Plant	Activity	Mechanism	Reference
Flavonoid	Cathecin	*Uncaria Rhynchophylla*	Reduced immobility time in doses 80, 40, and 20 mg/kg (FST and TST)	Melatonin receptor agonists (MT1 and MT2)	Geng *et al*., 2019
	Fractions 13-20: medicarpin-3-o-glucoside (an isoflavonoid derivative), gossypetin-3-o-glucoside, naringenin-7-o-glucoside (flavanone)	*Lotus Corniculatus L.*	A dose of 100 mg/kg can reduce immobility time (FST, TST), inhibit MAO-A and MAO-B enzymes	Reversal of monoamine neurotransmitter attenuation and up-regulation of BDNF expression	Dereli *et al*., 2020
	Curcumin	*Curcuma Longa*	Dose 50 mg/kg increasing time spent in open arm (antianxiety EPM)	Affects the transmission of dopamine and norepinephrine, serotonin, and iNOS, weakens the regulation of GABAA receptors	Ceremuga *et al*., 2017
	Torvanol a (isoflavonoid)	*Solanum torvum*	Doses 10 and 30 mg/kg decreased the immobility period, and the time spent in closed arms, and in dark areas. Increased the time spent in open arms and the light area.	Increase noradrenaline (NE), 5-hydroxytryptamine (5-HT), and dopamine (DA) levels in the brain because they can interact with A1 adrenoceptors, 5-HT receptors, and D2 receptors	Mohan *et al*., 2013
	Fr3-3: kaempferol 3-(p-coumaryl) glucoside, quercetin 4'-o-β-d-glucopyranoside, apigenin 4' ,7-diglucoside, schaftoside, isoschaftoside and apigenin 8-c-α-d-glucopyranoside (Schaftoside) (quercetin 4'-o-β-d-glucopyranoside)	*Trigonella foenum-graecum*	Dose 35, 70, and 140 mg/kg reduced sucrose preference and increased immobility time	Regulate the KLF11-MAO-A and SIRT1-MAO-A signal pathways and regulate the levels of the monoamine neurotransmitters (NE, 5-HT, DA, and their metabolites) in the prefrontal cortex, hippocampus, and striatum in chronic restraint stress rats to inhibit MAO-A expression and activity	J. Wang *et al*., 2019

Tabel IV Continue

	Active Compound	Plant	Activity	Mechanism	Reference
Triterpenoid	Asiaticoside	*Centella asiatica*	Dose 20 and 40 mg/kg decreased sucrose consumption and reduced the immobility time in TST and FST in CMS mice	Increased levels of pcreB and BDNF, and CAMP/PKA signaling in the CMS model, increased levels of monoamine neurotransmitters	L. Wang *et al.*, 2020
	Asiatic acid	*Centella asiatica*	Reduced immobility time in doses 5, 10, and 20 mg/kg (FST and TST)	Protect dopaminergic neurons by antagonizing 1-methyl-4 phenyl 1,2,3,6 tetrahydropyridine (MPTP) and has also been found to decrease the glutathione levels significantly, and decrease corticosterone levels and increase the content of monoamine neurotransmitters	Girish & Sanjay, 2020
Alkaloid	Mitragynine	*Mitragyna speciosa* Korth	At doses of 10 mg/kg and 30 mg/kg reduces corticosterone release in mice exposed to FST and TST	The effect is due to interaction with neuroendocrine HPA axis systems	Farah Idayu *et al.*, 2011
	Amide alkaloid (piperine)	*Piper nigrum* L.		Counteracting 6-OHDA-induced injury in human dopaminergic cells. Therefore, it can increase cell viability induced by 6-OHDA.	Yu *et al.*, 2022
	Caffeine	*Coffea sp*	Dose 5 mg/kg reduced immobility time (FST)	The primary way that caffeine affects neurons is by blocking the adenosine inhibitory A1 and stimulatory A2A receptors, which regulate neuronal excitability and the release of several neurotransmitters	Szopa *et al.*, 2016

Tabel IV Continue

	Active Compound	Plant	Activity	Mechanism	Reference
Lignan Glycoside	(−)-Syringaresnol-4-o-β-d-apiofuranosyl-(1→2)- β-d-glucopyranoside (sag)	*Albizzia julibrissin* Durazz	Dose 3,6 mg/kg, p.o. can increase the quantity and length of time spent on the central entries in the OFT	Increases concentrations of NE, DA, HVA, 5-HT, and 5-HIAA throughout the cerebral cortex, and NE, 5-HT, and 5-HIAA act in the hippocampus of the brain	Liu *et al*., 2017
Hydrocarbons, Aromatic	Barakol	*Cassia siamea* Lamk	Dose 5, 10, 15, and 30 mg/kg increased swimming time (FST)	At the pre-synaptic nerve terminal, barakol inhibit dopamine release at both dopamine D2 and D3 receptor. At the post-synaptic nerve terminal, a low dose of barakol (10 mg/kg) can produce anxiolytic activity at her D2 receptors, whereas high doses of barakol produce hypokinesis and sedation at her D3 receptors	Pumpaisalchai *et al*., 2005
Lactone	Kavalactones (dihydrokavain, methysticin, dihydromethysticin, yangonin, and desmethoxyyangonin) (dihydrokavain)	*Piper methysticum*	The strongest MAO inhibitor has IC50 values for MAO-A and MAO-B of 1,29 and 0,085 μm, respectively	Inhibitors of MAO-A	Prinsloo *et al*., 2019
Carboxylic Acid	Docosanyl ferulate	*Withania somnifera* (WS) (L.) Duna	0,05; 0,25; and 2 Mg/Kg	Interact with the GABAAR to induce bdzs'-Like anxiolytic effects	Maccioni *et al*., 2021
	Rosmainic acid	*Perilla frutescens*	Dose 2,0 and 4,0 mg/kg increased the number of BrdU-positive cells and reduced the duration of immobility in FST	Up-regulatory action of RA-induced cell proliferation	Ito *et al*., 2008

signaling pathways (Ceremuga *et al*., 2017; Geng *et al*., 2019; Hritcu *et al*., 2017; J. Wang *et al*., 2019).

Triterpenoids and alkaloids have also been found to have antidepressants such as asiatic acid, asiaticoside for triterpenoids, and alkaloids including caffeine, mitragynine, and amide alkaloids. These five compounds have the potential to overcome depressive disorders. The mechanism of terpenoids and alkaloids in dealing with depressive disorders is not different from flavonoids. Asiatic acid shows protective effects on dopaminergic neurons by antagonizing 1-Methyl-4 phenyl 1,2,3,6 tetrahydropyridine (MPTP). The capacity to significantly decrease glutathione levels and reduce corticosterone levels is also showed (Girish & Sanjay, 2020). Alkaloids have antidepressant effects caused by interactions with the neuroendocrine HPA axis system (Idayu *et al*., 2011). The ability to counteract 6-OHDA-induced injury to human dopaminergic cells is also reported to increase cell viability (Yu *et al*., 2022). Alkaloids function as antagonists of A1 adenosine inhibitors, while stimulating A2A receptors. These receptors play a crucial role in regulating nerve excitability and the release of various neurotransmitters (Yu *et al*., 2022). Besides flavonoids, triterpenoids, and alkaloids, there are aromatics, lactones, carboxylic acids, and lignans. Aromatics and lactones are antidepressants, while lignans and carboxylic acids act as antianxiety agents. The mechanism of action for the four groups is almost like flavonoids.

Depressive symptoms are also associated with central and peripheral inflammation, oxidative and nitrosative stress (redox imbalance), increased apoptosis, and hypothalamic-pituitary-adrenal (HPA) axis hyperactivity due to exposure to chronic stress. Flavonoids acting as antidepressants are also associated with the inclusion of inflammatory mechanisms in depression (Ramos-Hryb *et al*., 2017). This is because patients with chronic inflammation often show symptoms of depression. This condition occurs due to repeated exposure to oxidative and nitrosative stress. Czarny *et al*., (2018) reported that the cause of oxidative DNA damage in depressed patients was increased levels of reactive oxygen species and nitrogen (ROS and RNS). The mechanism of flavonoids in treating the condition is closely related to the potential of flavonoids as antioxidants and anti-inflammatories. Flavonoids have phenolic groups that can accept electrons to form more stable phenoxyl radicals and prevent lipid peroxidation. Triterpenoids also have antioxidant activity with long carbon chains partitioned into lipid membranes and interact with free radicals (Ramos-Hryb *et al*., 2017).

Previous results have studied the effect of the structure of flavonoid compounds on antidepressant activity. Guan & Liu, (2016) showed that hydroxyl groups at positions 2, 4, or 4 on the A ring of flavonoids had antidepressant activity. The flavone compound C-glucoside also reported better antidepressant activity. Therefore, the number and position of the hydroxy groups affected the antidepressant effect. Furthermore, Sui *et al*., (2012) conducted FST and TST tests on the synthesized chalcone derivatives, which were also halogen-substituted. The results showed that the halogen-substituted compounds affected the antidepressant activity, with the level of activity Br > Cl > F. The effect of electron donors was also tested, where the level of 3,4-$(OH)_2$ > 4-OH (I) > 3-OCH_3- 4-OH > 3,4-$(OCH_3)_2$ > 4-CH_3 > H > 3,4-$(CH_3)_2$ > 4-OCH3. According to Xiang *et al*., (2007), MAO inhibitory activity would decrease with an increasing number of hydroxyphenyls in the B ring of flavone, and also the inhibition by flavonoids was dependent on the presence of a phenyl or hydroxyphenyls ring at position 2. The sequence of MAO inhibitory activity is flavonol flavones> flavones glycosides > flavanonols. Based on the results, several analyses need to be conducted in determining the effect of the structure and mechanism of flavonoids as antidepressants, including other active compounds such as terpenoids, and alkaloids. Many plants play a role in overcoming mental health disorders whose active compounds have not been studied. Therefore, further research is needed to determine the active compounds further developed into traditional and modern medicines.

CONCLUSION

In conclusion, 39 Indonesian medicinal plants were reported to treat mental health disorders. A total of 14 species were scientifically proven until their active compound was obtained by preclinical research. Therefore, further investigation into Indonesian medicinal plants was important, including preclinical trials for assessing potential therapeutic effects, identification of active compounds, and subsequent clinical trials to validate their efficacy and safety for potential medical applications. This research was crucial to generating comprehensive insights from Indonesian medicinal plants, contributing valuable knowledge for the development of drugs targeting

mental health disorders. Additionally, ongoing efforts were necessary to investigate the activities of unproven plants, substantiating and disseminating information on their potential as therapeutic agents.

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CONFLICT OF INTEREST

All authors declare that they do not have any conflicts of interest.

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