



Phytochemical Heterocycles in Depression Management: A Sustainable Strategy

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Abstract

According to WHO, depression is raising globally and expected as global burden by 2030. After COVID-19, drastic incline led to 17 % of total world population that suffered from well-known mental disorder depression and around 140,000 suicides annually attributed to depression. Owing to the diverse adverse effects associated with marketed antidepressants, research has increasingly shifted towards traditional herbal medicines for curing the both physical and emotional symptoms associated with depression. In recent years, natural products, particularly plant-derived secondary metabolites have with heterocyclic backbones, has become promising candidates for depression therapy. This review explores the medicinal potential of various plant-based compounds, including indole alkaloid, pyridine alkaloid, saponins, polyphenols. The secondary metabolites of these plants have demonstrated markable antidepressant-like effects in preclinical studies by modulating neurotransmitter system, reducing inflammation and promoting neurogenesis. For instance, compounds such as psychollatine and mitragynine (indole alkaloid), saikosaponin (saponins) and polyphenolic compounds like crocin and curcumin have resultant biological activity. Herbal remedies like St John's Wort (*Hypericum perforatum*), saffron, turmeric and ginseng have been used from centuries for mood regulation. By combining traditional knowledge with modern scientific researches, researchers can utilise the nature's therapeutic power to innovate safer and effective treatments for depression. However, further investigation is necessary to elucidate the accurate mechanism of these compounds through which they exert their effect, optimise dosing, quality control and rigorous clinical trials. Ultimately, combining the best of both traditional medicine and modern science can be revolution in the treatment of depression and lives of countless individuals can be improved.

Key words: CNS; Depression; Antidepressive agents; Heterocyclic compounds; Secondary metabolites, plant.

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Introduction

Depression is more than mood fluctuations and non-consistent emotional responses in daily life. Depression is life-suffering disease that affect millions of people all over the globe.¹ Depression,

is a serious neuropsychiatric disorder and its occurrence is due to genetic, immunological, physical and mental abuse, traumatic events, accidents and health problems, conflicts in job and family,

substance abuse and post-partum, as outlined in Figure 1. Depression is no longer an isolated problem, but has become a challenge for society.²

According to WHO data, 280 million people suffer from depression and 1.9 million children aged 7 to 12 years are also part of it.³ According to National Statics Health Services 2022, depression exists in more than one form and claims death of 14.8 % by suicide per 100,000 population.⁴ Depression is associated with number of chronic illnesses such as 51 % of individuals with Parkinson's disease, 42 % patients with cancer, 27 % of individuals with diabetes and 17 % of patients suffering with cardiovascular problems experiencing depression.⁵⁻⁸ In US 32.3 % population are dealing with depression and anxiety.⁹ The highest suicide rates among the age group of 85 or above were reported as 23.39 per 100,000 people, followed by 75 to 84 age group, with rate of 19.49 per 100,000 and the age group of 25 to 34 at 19.48 per 100,000 people.¹⁰ In the US more

than 1 in 10 young people from the 12 to 17 age group are living with depression and have had major depression episodes within the past year.¹¹ In India, the depression rates doubled after 2018 and reached a peak during the pandemic in 2020 which is nearly 45 million of the population and the onset is upward trajectory afterward.¹² People suffering from depression feel persistent sadness, hopelessness, diminished interest in enjoyable activities, low performance in academic, loss of appetite and sleep cycle disturbance.¹³⁻¹⁶ Even with successful treatment, the risk of relapse persists, often leading to cognitive impairment, social distress and strong emotional distress.¹⁷ Depression manifests in two forms, one is unipolar depression (major depression disorder) which is characterised by persistent low mood and the other is bipolar disorder, involving alternating periods of depression and mania.¹⁸ The prevalence of major depression episodes is higher among adult women, with a rate of 10.5 %, compared to 6.2 % among adult men.¹⁹

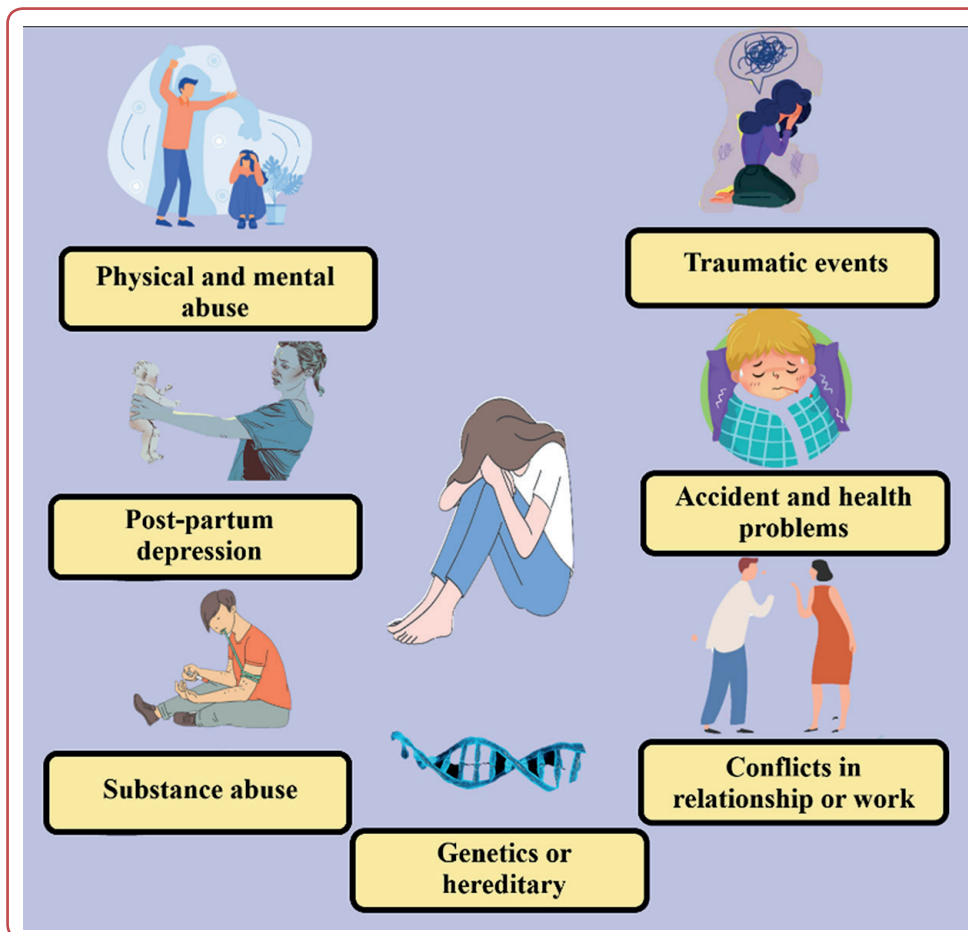


Figure 1: Causes of depression

Depression is primarily of the following types:

- Major depression disorder: which affects 8.3 % of total adults in the US and suffered at least one occurrence of major depression in 2021;
- Persistent depressive disorder: a long-term form of depression that persists for 2 years or longer;
- Bipolar disorder: is estimated to impact 2.8 % of adult men and women in the US;
- Seasonal depression: the symptoms return each year and almost 70 % are living with this condition.
- Postpartum depression: 6.5-20 % of women after giving birth experience postpartum depression.
- Psychotic depression: according to a 2021 research review about 4 in every 1000 adults go through this condition.²⁰⁻²⁵

Modern depression therapy relies on the drugs developed in the 1960s and early 1970s.²⁶ The widely prescribed drugs paroxetine, escitalopram and citalopram under selective serotonin reuptake inhibitor (SSRIs), serotonin-norepinephrine reuptake inhibitor (SNRI) and alternative of SSRIs and SNRIs- atypical antidepressant, commonly used bupropion.²⁷⁻²⁹ In addition, the U.S. Food and Drug Administration (FDA)-approved drug esketamine, administered as a nasal spray acts as N- methyl-D-aspartate (NMDA) receptor antagonist which is a clinically effective drug to relief suicidal symptoms associated with depression (Figure 2).³⁰ Antidepressants work on the monoamine hypothesis and have played a crucial role in treating major depression disorder. Current treatment prioritises SSRIs and SNRIs as

first-line therapies, while the combination of other antidepressants could also be considered if the initial monotherapy fails to work.^{31, 32} Regardless of their widespread uses, antidepressants pose significant challenges. Notably, their therapeutic effects are delayed with clinical trials.³³

There are several mechanisms which involves in psychiatric conditions such as systemic lipopolysaccharide challenge, bacterial infection, activated peripheral immune response, mimicking the acute inflammatory responses, neuroinflammation and microglia activation which together give rise to depression, Parkinson, Alzheimer and multiple sclerosis (Figure 3).³⁴ Chronic stress activates microglial activity by enhancing the infiltration of peripheral monocytes and increasing blood brain barrier (BBB) permeability. Neuroinflammation can disrupt neural-circuits, contributing to depression symptoms.³⁵ M1- phenotype microglia associated with pro-inflammatory role in the synthesis of inflammatory mediators that may lead to depression symptoms.³⁶ Gut microbiota (GM) is associated with various functions, including the creation and distribution of neurotransmitter. GM can have a significant effect on serotonin levels by sequestering tryptophan which is a precursor for serotonin production and convert it to tryptamine, thus denying the brain of supplying of tryptophan.³⁷

Depression treatment is majorly based on modern medication, classified into six types with distinct mechanisms of action. However, they cause various side effects such as sexual dysfunctions, heart problems, weight gain, dry mouth, suicidal thoughts and excess sleep, anxiety and constipa-

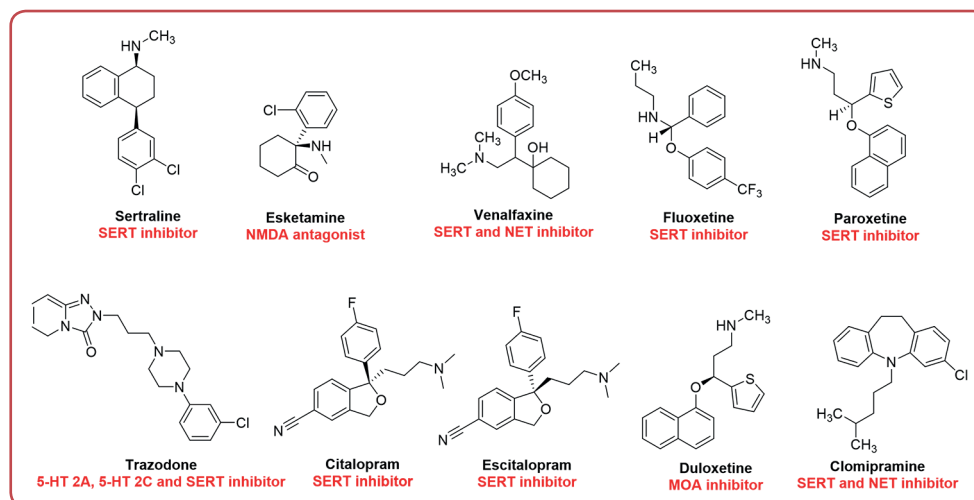


Figure 2: Different marketed anti-depressant with their structures

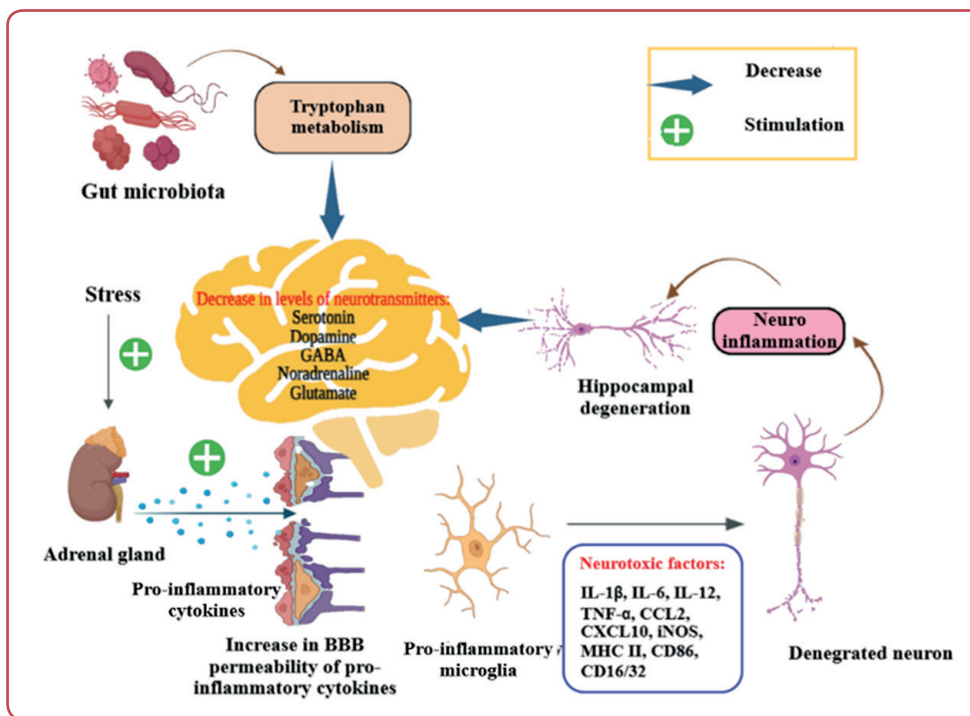


Figure 3: Different mechanism of causing depression

TNF- α : tumour necrosis factor-alpha; BBB: blood brain barrier; IL-12: interleukin 12; IL-6: interleukin 6; IL-1 β : interleukin 1 β ; CCL2: chemokine C-C motif ligand; iNOS: inducible nitric oxide synthase; CD86: cluster of differentiation 86; CXCL10: C-X-C motif chemokine ligand 10; CD16/32: cluster of differentiation; MHCII: major histocompatibility complex;

tion, these side effects can lead people to stop taking antidepressants (Table 1).^{38,39} Antidepressants are multi-target agents for the brain, targeting the different chemical messengers such as adrenergic and serotonergic pathways and indirectly by histaminergic, dopaminergic and cholinergic systems. However, some of these messengers also influence blood pressure.^{40,41} The distinct classes of antidepressants associated with weight changes in patients such as the atypical antidepressant drug, mirtazapine, is associated with weight gain due to off-target effects of the histamine and serotonin in appetite-promoting pathways, while another drug, bupropion is linked to weight loss effects.⁴² In light of the associated side effects, it is important to explore plant-based alternatives for managing depression.

This review summarises on antidepressant action of various plant-based secondary metabolites and explores clinical evidence regarding the efficacy of metabolites such as indole alkaloid and pyridine alkaloid, saponins, flavonoids and polyphenols in alleviating depressive symptoms. Depression patients are dependent on synthetic drugs, which lead to many lethal side effects, whereas new investigations emphasis on medicinal plants and their potential as antidepressants. Herbal and alternative therapy, as part of traditional medicine have been used for centuries to treat or manage depression.⁵⁰ Herbal medicines such as traditional Chinese medicine, African medicines and Islamic medicines, are widely used to treat and manage mental disorders around the world.^{51,52} *Hypericum per-*

Table 1: A Classification of antidepressant drugs: mechanism of action and side effects⁴³⁻⁴⁹

SN	Class of antidepressants	Antidepressant drugs	Mechanism of action	Side effects
1	Tricyclic antidepressants	Imipramine, desipramine, doxepin, amitriptyline	SERT, NET inhibition, Act on α_1 , α_2 , H ₁ and M ₁	Constipation, sexual dysfunction, suicidal thoughts, tachycardia, orthostatic hypertension
2	Serotonin selective reuptake inhibitor	Fluoxetine, paroxetine, citalopram, fluvoxamine	Increase serotonin transmission, SERT inhibitor	Serotonin syndrome, nausea, suicidal thoughts, cognitive impairment, prolonged QT interval

3	Serotonin- noradrenaline reuptake inhibitor	Duloxetine, desvenlafaxine, venlafaxine	SERT and NET inhibitor	Constipation, nausea, back pain high diastolic blood pressure, suicidal thoughts, serotonin syndrome
4	Atypical antidepressant	Trazodone, bupropion, vilazodone, mirtazapine	DAT inhibitor, antagonist of α_1 , 5-HT ₂ and 5-HT ₃	Dry mouth, agitation, headache, insomnia, seizures, sexual dysfunction, abnormal bleeding
5	Monoamine oxidase inhibitors	Phenelzine, selegiline, isocarboxazide	Inhibitors of MAO-A and MAO-B, Increase neurotransmitter levels	Insomnia, serotonin syndrome, headache, sexual dysfunction
6	N-methyl-D-aspartate receptor antagonist	Esketamine	AMPA receptor activation, Increase, neurotropic factor	Anxiety, blurred vision, abnormal feeling

SERT: serotonin transporter; NET: norepinephrine transporter; H: histamine receptor; M: muscarinic receptor; MAO: monoaminoxidase; DAT: dopamine transporter;

foratum (also named St John's Wort) is an herbal supplement ease depression's symptom and has been used for centuries. It is also available over the counter in the US.^{53, 54} Saffron, derived from the flower of the plant *Crocus sativus*, has been

showing effectiveness in reducing depression symptoms.^{55, 56} There are numerous active constituents derived from plants that as the potential to mitigate the depression symptoms, as outlined in Table 2.

Table 2: Overview of naturally occurring antidepressant plants: families, active constituents and mechanism of action⁵⁷⁻⁷⁰

SN	Plant name	Family	Active chemical constituents	Possible mechanism of action
1	<i>Hypericum perforatum</i> (St John's Wort)	Hypericaceae	Hypericin, hyperforin	Blocks reuptake of neurotransmitters such as serotonin, dopamine, gamma-aminobutyric acid (GABA), norepinephrine, glutamate
2	<i>Crocus sativus</i> (Saffron)	Iridaceae	Crocin, safranal	Serotonergic, anti-inflammatory, neuro-endocrine, neuro-protective effects
3	<i>Centella asiatica</i> (Asiatic Pennywort)	Umbellifere	Asiatic acid, asiaticoside, madecassic acid, madecassoside	Inhibit monoaminoxidase A (MAO-A) and MAO-B activity
4	<i>Ciltoria tematea</i> (<i>Ciltoria bracteata</i>)	Fabaceae	Anthocyanins	Inhibit the active site of MAO-A and MAO-B
5	<i>Besalla alba L</i> (Malabar spinach)	Basellaceae	Betacyanin, carotenoids, bioflavonoids, β -sitosterol, lupeol	Act on neurotransmitter levels
6	<i>Artemisia absinthium</i> (Common wormwood)	Asteraceae	Lactones, terpenoids, quercetin	Modulating MAO activity, increase neurotransmitter levels
7	<i>Rosa damascene</i> (Damask rose)	Rutaceae	Myrcene, carboxylic acid, kaempferol, quercetin, vitamin C	Hypotonic effect and decrease in locomotors activities
8	<i>Bacopa monniera</i> (Brahmi)	Plantaginaceae	Bacosides	Increase serotonin levels
9	<i>Urtica dioica</i> (Burn nettle)	Urticaceae	Chlorophylls, carotenoids, phenolic compounds	Inhibition of dopamine receptor
10	<i>Aegle marmelos</i> (Bael)	Rutaceae	Aegeline, marmeline, xanthotoxol, coumarin	Serotonergic and glutamatergic systems

11	<i>Tecoma stans</i> (Yellow bells)	<i>Bignoniaceae</i>	Tetradecanoic acid	Anti-oxidant
12	<i>Melissa officinalis</i> (Lemon balm)	<i>Lamiaceae</i>	Geranial, neral, urosolic acid, rosamarinic acid	Locomotion activity
13	<i>Cucurbita pepo</i> (Zucchini)	<i>Curcubitaceae</i>	Protocatechuric acid, vanillic acid, feulic acid, luteolin	Reduction in caspase and glial fibrillary acidic protein (GFAP)
14	<i>Alafia multiflora</i> (<i>Alafia malouetioides</i>)	<i>Apocynaceae</i>	Flavonoids, polyphenols, glycosides, triterpens, saponins, tannis	Non-adrenergic system
15	<i>Eicchornea crasspies</i> (<i>Pontederia crasspies</i>)	<i>Pontederiaceae</i>	Linolenic, hexadecenoic, myristic, stearic acids	Block reuptake of serotonin in presynaptic neuron
16	<i>Bacopa monnieri</i> (<i>Brahmi</i>)	<i>Plantaginaceae</i>	Bacosides A and B, flavonoids, alkaloids	Modulation of serotonin and dopamine pathways, neuroprotection via reduction of oxidation stress

Medicinal plants as new leads for antidepressant activity

Researchers are inclined towards plants as a treasure trove of promising new drug candidates.⁷¹ The current data regarding the precise mechanisms through which phytochemicals modulate neurochemical pathways within the central nervous system (CNS) to achieve therapeutic outcomes in depression disorders remains scarce.⁷²⁻⁷⁴

Indole alkaloids

Indole (C_8H_7N) (Figure 4) is a compound consists five-membered pyrrole ring fused to six-membered benzene ring, basic environment of IAs is arises from the delocalisation of nitrogen lone pair within the ring system.⁷⁵ Most of indole alkaloids-based metabolites are found in *Apocynaceae*, *Rubiaceae*, *Annonaceae* and *Loganiaceae* family-based plants.⁷⁶⁻⁷⁸

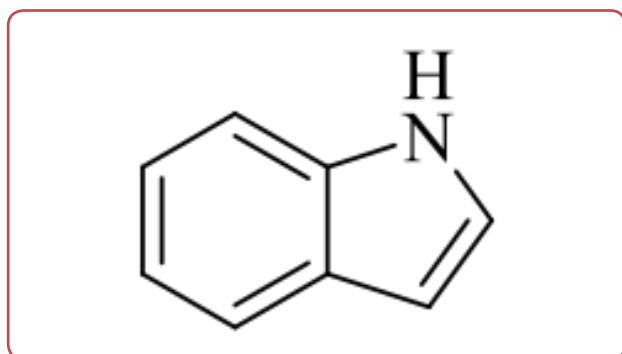


Figure 4: Chemical structure of indole

Mitragyna speciosa

M speciosa is known as Karotom, a herbal plant of family *Rubiaceae* and it is rich with indole alkaloid, mitragynine (Figure 5).⁷⁹ *M speciosa* is used as an opium substitute in Southeast Asia. Mitragynine has been suggested to the influence of serotonergic system in the brain. Kumarnsit et al, 2007a, Kumarnsit et al, 2007b, in two different animal models, forced swim test (FST) and tail suspension test (TST), examined aqueous extract of *M speciosa*, without affecting the locomotor activity there was marked inclined in the immobility periods at the dose of 10 and 30 mg/kg.⁸⁰

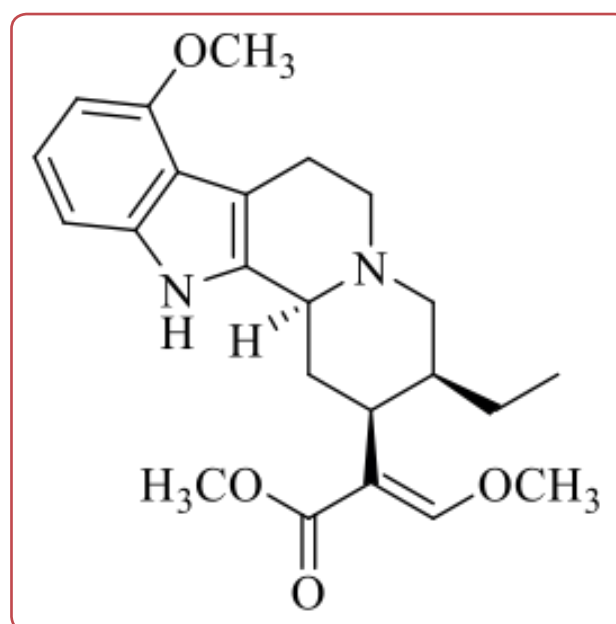


Figure 5: Chemical structure of mitragynine

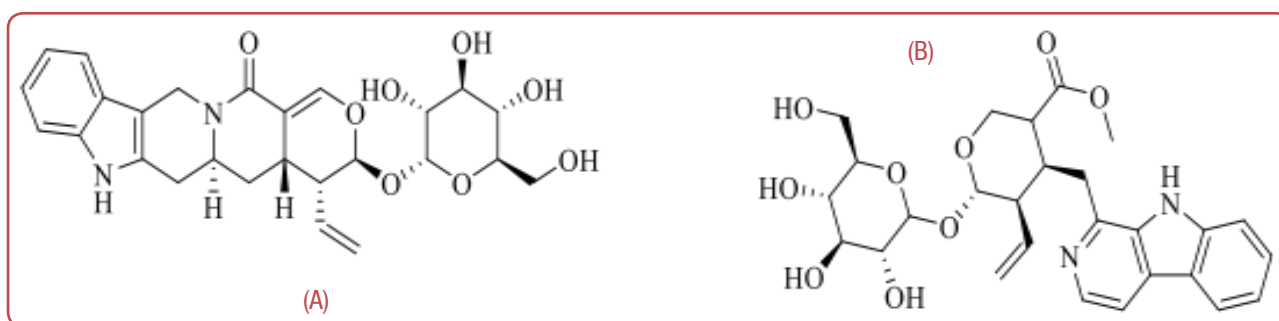


Figure 6: Chemical structure of A) lyaloside and B) strictosamide

Psychotria suterella and *Psychotria laciniata*

These are the species of the genus *Psychotria* that belongs to family *Rubiaceae* and these are topical species consisting bioactive glycosidic monoterpene indole alkaloids (MIAs) that potentially inhibit *in vitro* polymorphonuclear leukocytes (PMN) chemo-taxis, also showed antipyretic and peripheral analgesic activity in mice after oral administration.⁸¹ Dos Santos Passos et al conducted the pre-clinical studies for antidepressant activity by inhibition of MAO in brain.⁸² The bioactive MIAs of *P suterella* and *P laciniata* are lyaloside and strictosamide, respectively (Figure 6). These compounds exhibit activity against MAO-A, with half-maximal inhibitory concentration (IC_{50}) ie $50.40 \pm 1.09 \mu\text{g}/\text{mg}$ of lyaloside and $132.5 \pm 1.33 \mu\text{g}/\text{mg}$ of strictosamide. Their MAO-B inhibition activity examined at IC_{50} values of $306.6 \pm 1.40 \mu\text{g}/\text{mL}$ for lyaloside and $162.8 \pm 1.26 \mu\text{g}/\text{mL}$ for strictosamide.⁸³

Psychotria umbellata

P umbellata is another species of the genus *Psychotria* that belongs to family *Rubiaceae* and it is commonly known as "umbrella leaf." It consists of several bioactive groups such as alkaloids, flavonoids, triterpenes, phenolic compound and other essential oils. Whereas, its bioactive glycosidic monoterpene alkaloid named as psychollatine (Figure 7) that exerts the analgesic, anxiolytic, antidepressant and amnesic effects in mice models.⁸⁴ Bristy et al demonstrated the antidepressant action by two different tests, a hole-board test and a light/dark test. At doses of 7.5 mg/kg and 15 mg/kg in hole-board test, psychollatine demonstrated enhanced in crossings, rearing and head-dips in mice. In light/dark test, at the dose of 7.5 mg/kg significantly increased the time expenditure in the light compartment and prolonged latency to first enter in dark area. In the other study where FST was conducted at

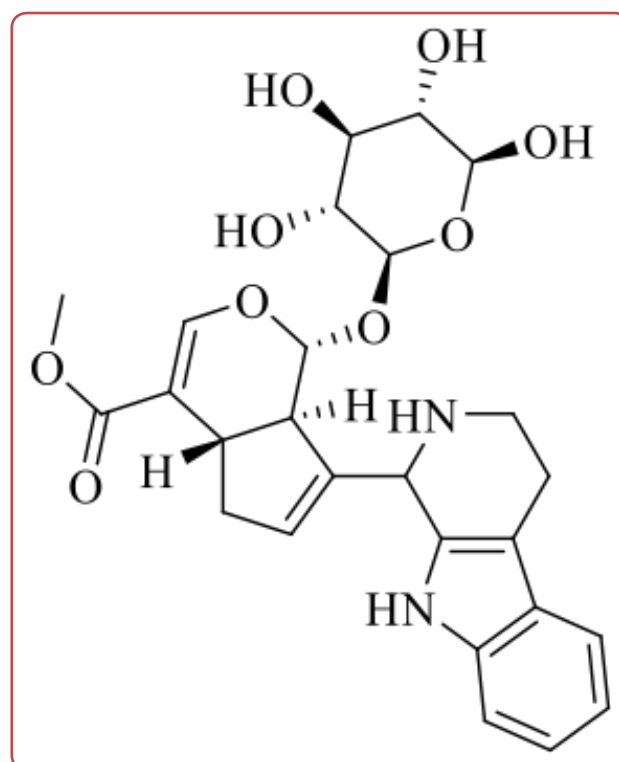


Figure 7: Chemical structure of psychollatine

doses 3 mg/kg and 7.5 mg/kg, psychollatine diminished the period of immobility in mice.⁸⁵

Psychotria nemorosa

P nemorosa the one of potent species of genus *Psychotria* belongs to family *Rubiaceae* commonly known as rainforest quinine. It is used as traditional herb for antipyretic, anti-inflammatory and antimicrobial problems.⁸⁶ The bioactive azepine-indole alkaloid, isolated from aerial parts of *P nemorosa*, exhibited wide effect on CNS. *P nemorosa* consist of three bioactive azepine-indole alkaloids named are cimitrypazepine, nemorosine A and fargesine (Figure 8). These causes neurodegeneration by affecting the enzymes acetylcholinesterase (AChE), butyrylcholinesterase (BChE), MAO-A and MAO-B.⁸⁷ Further,

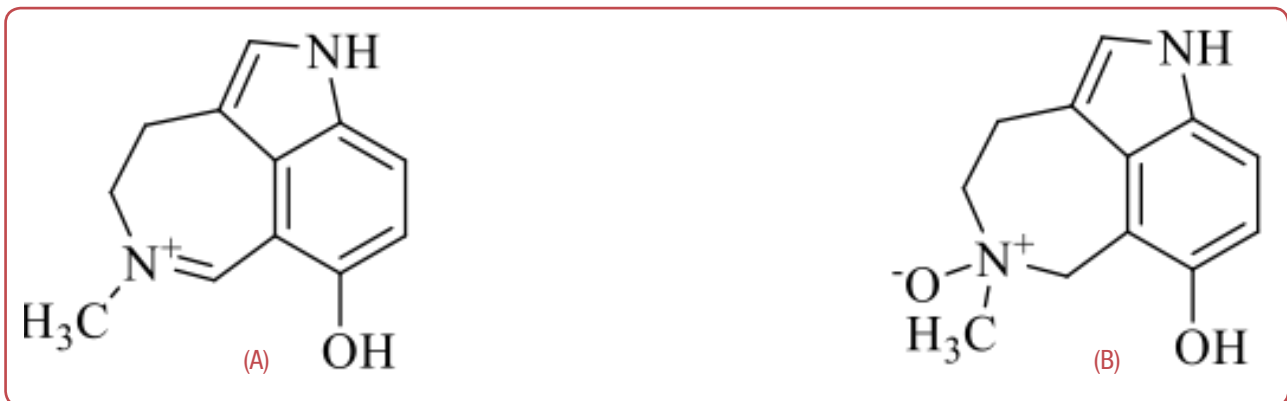


Figure 8: Chemical structure of A) cimitrypazepine and B) fargesine

Kirchweger et al demonstrated Ellman's method to determine MAO-A and MAO-B inhibition activity at IC_{50} 1.4, 1.4 and 0.9 μ m for cimitrypazepine, fargesine and nemorosine A, respectively, whereas inhibition of BChE for cimitrypazepine, fargesine and nemorosine A at IC_{50} 18, 41 and 21, respectively that leads to minimising the depression symptoms.⁸⁸

Peganum harmala

P. harmala, commonly known as wild rue belongs to family *Nitrariaceae*, composed of total 17 alkaloids of quinazoline and indole moiety.⁸⁹ It contains β -carbonyl compounds such as harmane, harmine and harmaline (Figure 9) that exhibits the inhibition action on MAO.⁹⁰ Adrielly et al demonstrated FST test, by intraperitoneal (ip) administration of harmane (11.5 mg/kg), harmine (8.5 mg/kg ip) and harmaline (8 mg/kg ip), decreased the immobility duration.⁹¹

Uncaria gambir

U. gambir, species of *Uncaria* belongs to family *Rubiaceae*. It is used as traditional medicine for sedation, antihypertension, analgesic and anti-convulsant.⁹² The studies supported by Hsu, Lieh-Ching, et al for antidepressant action of *U. gambir*

active monoterpene indole alkaloid compound, corynoxine (Figure 10) along with its anti-inflammatory and neuromodulator actions.⁹³ The oral absorption was found to be 27.3 % by using ultraperformance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method.⁹⁴

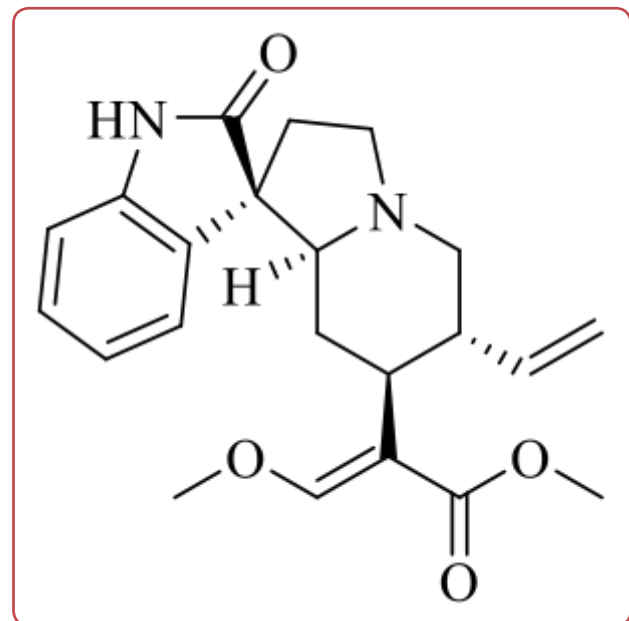


Figure 10: Chemical structure of corynoxine

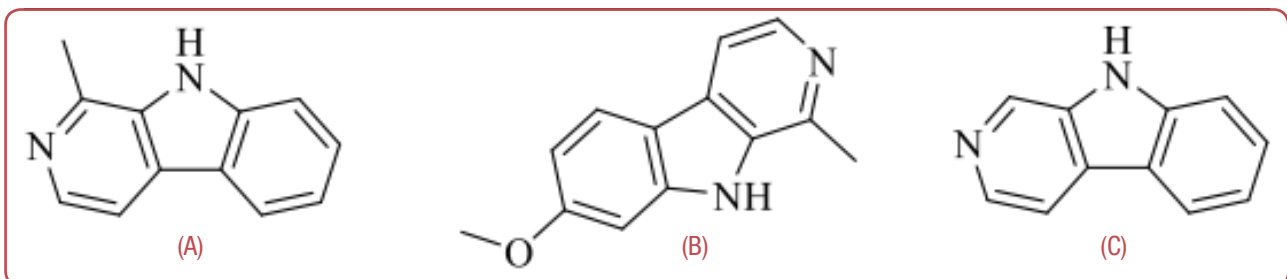


Figure 9: Chemical structure of A) harmane, B) harmine and C) harmaline

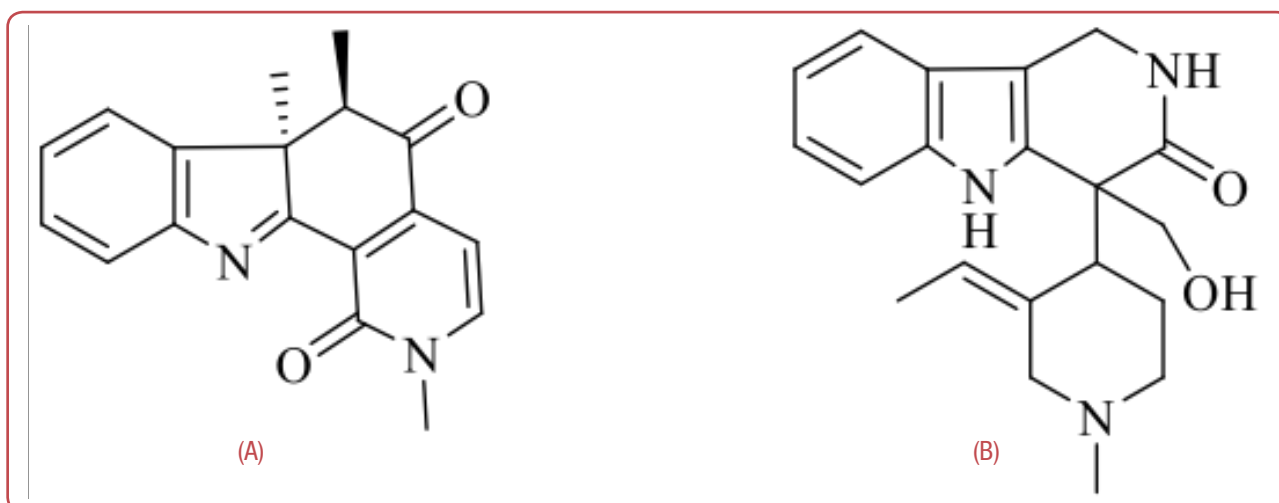


Figure 11: Chemical structure of A) alstoscholarisine F and B) alstoscholarisine G

Alstonia scholaris

A scholaris commonly known as blackboard tree which belongs to *Apocynaceae*. It is commonly used as herbal drug for treating cancer, psychosis and nociception.⁹⁵ *A scholaris* consist bioactive mono-terpenoid indole alkaloid named as alstoscholarisine F and alstoscholarisine G (Figure 11).⁹⁶ A study conducted by Kulkarni and Juveka et al examined the effect of *A scholaris* on stress induced depression and concluded methanolic extract cure the stress-induced indications after oral administration of 300 gm for 5 days. The studies demonstrated reducing in the dopamine levels in the frontal cortical regions of the brain of rats.⁹⁷

Pyridine alkaloid

Pyridine (Figure 12), privileged moiety containing the nitrogen atom within the pyridine ring crucial for its pharmacological activity.⁹⁸ Pyridine alkaloids which shows the activity on CNS are generally isolates from plants, fungi, bacteria and marine sources.⁹⁹

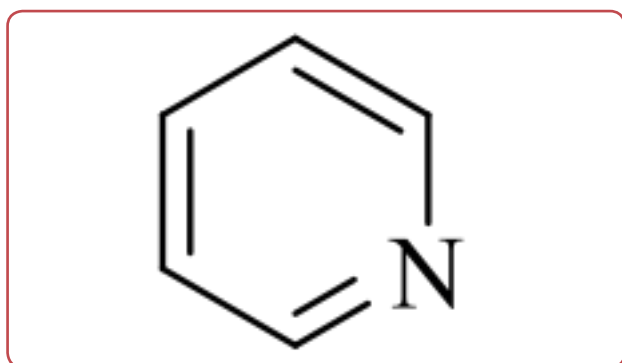


Figure 12: Chemical structure of pyridine

Areca catechu nut

It is an evergreen tree belonging to genus *Areca* of the palm family, *Arecaceae*. It is widely distributed in China, India, Indonesia, Malaysia.¹⁰⁰ *A catechu* traditionally used in Chinese medicine, target blood circulatory system, targets the nervous, digestive system. Additionally, exhibits potential activity as anti-oxidant, anti-inflammatory, anti-depressant and antimicrobial properties.¹⁰¹

The dichloromethane fraction of *A catechu* exhibits antidepressant action by inhibiting MAO-A receptor in rat brain homogenates. The studies found the compound found in *A catechu*, arecoline (Figure 13) possess the property to cross the BBB and work by activating the neuronal receptors which leads to increase in excitability that often linked to antidepressant activity. Some advance studies suggested that *A catechu* consist alkaloids that has potential to treat depression.¹⁰²

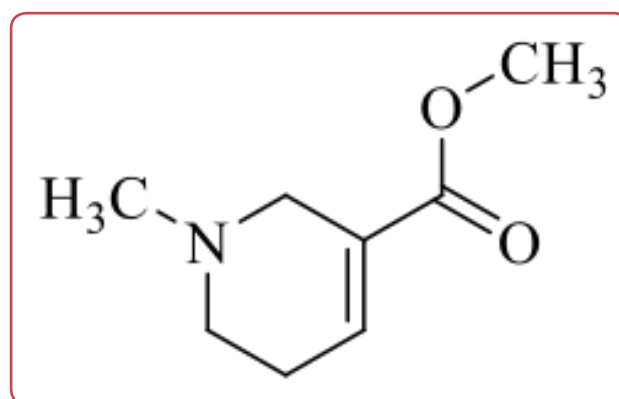


Figure 13: Chemical structure of arecoline

Salehi et al applied the both sub-chronic and acute FST on rats to evaluate the antidepressant activity of both ethanolic and aqueous extracts, with IC_{50} values of 50 mg/kg and 20 mg/kg, respectively. It was also discovered that both the ethanol and aqueous extracts notably increased the norepinephrine levels by nearly 30 % and serotonin levels by roughly 35 %.¹⁰³ Additionally, saponins present in *Areca catechu* also reported to be responsible for increase in monoamines in hippocampal of rat brain that act as an antidepressant activity, this was supported by chemical analysis.¹⁰⁴

Tabernaemontana divaricata

T. divaricate, commonly named as pinwheel flower, East India rosebay and belongs to family *Apocynaceae*.¹⁰⁵ The plant stem exudes a milky sap, so known as milk flower. Traditionally these plant used for several diseases such as diarrhoea, abdominal tumours, arthralgia, asthma, oedema, paralysis, piles, inflammation, leprosy, mania.¹⁰⁶ Faruq et al demonstrated the open field test for the methanolic extracts of *T. divaricate* exhibits decrease in the locomotor movement of the animal models at two doses level (200 and 400 mg/kg), while another hole-cross test of same extract exhibits the movement of mice models at dose from 1-40 mg/kg. In the TST and FST the decrease in the movements of mice models were noted at dose varying from 1-400 mg/kg.¹⁰⁷

Saponins

Saponins are bioactive compounds with surface-active glycosides of steroids and foaming characteristics which is due to fat-soluble saponin (aglycone) and water-soluble sugar (glycone). They naturally occur in plants, animals and insects but it named after soapwort plant (*Saponaria*) and historically used as a soap.¹⁰⁸⁻¹¹⁰ Saponins have bitter and unpleasant taste and historically these are used due to their plasma cholesterol lowering property, cardioprotective action, antidiabetic activity, cancer inhibition and anti-obesity properties.¹¹¹

Asparagus racemases

Asparagus derived from Greek word stands for "shoot" or "stalk," belonging to family, *Asparagaceae* and sub-family *Asparagoideae* and commonly known as Shatavari. It is well documented plant as traditional medicine in Siddha, Unani, Ayurveda and its medicinal properties are well-documented in both India and British Pharmacopoe-

ias.¹¹² The phytochemical studies shown that *A. racemosus* roots consist of alkaloids, carbohydrates, flavonoids, tannins and phenolic compounds have been identified in the hydroethanolic extract, whereas terpenes, saponins and steroids are identified in the ethanolic extract.¹¹³ The aqueous extract of *A. racemosus* elucidated that the bioactive compound of *A. racemosus*, sarsasapogenin (Figure 14) act as neuroprotective agent.¹¹⁴ Pahwa et al demonstrated the FST and learned helplessness (LH) on animal models for evaluating the anti-depressant activity of *A. racemosus* (methanolic extract) in rodents, at dosage of 200 mg/kg effectively worked as antioxidant and has potentially activity on both noradrenergic and serotonergic, however, not significantly impact the dopaminergic pathway. Further, hydroethanolic extract of *A. racemosus* at different doses (ie 200-800 mg/kg) were worked effectively by decreasing the seizure severity and improve the depression symptoms by enhancing memory and leaning ability.¹¹⁵

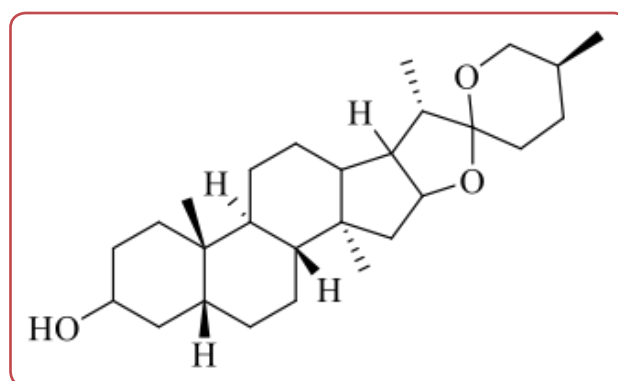


Figure 14: Chemical structure of sarsasapogenin

Bupleurum falcatum

Bupleurum falcatum is the dried roots of *B. falcatum* which belongs to *umbelliferae*, used mainly in China, Korea and Japan. *Bupleurum falcatum* contains the groups of triterpene glycosides, known as saikosaponins.¹¹⁶ For centuries, *B. falcatum* has been used as an antidepressant and referenced in the *Shennong Classic of Materia Medica*. The researches has been shown the result of extract of *B. falcatum*, saikosaponins reduce the depression symptoms in mice and the oral administration of *B. falcatum* (8 g/kg) notably inclined the immobility time in FST and TST.¹¹⁷

Saikosaponin A ($C_{42}H_{68}O_{13}$) and saikosaponin B ($C_{42}H_{68}O_{13}$) (Figure 15) reported as most potent bioactive saponins of the *B. falcatum*. Research has indicated that saikosaponin A and saikosaponin D

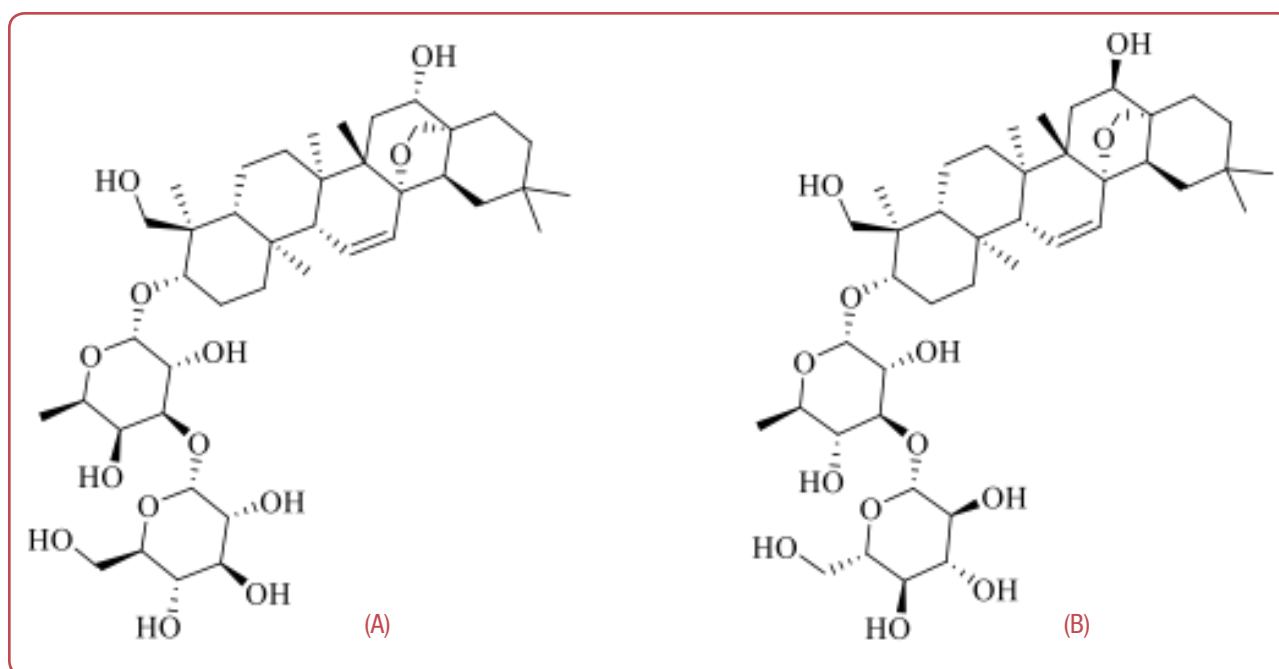


Figure 15: Chemical structure of A) saikosaponin A and B) saikosaponin B

exhibit antidepressant-like effects in perimenopausal rats. This effect is associated with the reduction of neuroinflammation, neurotropic systems and restoration of neuroendocrine in the hippocampus of rats.¹¹⁸ Liu, Chen-Yue, et al examined saikosaponin A at the dose of 50 mg/kg exerted the antidepressant effect induced by chronic unpredictable mild stress (CUMS) by increasing the dopamine level in the hippocampus

but had no effect on the levels of 5-HT and norepinephrine. Saikosaponin D a natural neuroprotective agent, increases glutamate levels in the hippocampus CA1 region in rat models, potentially alleviating depression symptoms.¹¹⁹

Panax ginseng

P. ginseng (Korean ginseng) is the herbal plant that founds in the mountains of East Asia and

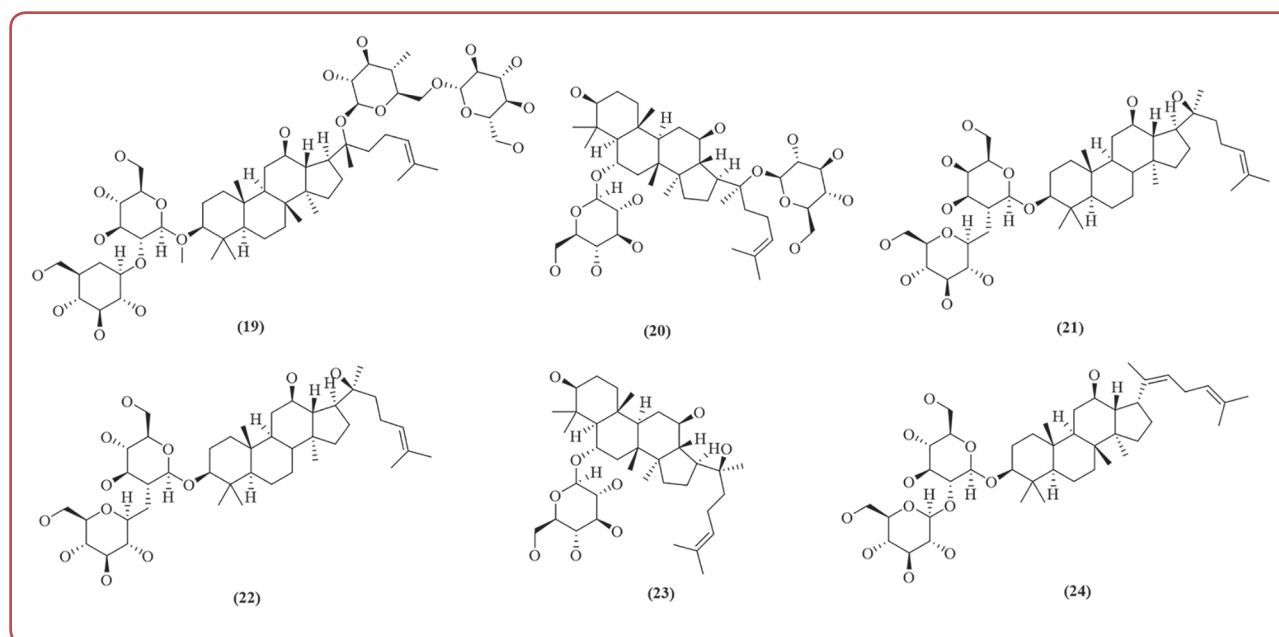


Figure 16: Chemical structure of six bioactive ginsenosides

19: 20(S)-Ginsenoside-Rb1; 20: 20(S)-Ginsenoside-Rg1; 21: 20(S)-Ginsenoside-Rg2; 22: 20(S)-Ginsenoside-Rg3; 23: 20(S)-Ginsenoside-Rg5; 24: 20(S)-Ginsenoside-Rh1;

belongs to family *Araliaceae*, in China it is considered as "The Lord of the herbs".¹²⁰ *P. ginseng* contains secondary metabolites, ginsenosides that exert several pharmacological effects on the nervous system and immune system.¹²¹ Ginsenosides are triterpene saponins with 30 carbon atom skeletons, classified into two primary groups: dammarane-type possess four rings carbon skeleton and oleanane-type containing five ring carbon skeleton.¹²² The studies reveal the six bioactive ginsenosides which show antidepressant action, named as 20(S)-Ginsenoside-Rb1, 20(S)-Ginsenoside-Rg1, 20(S)-Ginsenoside-Rg2, 20(S)-Ginsenoside-Rg3, 20(S)-Ginsenoside-Rg5, 20(S)-Ginsenoside-Rh1 (Figure 16).¹²³

P. ginseng regulates the monoamine neurotransmitters, upregulating the neurotrophic factors, has anti-inflammatory action and also regulates the function of HPA axis.¹²⁴ The studies have demonstrated that the extract of *P. ginseng* can reduce the morphine-induced anxiety and depression behaviour in rats.¹²¹

Panax notoginseng

P. notoginseng (Chinese ginseng) is the traditional Chinese plant belongs to family *Araliaceae*. It contains dammarane-type ginsenosides, further classified as 20(S)-protopanaxadiol and

20(S)-protopanaxatriol (Figure 17). It is traditionally used in the treatment of cardiovascular diseases, immune system and also has been reported for anti-tumour and anti-atherosclerotic action.¹²⁵ The pharmacological determination suggested that the antidepressant action may occur by enhancing the levels of norepinephrine, 5-HT in CNS.¹²⁶

In the conducted experiment FST, *P. ginseng* notably decreased the immobility in the test and had an impression on locomotor activity in the chronic mild stress model.¹²⁷ It also modulates the gamma-aminobutyric acid (GABA), BDNF and its intracellular signalling pathways in the CNS, additionally also had anti-inflammatory, anti-oxidative, inhibitory neuronal apoptosis actions.¹²⁸

Lepidagathis hyaline Nees

L. hyaline is a subtropical wild herbal plant of the family *Acanthaceae*, also known as curved *Lepidagathis*. The plant has been utilised in Ayurvedic practice to address coughs and cardiovascular ailments. The new studies found that the bioactive saponin constituent of *L. hyaline* consists of the antidepressant activity that has been demonstrated by FST and TST tests. The bioactive triterpenoid saponin (3-β-O-[α-L-rhamnopyranosyl(1→4)O-β-D-glucopyranosyl]16-α-hydroxy-olean-12-en(13)-28-oic acid) (Figure 18) was isolated and evaluated for its

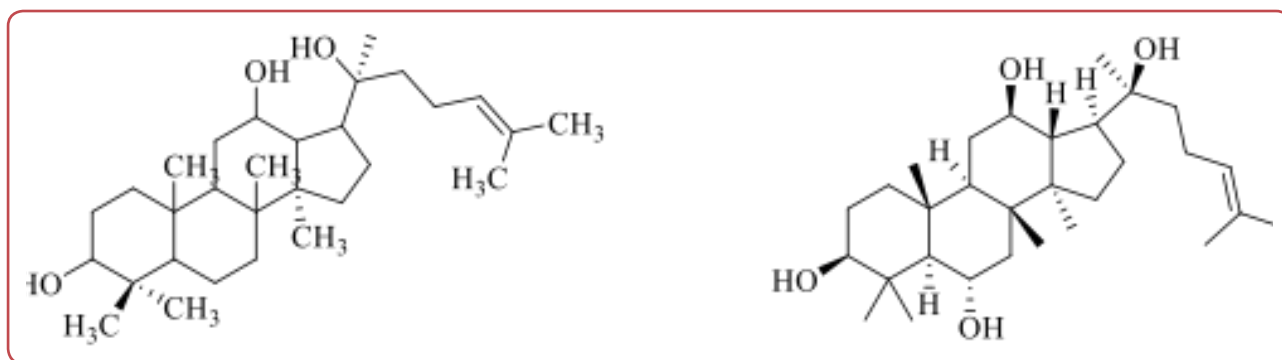


Figure 17: Chemical structure of A) 20(S)-protopanaxadiol and B) 20(S)-protopanaxatriol

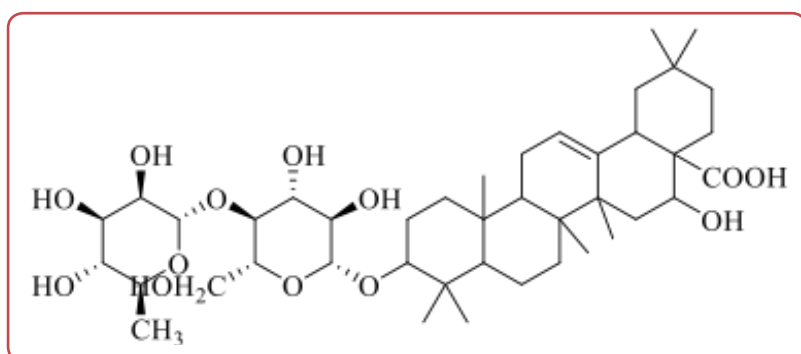


Figure 18: Chemical structure of bioactive triterpenoid saponin found in *Lepidagathis hyaline* Nees

antidepressant action.¹²⁹ In the TST and FST tests the results showed the declined in the immobility time at the dose of 200-400 mg/kg.¹³⁰

Polyphenols

Polyphenols, chemically classified as phenylpropanoids, are secondary metabolites synthesised by plants, consisting at least one aromatic ring with one or more -OH groups. These can be classified in different classes due to its varied chemical structures such as phenolic acid, lignans, flavonoids, stilbenes.¹³¹ Flavonoids abundantly present in foods as conjugated with sugar, acids, or alcohols. However, non-flavonoids include phenolic acids (vanillic acid and gallic acid) and cinnamic acids (ferulic acid and caffeic acid).¹³² Polyphenols (flavonoids and non-flavonoids) exhibits anti-inflammatory, anti-oxidant and neuroprotective properties and therefore, explored as complementary therapies in the treatment of mental disorders.¹³³⁻¹³⁷

Flavonoids

Flavonoids, naturally occurring polyphenols found abundantly in fruits, grains, vegetables, alcohol and tea and extensively studied due to their vast pharmacological actions.¹³⁸ Several preclinical studies relieved that flavonoids have antidepressant activity that has discovered due to their potential to reverse the depression behaviour of rodents in animal models, such plants are *Hypericum perforatum* and *Passiflora coerulea*.

Hypericum perforatum

H perforatum is commonly known as St John's wort, belongs to family *Hypericaceae*. The crude drug consists of wide range of compounds such as flavanol, flavanones, phenylpropanes, xanthones, phloroglucinols, proanthocyanidins, naphthodianthrones, some amino acids and essential oil constituents.¹³⁹ Studies have revealed that *H perforatum* consist of 150 constituents among them hypericin and hyperforin (Figure 19) found to be most active. In 2009, European Medicines Agency (EMA) standardised dry hydroalcoholic extracts of the aerial parts of *H perforatum* for official use in depressive disorder, ensuring therapeutic efficacy and consistent quality. Hyperforin act as broad-spectrum reuptake inhibitor of neurotransmitters such as dopamine, serotonin, noradrenaline, GABA and L-glutamate.¹⁴⁰ Hypericin reversed the carbenoxolone-induced gap junction dysfunction in rat prefrontal cortex that notably suggested it's potential role in pathophysiology of depression.¹⁴¹

Passiflora coerulea

P coerulea belongs to family *Passifloraceae* and a flavonoid named chrysin (5,7-dihydroxyflavone) (Figure 20) has been isolated from plant's leaves, stem and flowers. Chrysin exerts several pharmacological activities such as anti-cancer, anti-oxidant, anti-apoptotic, anti-inflammatory and neuroprotective.^{141, 142} The various studies confirmed that chrysin exhibits anxiolytic and antidepressant properties, due to its particular

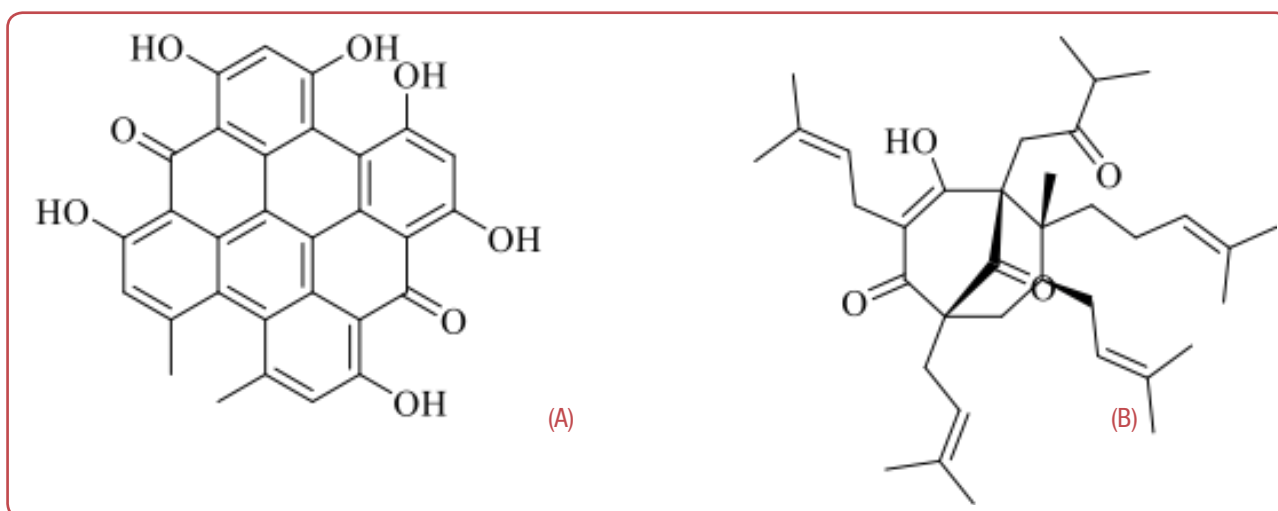


Figure 19: Chemical structure of A) hypericin and B) hyperforin

action on some neurotransmitter systems. Filho et al reported that chrysin at the dose of 5 and 20 mg/kg for 28 days, led to increase sucrose consumption and reduced immobility in the TST in female mice and at dose of 20 mg/kg given for 14 days induced antidepressant-like behaviour in male mice model when subjected to FST. This behavioural effects were associated with increased level of serotonin, BDNF and NGF and decreased in TNF- α , IFN- γ , IL-6 in the prefrontal cortex and hippocampus of mice.¹⁴³ Chrysin exhibits antidepressant-like activity similar to fluoxetine at 1 mg/kg dose after 28 days of treatment.¹⁴⁴

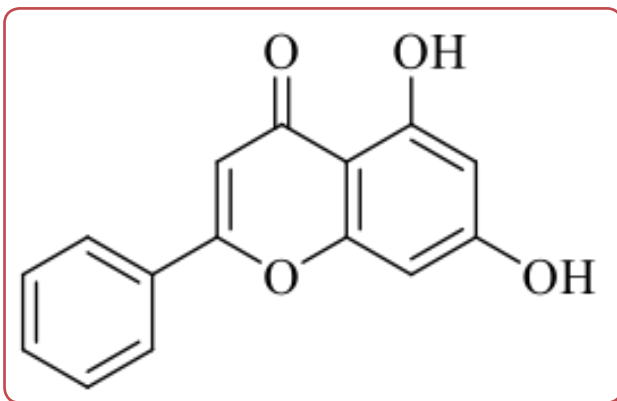


Figure 20: Chemical structure of chrysin (5,7-dihydroxyflavone)

Non-flavonoids

Curcuma longa

C longa (turmeric) and belongs to family *Zingiberaceae*. The active constituent curcumin (Figure 21) has growing evidence to support antidepressant action via multiple mechanism of action, including; modulation of neurotransmitters by increasing the noradrenaline, dopamine and serotonin, lowers the oxidative markers and nitric oxide

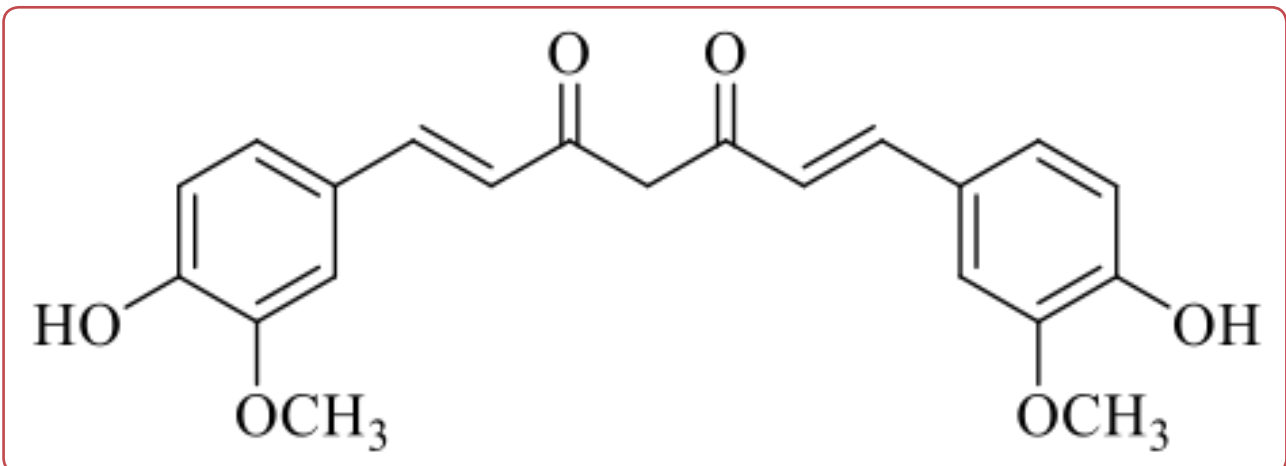


Figure 21: Chemical structure of curcumin

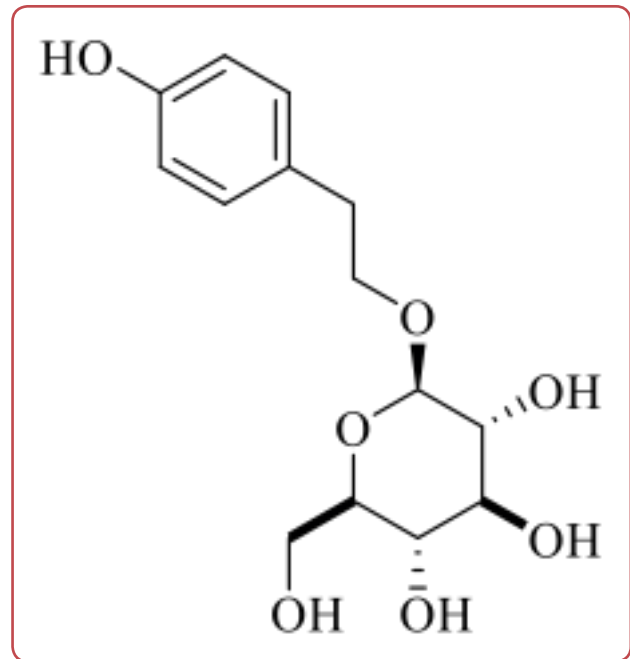


Figure 22: Chemical structure of glycyrrhizic acid

while increasing the antioxidant enzymes activity, anti-immune inflammatory action by reducing the levels of inflammatory cytokines like TNF- α , IL-6, NF- κ B, IL-1, COX-2 and neuroprotective effect by decreasing neurotoxicity levels.^{145, 146} The studies has been demonstrate that curcumin showing consistently decreased immobility time during the FST and TST tests in animal models.¹⁴⁷

Rhodiola rosea

R rosea commonly known as golden root and belongs to family *Crassulaceae*. It is the herbal medicine that have several actions such as anti-inflammatory, hepatoprotective, antimicrobial, anti-tumour, neurotrophic and neuro-protective action.^{148, 149} Over 140 compounds have been de-

tected in *R rosea* and main bioactive compound is salidroside glycone (Figure 22).¹⁵⁰ The antidepressant activity of *R rosea* has been validated in a phase 3 clinical trials in which 340 or 680 mg/day of *R rosea*, significantly improved the depression in subjects without causing any other side effects.¹⁵¹ Preclinical studies suggested that it modulate the several neurotransmitter such as dopamine, serotonin, noradrenaline and acetylcholine in the selective region of rat brain.¹⁴⁸

Crocus sativus

C sativus commonly known as saffron crocus belongs to family *Iridaceae*. Saffron has been used as Indian species from centuries and become

one of the most expensive ingredients in the world.¹⁵² The dried *C sativus* contain 150 volatile compounds and the studies demonstrate the bioactive components are safranal, crocin, crocetin and picrocrocin exhibits the antidepressant like action (Figure 23).^{153, 154}

The numerous *in vitro*, clinical trials and *in vivo* studies have showed the antidepressant effects on both and petals of plant and dried stigmas in rodent and humans.¹⁵⁵ The proposed mechanism of *C sativus* as antidepressant are: monoamine reuptake inhibition, as supported by clinical studies and NMDA receptor antagonism, as demonstrated in preclinical investigations.¹⁵⁶⁻¹⁵⁸

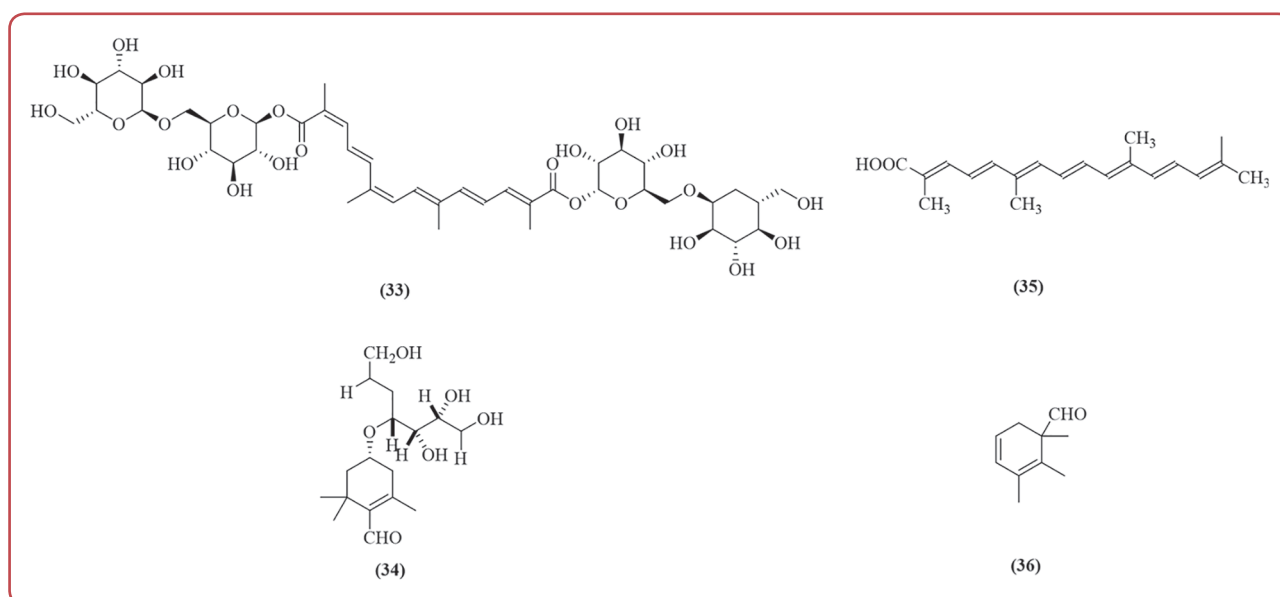


Figure 23: Chemical structure of 33) safranal, 34) crocin, 35) crocetin and 36) picrocrocin

Challenges associated with herbal drugs as antidepressants

I. Standardised clinical trials: Many herbal drugs lack precise clinical trials to establish their efficacy, dosage and potential adverse effects. This hinders acceptance by researchers.

II. Quality control: The quality and potency of herbal compounds can vary significantly according to the plant species, geographical origin, harvesting time. Additionally, extracting the active compounds, purifying and formulating them into standardised products with established quality control parameters such as absence of microbial

growth and heavy metals can be challenging and costly.

III. Regulatory challenges: Global regulatory authorities should collaborate to establish broad guidelines for good manufacturing practices (GMP) in phytochemistry. These guidelines should address various aspects such as quality assurance, formulation, clinical trials and dosage.

IV. Precise mechanism of action: The accurate mechanism of many herbal compounds is not yet

fully understood. While a few studies have proposed possible mechanisms, such as modulation of neurotransmitter levels, additional research is needed to decode the specific pathways involved for therapeutic activity.

By addressing these obstacles, researchers can explore the potential of herbal medicines, paving the way for innovative and effective therapeutic strategies for depression.

Conclusion

Considering the growing global burden of depression, there is crucial need for effective and safer treatment choices. While the modern antidepressants have been extensively used for treatment, however, their limitations such as delayed onset of action, adverse side effects and variable efficacy, have prompted the research of alternative therapeutic approaches.

Medicinal plants, with their historical use as traditional medicine, offer the potential for the development of novel antidepressant therapies with minimal adverse effects. Numerous scientific investigations have disclosed the potential of various plant's secondary metabolites as antidepressants, such as indole alkaloids, pyridine alkaloids, saponins and polyphenols. These metabolites contributing their therapeutic potential by modulating neurotransmitter system and reducing inflammation. However, precise clinical trials are crucial to validate the safety and efficacy of these metabolites. Standardise clinical trials are necessary to establish their clinical applicability and optimise their therapeutic efficacy.

By integrating the knowledge of traditional medicine with scientific research, holds the assurance of addressing the unmet needs of patients suffering from depression, ultimately improving their quality of life and well-being.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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References

- Pahlavani AH. Possible role of exercise therapy on depression: effector neurotransmitters as key players. *Behav Brain Res.* 2024 Feb;459:114791. doi: 10.1016/j.bbr.2023.114791.
- Jalali A, Ziapour A, Karimi Z, Rezaei M, Emami B, Kalhori RP, et al. Global prevalence of depression, anxiety, and stress in the elderly population: a systematic review and meta-analysis. *BMC Geriatr.* 2024 Oct 4;24(1):809. doi: 10.1186/s12877-024-05311-8.
- Deng MG, Liu F, Liang Y, Wang K, Nie JQ, Liu J. Association between frailty and depression: a bidirectional Mendelian randomisation study. *Sci Adv.* 2023 Sep 22;9(38):eadi3902. doi: 10.1126/sciadv.adi3902.
- Rashid R, Aamodt WW, Horn S, Dahodwala N. Association of caregiver depression risk with patient outcomes in Parkinson disease. *JAMA Netw Open.* 2023 Aug 11;6(8):e2327485. doi: 10.1001/jamanetworkopen.2023.27485.
- Wu X, Zhang W, Zhao X, Zhang L, Xu M, Hao Y, et al. Investigating the relationship between depression and breast cancer: observational and genetic analyses. *BMC Med.* 2023 May 4;21(1):170. doi: 10.1186/s12916-023-02876-w.
- Barker MM, Davies MJ, Zaccardi F, Brady EM, Hall AP, Henson JJ, et al. Age at diagnosis of type 2 diabetes and depressive symptoms, diabetes-specific distress, and self-compassion. *Diabetes Care.* 2023 Mar 1;46(3):579–86. doi: 10.2337/dc22-1237.
- Kalinderi K, Papaliagkas V, Fidani L. Current genetic data on depression and anxiety in Parkinson's disease patients. *Parkinsonism Relat Disord.* 2024 Jan;118:105922. doi: 10.1016/j.parkreldis.2023.105922.
- Lu D, Valdimarsdóttir UA, Wei D, Chen Y, Andreassen OA, Fang F, et al. Perinatal depression and risk of maternal cardiovascular disease: a Swedish nationwide study. *Eur Heart J.* 2024 Aug 16;45(31):2865–75. doi: 10.1093/eurheartj/ehae170.
- Revet A, Montastruc F, Roussin A, Raynaud JP, Lapeyre-Mestre M, Nguyen TTH. Antidepressants and movement disorders: a postmarketing study in the world pharmacovigilance database. *BMC Psychiatry.* 2020 Dec;20(1):308. doi: 10.1186/s12888-020-02711-z.
- Accardo AL, Pontes NMH, Pontes MCF. Heightened anxiety and depression among autistic adolescents with ADHD: findings from the National Survey of Children's Health 2016–2019. *J Autism Dev Disord.* 2024;54(2):563–76. doi: 10.1007/s10803-022-05803-9.
- Qato DM, Ozenberger K, Olsson M. Prevalence of prescription medications with depression as a potential adverse effect among adults in the United States. *JAMA.* 2018 Jun 12;319(22):2289. doi: 10.1001/jama.2018.6741.
- Verma S, Mishra A. Depression, anxiety, and stress and socio-demographic correlates among general Indian public during COVID-19. *Int J Soc Psychiatry.* 2020 Dec;66(8):756–62. doi: 10.1177/0020764020934508.
- Barros MBDA, Lima MG, Malta DC, Szwarcwald CL, Azevedo RCS, Romero D, et al. Report on sadness/depression, nervousness/anxiety and death problems in the Brazilian adult population during the COVID-19 pandemic. *Epidemiol Serv Saude.* 2020;29(4):e2020427. doi: 10.1590/S1679-49742020000400018.
- Andreae C, Van Der Wal MHL, Van Veldhuisen DJ, Yang B, Strömberg A, Jaarsma T. Changes in appetite during the heart failure trajectory and association with fatigue, depressive symptoms, and quality of life. *J Cardiovasc Nurs.* 2021 Nov;36(6):539–45. doi: 10.1097/JCN.0000000000000756.
- Recchia F, Bernal JDK, Fong DY, Wong SHS, Chung PK, Chan DKC, et al. Physical activity interventions to alleviate depressive symptoms in children and adolescents: a systematic review and meta-analysis. *JAMA Pediatr.* 2023 Feb 1;177(2):132. doi: 10.1001/jamapediatrics.2022.5090.
- Pandi-Perumal SR, Monti JM, Burman D, Karthikeyan R, BaHammam AS, Spence DW, et al. Clarifying the role of sleep in depression: a narrative review. *Psychiatry Res.* 2020 Sep;291:113239. doi: 10.1016/j.psychres.2020.113239.
- Cuijpers P, Karyotaki E, Ciharova M, Miguel C, Noma H, Furukawa TA. The effects of psychotherapies for depression on response, remission, reliable change, and deterioration: a meta-analysis. *Acta Psychiatr Scand.* 2021 Sep;144(3):288–99. doi: 10.1111/acps.13335.
- Grover S, Adarsh H. A comparative study of prevalence of mixed features in patients with unipolar and bipolar depression. *Asian J Psychiatry.* 2023 Mar;81:103439. doi: 10.1016/j.ajp.2022.103439.
- Liu X, Wang S, Wang G. Prevalence and risk factors of postpartum depression in women: a systematic review and meta-analysis. *J Clin Nurs.* 2022 Oct;31(19–20):2665–77. doi: 10.1111/jocn.16121.
- Abdoli N, Salari N, Darvishi N, Jafarpour S, Solaymani M, Mohammadi M, et al. The global prevalence of major depressive disorder (MDD) among the elderly: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2022 Jan;132:1067–73. doi: 10.1016/j.neubiorev.2021.10.041.
- Walter HJ, Abright AR, Bukstein OG, Diamond J, Keable H, Ripperger-Suhler J, et al. Clinical practice guideline for the assessment and treatment of children and adolescents with major and persistent depressive disorders. *J Am Acad Child Adolesc Psychiatry.* 2023 May;62(5):479–502. doi: 10.1016/j.jaac.2022.10.001.
- Do A, Li VW, Huang S, Michalak EE, Tam EM, Chakrabarty T, et al. Blue-light therapy for seasonal and non-seasonal depression: a systematic review and meta-analysis of randomised controlled trials. *Can J Psychiatry.* 2022 Oct;67(10):745–54. doi: 10.1177/07067437221097903.
- Dubovsky SL, Ghosh BM, Serotte JC, Cranwell V. Psychotic depression: diagnosis, differential diagnosis, and treatment. *Psychother Psychosom.* 2021;90(3):160–77. doi: 10.1159/000511348.

24. Sharma V, Sharkey KM, Palagini L, Mazmanian D, Thomson M. Preventing recurrence of postpartum depression by regulating sleep. *Expert Rev Neurother.* 2023 Aug 3;23(8):1-9. doi: 10.1080/14737175.2023.2237194.
25. Kwaśna J, Kwaśny A, Wilkowska A, Bychowski M, Cubała WJ. Residual hypersomnia in unipolar and bipolar depression: a systematic review. *World J Biol Psychiatry.* 2024 Nov 25;25(10):575-91. doi: 10.1080/15622975.2024.2429429.
26. Samouco AICB, Alves SP. Isoniazid-induced mania and the history of antidepressant drugs: case report and literature review. *Bipolar Disord.* 2023 Feb;25(1):84-7. doi: 10.1111/bdi.13272.
27. Heesbeen EJ, Bijlsma EY, Verdouw PM, Van Lissa C, Hooijmans C, Groenink L. The effect of SSRIs on fear learning: a systematic review and meta-analysis. *Psychopharmacology (Berl).* 2023 Nov;240(11):2335-59. doi: 10.1007/s00213-023-06333-7.
28. Pukall C. Post-SSRI/SNRI sexual dysfunction: a review. *J Sex Med.* 2023 Jun 27;20(Suppl_3):qdad068.019. doi: 10.1093/jsxmed/qdad068.019.
29. Pannu A, Goyal RK. From evidence to practice: a comprehensive analysis of side effects in synthetic antidepressant therapy. *Curr Drug Saf.* 2024 Apr 25;19. doi: 10.2174/0115748863301630240417071353.
30. Moore TJ, Alami A, Alexander GC, Mattison DR. Safety and effectiveness of NMDA receptor antagonists for depression: a multidisciplinary review. *Pharmacother J Hum Pharmacol Drug Ther.* 2022 Jul;42(7):567-79. doi: 10.1002/phar.2707.
31. Brown SL, Bleich A, Praag HMV. The monoamine hypothesis of depression. In: *Role of Serotonin in Psychiatric Disorders*. 1st ed. New York: Routledge; 2023. p.91-128. doi: 10.4324/9781315825861-5.
32. Altaf R, Gonzalez I, Rubino K, Nemeč EC. Folate as adjunct therapy to SSRI/SNRI for major depressive disorder: systematic review & meta-analysis. *Complement Ther Med.* 2021 Sep;61:102770. doi: 10.1016/j.ctim.2021.102770.
33. Garg U, Ferguson A. Challenges in therapeutic drug monitoring of classical tricyclic and newer antidepressants. In: *Therapeutic Drug Monitoring*. Elsevier; 2024. p.217-40. doi: 10.1016/B978-0-443-18649-3.00002-1.
34. Yamada Y, Sumiyoshi T. Neurobiological mechanisms of transcranial direct current stimulation for psychiatric disorders: neurophysiological, chemical, and anatomical considerations. *Front Hum Neurosci.* 2021 Feb 4;15:631838. doi: 10.3389/fnhum.2021.631838.
35. Han KM, Ham BJ. How inflammation affects the brain in depression: a review of functional and structural MRI studies. *J Clin Neurol.* 2021;17(4):503. doi: 10.3988/jcn.2021.17.4.503.
36. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol.* 2021 Jan;19(1):55-71. doi: 10.1038/s41579-020-0433-9.
37. Fang S, Wu Z, Guo Y, Zhu W, Wan C, Yuan N, et al. Roles of microglia in adult hippocampal neurogenesis in depression and their therapeutics. *Front Immunol.* 2023 Oct 10;14:1193053. doi: 10.3389/fimmu.2023.1193053.
38. Saha K, Torous J, Kiciman E, De Choudhury M. Understanding side effects of antidepressants: large-scale longitudinal study on social media data. *JMIR Ment Health.* 2021 Mar 19;8(3):e26589. doi: 10.2196/26589.
39. Oliva V, Lippi M, Paci R, Del Fabro L, Delvecchio G, Brambilla P, et al. Gastrointestinal side effects associated with antidepressant treatments in patients with major depressive disorder: a systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry.* 2021 Jul;109:110266. doi: 10.1016/j.pnpbbp.2021.110266.
40. Cao H, Baranova A, Zhao Q, Zhang F. Bidirectional associations between mental disorders, antidepressants and cardiovascular disease. *BMJ Ment Health.* 2024 Jan;27(1):e300975. doi: 10.1136/bmjment-2023-300975.
41. Tang SW, Tang WH, Leonard BE. Treatment-induced mood switching in affective disorders. *Acta Neuropsychiatr.* 2022 Apr;34(2):55-68. doi: 10.1017/neu.2021.47.
42. Gill H, Gill B, El Halabi S, Chen Li D, Lipsitz O, Rosenblatt JD, et al. Antidepressant medications and weight change: a narrative review. *Obesity (Silver Spring).* 2020 Nov;28(11):2064-72. doi: 10.1002/oby.22969.
43. Ziszo J, Reddy R, Kulkarni N, Blachman-Braun R, Ramasamy R. Impact of low-dose melatonin supplementation on testosterone levels in U.S. adult males. *Urology.* 2022 Nov;169:92-5. doi: 10.1016/j.urology.2022.07.048.
44. Edinoff AN, Akuly HA, Hanna TA, Ochoa CO, Patti SJ, Ghaffar YA, et al. Selective serotonin reuptake inhibitors and adverse effects: a narrative review. *Neurol Int.* 2021 Aug 5;13(3):387-401. doi: 10.3390/neurolint13030038.
45. Stahl ST, Jung C, Weiner DK, Peciña M, Karp JF. Opioid exposure negatively affects antidepressant response to venlafaxine in older adults with chronic low back pain and depression. *Pain Med.* 2020 Aug 1;21(8):1538-45. doi: 10.1093/pm/pnz279.
46. Roszkowska A, Plenis A, Kowalski P, Bączek T, Ołędzka I. Recent advancements in techniques for analyzing modern, atypical antidepressants in complex biological matrices and their application in biomedical studies. *TrAC Trends Anal Chem.* 2022 Jul;152:116609. doi: 10.1016/j.trac.2022.116609.
47. Chindo BA, Howes MJR, Abuhamdah S, Yakubu MI, Ayuba GI, Battison A, et al. New insights into the anticonvulsant effects of essential oil from *Melissa officinalis* L. (lemon balm). *Front Pharmacol.* 2021 Oct 14;12:760674. doi: 10.3389/fphar.2021.760674.
48. Bahji A, Vazquez GH, Zarate CA. Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. *J Affect Disord.* 2021 Jan;278:542-55. doi: 10.1016/j.jad.2020.09.071.
49. Shafique H, Demers JC, Biesiada J, Golani LK, Cerne R, Smith JL, et al. (R)-(-)-Ketamine: the promise of a novel treatment for psychiatric and neurological disorders. *Int J Mol Sci.* 2024 Jun 20;25(12):6804. doi: 10.3390/ijms25126804.
50. Dobrek L, Głowacka K. Depression and its phytotherapy: a narrative review. *Int J Mol Sci.* 2023 Mar 1;24(5):4772. doi: 10.3390/ijms24054772.
51. Zhuang W, Liu SL, Xi SY, Feng YN, Wang K, Abduwali T, et al. Traditional Chinese medicine decoctions and Chinese patent medicines for the treatment of depression: efficacies and mechanisms. *J Ethnopharmacol.* 2023 May;307:116272. doi: 10.1016/j.jep.2023.116272.
52. Lee MT, Peng WH, Kan HW, Wu CC, Wang DW, Ho YC. Neurobiology of depression: chronic stress alters the glutamatergic system in the brain—focusing on AMPA receptor. *Biomedicines.* 2022 Apr 27;10(5):1005. doi: 10.3390/biomedicines10051005.
53. Otero MC, Ceric F, Miranda-Rojas S, Carreño C, Escobares R, Escobar MJ, et al. Documentary analysis of *Hypericum perforatum* (St. John's Wort) and its effect

- on depressive disorders. *Pharmaceuticals*. 2024 Dec 3;17(12):1625. doi: 10.3390/ph17121625.
54. Xu Z, Rasteh AM, Dong A, Wang P, Liu H. Identification of molecular targets of *Hypericum perforatum* in blood for major depressive disorder: a machine-learning pharmacological study. *Chin Med*. 2024 Oct 9;19(1):141. doi: 10.1186/s13020-024-01018-5.
 55. Siddiqui M, Saleh MM, Basharuddin SBB, Zamri SB, Mohd Najib MB, Che Ibrahim M, et al. Saffron (*Crocus sativus* L.): as an antidepressant. *J Pharm Bioallied Sci*. 2018;10(4):173. doi: 10.4103/JPBS.JPBS_83_18.
 56. Philpotts R, Gillan N, Barrow M, Seidler K. Stress-induced alterations in hippocampal BDNF in the pathophysiology of major depressive disorder and the antidepressant effect of saffron. *J Affect Disord Rep*. 2023 Dec;14:100630. doi: 10.1016/j.jadr.2023.100630.
 57. Hasnat H, Riti SJ, Shompa SA, Alam S, Islam MdM, Kabir F, et al. Unveiling the therapeutic potentials of water hyacinth (*Eichhornia crassipes* (Mart.) Solms) flower against oxidative stress, inflammation and depressive disorders: GC MS/MS, in vitro, in vivo and in silico approaches. *Chem Biodivers*. 2024 Dec;21(12):e202401268. doi: 10.1002/cbdv.202401268.
 58. Moragrega I, Ríos JL. Medicinal plants in the treatment of depression: evidence from preclinical studies. *Planta Med*. 2021 Aug;87(9):656–85. doi: 10.1055/a-1338-1011.
 59. Riszo P, Altschmied L, Ravindran BM, Rutten T, D'Auria JC. The biochemical and genetic basis for the biosynthesis of bioactive compounds in *Hypericum perforatum* L., one of the largest medicinal crops in Europe. *Genes (Basel)*. 2020 Oct 16;11(10):1210. doi: 10.3390/genes11101210.
 60. Menegazzi M, Masiello P, Novelli M. Anti-tumor activity of *Hypericum perforatum* L. and hyperforin through modulation of inflammatory signaling, ROS generation and proton dynamics. *Antioxidants (Basel)*. 2020 Dec 28;10(1):18. doi: 10.3390/antiox10010018.
 61. Ramos da Silva L, Carlson PT, Silva Costa LC, Martins de Souza D, De Almeida V. Molecular mechanisms associated with antidepressant treatment on major depression. *Complex Psychiatry*. 2021;7(3–4):49–59. doi: 10.1159/000518098.
 62. Chotritthirong Y, Chulikhit Y, Daodee S, Boonyarat C, Maneenet J, Khamphukdee C, et al. Possible mechanisms for the prevention of anxiety and depressive like behavior in a chronic mild stress mouse model by the Thai herbal medicine with *Nelumbo nucifera*, *Centella asiatica*, and *Piper nigrum*. *Rev Bras Farmacogn*. 2023 May 13;33(4):756–67. doi: 10.1007/s43450-023-00401-x.
 63. Margret AA, Dhayabaran V, Suvaitenamudhan S, Parthasarathy S. Analysing the antidepressant and drug efflux competence of *Clitoria ternatea* L. as P glycoprotein inhibitor to facilitate blood–brain barrier. *Acta Sci Biol Sci*. 2019 Dec 6;41:e46629. doi: 10.4025/actascibiols.v41i1.46629.
 64. Alkahtani J, Elshikh MS, Dwiningsih Y, Ahalliya Rathi M, Sathya R, Vijayaraghavan P. In vitro antidepressant property of methanol extract of *Bacopa monnieri*. *J King Saud Univ Sci*. 2022 Nov;34(8):102299. doi: 10.1016/j.jksus.2022.102299.
 65. Saunoriūtė S, Ragažinskienė O, Ivanauskas L, Marksa M, Laužikė K, Raudonė L. Phenolic diversity and antioxidant activity of *Artemisia abrotanum* L. and *Artemisia absinthium* L. during vegetation stages. *Separations*. 2023 Oct 23;10(10):545. doi: 10.3390/sep10100545.
 66. Akram M, Riaz M, Munir N, Akhter N, Zafar S, Jabeen F, et al. Chemical constituents, experimental and clinical pharmacology of *Rosa damascena*: a literature review. *J Pharm Pharmacol*. 2020 Feb 1;72(2):161–74. doi: 10.1111/jph.13185.
 67. Venthodika A, Chhikara N, Mann S, Garg MK, Sofi SA, Panghal A. Bioactive compounds of *Aegle marmelos* L., medicinal values and its food applications: a critical review. *Phytother Res*. 2021 Apr;35(4):1887–907. doi: 10.1002/ptr.6934.
 68. Sharma A, Singh T, Pathak D, Virmani T, Kumar G, Alhalmi A. Antidepressive like effect of *Aegle marmelos* leaf extract in chronic unpredictable mild stress induced depression like behaviour in rats. *BioMed Res Int*. 2022;2022:6479953. doi: 10.1155/2022/6479953.
 69. Khattab A, Awad NE, Abdel Fadeel D, Fadel M. Reviewing the reported pharmacognostic and pharmacological investigations on *Tecoma stans* Juss. ex Kunth. *J Herbmed Pharmacol*. 2022 Dec 31;12(1):25–40. doi: 10.34172/jhp.2023.03.
 70. Ayuob N, Shaker SA, Hawuit E, Al Abbas NS, Shaer NA, Al Jaouni S, et al. Cucurbita pepo alleviates chronic unpredictable mild stress via modulation of apoptosis, neurogenesis, and gliosis in rat hippocampus. *Oxid Med Cell Longev*. 2021;2021:6662649. doi: 10.1155/2021/6662649.
 71. Santini ZI, Thygesen LC, Krokstad S, Bonde LO, Donovan RJ, Koushede V, et al. Engagement with arts and culture activities in the Danish general population: longitudinal associations with new onset or persistent depression and mental wellbeing. *Br J Health Psychol*. 2023 Sep;28(3):844–59. doi: 10.1111/bjhp.12657.
 72. Wang H, Yang Y, Pei G, Wang Z, Chen N. Neurotrophic basis to the pathogenesis of depression and phytotherapy. *Front Pharmacol*. 2023 Apr 6;14:1182666. doi: 10.3389/fphar.2023.1182666.
 73. Barresi E, Robello M, Baglini E, Poggetti V, Viviano M, Salerno S, et al. Indol 3 ylglyoxylamide as privileged scaffold in medicinal chemistry. *Pharmaceuticals*. 2023 Jul 12;16(7):997. doi: 10.3390/ph16070997.
 74. Zhao K, Xie H, Fonzo GA, Tong X, Carlisle N, Chidharom M, et al. Individualised fMRI connectivity defines signatures of antidepressant and placebo responses in major depression. *Mol Psychiatry*. 2023 Jun;28(6):2490–9. doi: 10.1038/s41380-023-01958-8.
 75. Hamid HA, Ramli ANM, Yusoff MM. Indole alkaloids from plants as potential leads for antidepressant drugs: a mini review. *Front Pharmacol*. 2017 Feb 28;8:96. doi: 10.3389/fphar.2017.00096.
 76. Nautiyal KM, Hen R. Serotonin receptors in depression: from A to B. *F1000Res*. 2017 Feb 9;6:123. doi: 10.12688/f1000research.9736.1.
 77. Bremshey S, Groß J, Renken K, Maseck OA. The role of serotonin in depression—a historical roundup and future directions. *J Neurochem*. 2024 Sep;168(9):1751–79. doi: 10.1111/jnc.16097.
 78. Omar F, Tareq AM, Alqahtani AM, Dhama K, Sayeed MA, Emran TB, et al. Plant based indole alkaloids: a comprehensive overview from a pharmacological perspective. *Molecules*. 2021 Apr 15;26(8):2297. doi: 10.3390/molecules26082297.
 79. Chen L, Fei S, Olatunji OJ. LC/ESI/TOF MS characterisation, anxiolytic and antidepressant like effects of *Mitragyna speciosa* Korth extract in diabetic rats. *Mol-*

- ecules. 2022 Mar 28;27(7):2208. doi: 10.3390/molecules27072208.
80. Abushwreb H, Abdulatif A, Abdulmajeed A. The antidepressant like effect of *Mitragyna speciosa* Korth. *J Pharm Appl Chem*. 2018 May 1;4(2):109–13. doi: 10.18576/jpac/040205.
 81. Armah FA, Henneh IT, Amponsah IK, Biney RP, Malcolm F, Alake J, et al. Antidepressant and anxiolytic effects and subacute toxicity of the aerial parts of *Psychotria ankasensis* J.B.Hall (Rubiaceae) in murine models. *Evid Based Complement Alternat Med*. 2021;2021:5543320. doi: 10.1155/2021/5543320.
 82. Chaurasiya N, Leon F, Muhammad I, Tekwani B. Natural product inhibitors of monoamine oxidases—potential new drug leads for neuroprotection, neurological disorders, and neuroblastoma. *Molecules*. 2022 Jul 4;27(13):4297. doi: 10.3390/molecules27134297.
 83. Magedans YVDS, Rodrigues Corrêa KCDS, Costa CTD, Matsuura HN, Fett Neto AG. Sustainable production of bioactive alkaloids in *Psychotria L.* of southern Brazil: propagation and elicitation strategies. *Acta Bot Bras*. 2019 Dec;33(4):607–17. doi: 10.1590/0102-33062019abb0114.
 84. Atpadkar PP, Gopavaram S, Chaudhary S. Natural product inspired bioactive alkaloids agglomerated with potential antioxidant activity: recent advancements on SAR studies and future perspectives. In: *Vitamins and Hormones*. Elsevier; 2023. p.355–93. doi: 10.1016/bs.vh.2022.10.002.
 85. Bristy TA, Barua N, Montakim Tareq A, Sakib SA, Etu ST, Chowdhury KH, et al. Deciphering the pharmacological properties of methanol extract of *Psychotria calocarpa* leaves by in vivo, in vitro and in silico approaches. *Pharmaceuticals*. 2020 Aug 6;13(8):183. doi: 10.3390/ph13080183.
 86. Klein Júnior LC, Cretton S, Vander Heyden Y, Gasper AL, Nejad Ebrahimi S, Christen P, et al. Bioactive azepine indole alkaloids from *Psychotria nemorosa*. *J Nat Prod*. 2020 Apr 24;83(4):852–63. doi: 10.1021/acs.jnatprod.9b00469.
 87. Formagio ASN, Vilegas W, Kassuya CAL, De Almeida VP, Manfron J, Konkiewitz EC, et al. A comprehensive description of the anatomy and histochemistry of *Psychotria capillacea* (Müll. Arg.) Standl. and investigation into its anti-inflammatory effects in mice and role in scopolamine induced memory impairment. *Pharmaceuticals*. 2024 Apr 28;17(5):564. doi: 10.3390/ph17050564.
 88. Kirchweger B, Klein Júnior LC, Pretsch D, Chen Y, Cretton S, Gasper AL, et al. Azepine indole alkaloids from *Psychotria nemorosa* modulate 5 HT2A receptors and prevent in vivo protein toxicity in transgenic *Caenorhabditis elegans*. *Front Neurosci*. 2022 Mar 14;16:826289. doi: 10.3389/fnins.2022.826289.
 89. Doskaliyev A, Seidakhmetova R, Tutai DS, Goldaeva K, Surov VK, Adekenov SM. Alkaloids of *Peganum harmala L.* and their pharmacological activity. *Open Access Maced J Med Sci*. 2021 Sep 8;9(A):766–75. doi: 10.3889/oamjms.2021.6654.
 90. Ebrahimi Ghiri M, Nasehi M, Zarrindast MR. Anxiolytic and antidepressant effects of ACPA and harmaline co treatment. *Behav Brain Res*. 2019 May;364:296–302. doi: 10.1016/j.bbr.2019.02.034.
 91. Tekşen Y, Gündüz MK, Berikten D, Özatik FY, Aydın HE. *Peganum harmala L.* seed extract attenuates anxiety and depression in rats by reducing neuroinflammation and restoring the BDNF/TrkB signaling pathway and monoamines after exposure to chronic unpredictable mild stress. *Metab Brain Dis*. 2024 Aug 22;39(8):1523–90. doi: 10.1007/s11011-024-01416-6.
 92. Abdjan MI, Rosyda M, Aminah NS, Kristanti AN, sizwanto I, Shehzad W, et al. Synthesis of ester derivatives of catechin isolated from *Uncaria gambir* and their anticancer activity. *Eng Sci*. 2023. doi: 10.30919/es997.
 93. Kushida H, Matsumoto T, Ikarashi Y. Properties, pharmacology, and pharmacokinetics of active indole and oxindole alkaloids in *Uncaria Hook*. *Front Pharmacol*. 2021 Jul 14;12:688670. doi: 10.3389/fphar.2021.688670.
 94. Chen L, Ma J, Wang X, Zhang M. Simultaneous determination of six *Uncaria* alkaloids in mouse blood by UPLC–MS/MS and its application in pharmacokinetics and bioavailability. *BioMed Res Int*. 2020;2020:1030269. doi: 10.1155/2020/1030269.
 95. Kumar K, Muzibar S, Abdullah R, Ehsan A, Trina S, Mimi M. Comparative neuropharmacological and cytotoxic profiles of *Alstonia scholaris* and *Mimusops elengi* leaves. *Adv Tradit Med*. 2020. doi: 10.1007/s13596-020-00463-5.
 96. Yang XW, Song CW, Zhang Y, Khan A, Jiang LP, Chen YB, et al. Alstoscholarisines F and G, two unusual monoterpenoid indole alkaloids from the leaves of *Alstonia scholaris*. *Tetrahedron Lett*. 2015;54:8–11. doi: 10.1016/j.tetlet.2015.10.051.
 97. Chhajer M, Jain A, Pagariya A, Dwivedi S, Jain N, Taile V. *Alstonia scholaris* Linn. R. Br.: an assessment of its botany, conventional utilisation, phytochemistry and pharmacology. 2023. doi: 10.5530/097627870302.
 98. Hu Y, Ma S, Pang X, Cong M, Liu Q, Han F, et al. Cytotoxic pyridine alkaloids from a marine derived fungus *Arthrinium arundinis* exhibiting apoptosis inducing activities against small cell lung cancer. *Phytochemistry*. 2023 Sep;213:113765. doi: 10.1016/j.phytochem.2023.113765.
 99. Zhang X, Tao F, Cui T, Luo C, Zhou Z, Huang Y, et al. Sources, transformations, syntheses, and bioactivities of monoterpene pyridine alkaloids and cyclopenta[c]pyridine derivatives. *Molecules*. 2022 Oct 24;27(21):7187. doi: 10.3390/molecules27217187.
 100. Ansari A, Mahmood T, Bagga P, Ahsan F, Shamim A, Ahmad S, et al. *Areca catechu*: a phytopharmacological legwork. *Food Front*. 2021 Jun;2(2):163–83. doi: 10.1002/fft2.70.
 101. Salehi B, Konovalov DA, Fru P, Kapewangolo P, Peron G, Ksenija MS, et al. *Areca catechu*—from farm to food and biomedical applications. *Phytother Res*. 2020 Sep;34(9):2140–58. doi: 10.1002/ptr.6665.
 102. Wang Z, Guo Z, Luo Y, Ma L, Hu X, Chen F, et al. A review of the traditional uses, pharmacology, and toxicology of areca nut. *Phytomedicine*. 2024 Nov;134:156005. doi: 10.1016/j.phymed.2024.156005.
 103. Tong T, Xu A, Tan S, Jiang H, Liu L, Deng S, et al. Biological effects and biomedical applications of areca nut and its extract. *Pharmaceuticals*. 2024 Feb 8;17(2):228. doi: 10.3390/ph17020228.
 104. Guo Z, Wang Z, Luo Y, Ma L, Hu X, Chen F, et al. Extraction and identification of bioactive compounds from areca nut (*Areca catechu L.*) and potential for future applications. *Food Front*. 2024 Sep;5(5):1909–32. doi: 10.1002/fft2.443.
 105. Raja A, Ashokkumar S, Pavithra Marthandam R, Jayachandiran J, Khatiwada CP, Kaviyarasu K, et al. Eco friendly preparation of zinc oxide nanoparticles using *Tabernaemontana divaricata* and its photocatalytic and

- antimicrobial activity. *J Photochem Photobiol B.* 2018 Apr;181:53–8. doi: 10.1016/j.jphotobiol.2018.02.011.
106. Baskin V, Eroglu E, Harmanci N, Erol K. Antinociceptive, anxiolytic, and depression like effects of hydrogen sulfide, nitric oxide, and carbon monoxide in rats and the role of opioidergic and serotonergic systems in antinociceptive activity. *Fundam Clin Pharmacol.* 2022 Aug;36(4):674–86. doi: 10.1111/fcp.12763.
107. Faruq O, Munira S, Zaman S, Koly SF, Salam R, Das SR, et al. Central nervous system depressant effects of the methanolic leaves extracts of *Tabernaemontana divaricata*. *Int J Med Plants Nat Prod.* 2018;4(1):1. doi: 10.20431/2454-7999.0401001.
108. Sharma P, Tyagi A, Bhansali P, Pareek S, Singh V, Ilyas A, et al. Saponins: extraction, bio medicinal properties and way forward to anti viral representatives. *Food Chem Toxicol.* 2021 Apr;150:112075. doi: 10.1016/j.fct.2021.112075.
109. Juang YP, Liang PH. Biological and pharmacological effects of synthetic saponins. *Molecules.* 2020 Oct 27;25(21):4974. doi: 10.3390/molecules25214974.
110. Elekofehinti OO, Iwaloye O, Olawale F, Ariyo EO. Saponins in cancer treatment: current progress and future prospects. *Pathophysiology.* 2021 Jun 5;28(2):250–72. doi: 10.3390/pathophysiology28020017.
111. Shi ZY, Zeng JZ, Wong AST. Chemical structures and pharmacological profiles of ginseng saponins. *Molecules.* 2019 Jul 3;24(13):2443. doi: 10.3390/molecules24132443.
112. Chikhale RV, Sinha SK, Patil RB, Prasad SK, Shakya A, Gurav N, et al. In silico investigation of phytochemicals from *Asparagus racemosus* as plausible antiviral agent in COVID 19. *J Biomol Struct Dyn.* 2021 Sep 22;39(14):5033–47. doi: 10.1080/07391102.2020.1784289.
113. Hazra K, Mandal AK, Mondal DN, Ravte RK, Hazra J, Rao MM. Seasonal dynamics of Shatavarin IV, a potential biomarker of *Asparagus racemosus* by HPTLC: possible validation of the ancient Ayurvedic text. *Indian J Tradit Knowl.* 2019 Dec 27;19(1):174–81. doi: 10.56042/ijtk.v19i1.30864.
114. Kashyap P, Muthusamy K, Niranjana M, Tripathi S, Kumar S. Sarsasapogenin: a steroidal saponin from *Asparagus racemosus* as multi target directed ligand in Alzheimer's disease. *Steroids.* 2020 Jan;153:108529. doi: 10.1016/j.steroids.2019.108529.
115. Singh N, Garg M, Prajapati P, Singh PK, Chopra R, Kumari A, et al. Adaptogenic property of *Asparagus racemosus*: future trends and prospects. *Heliyon.* 2023 Apr;9(4):e14932. doi: 10.1016/j.heliyon.2023.e14932.
116. Yang L, Shergis JL, Di YM, Zhang AL, Lu C, Guo X, et al. Managing depression with *Bupleurum chinense* herbal formula: a systematic review and meta analysis of randomised controlled trials. *J Altern Complement Med.* 2020 Jan 1;26(1):8–24. doi: 10.1089/acm.2019.0105.
117. Guo J, Zhang F, Gao J, Guan X, Liu B, Wang X, et al. Proteomics based screening of the target proteins associated with antidepressant like effect and mechanism of saikosaponin A. *J Cell Mol Med.* 2020 Jan;24(1):174–88. doi: 10.1111/jcmm.14695.
118. Chen XQ, Chen SJ, Liang WN, Wang M, Li CF, Wang SS, et al. Saikosaponin A attenuates perimenopausal depression like symptoms by chronic unpredictable mild stress. *Neurosci Lett.* 2018 Jan;662:283–9. doi: 10.1016/j.neulet.2017.09.046.
119. Liu CY, Chen JB, Liu YY, Zhou XM, Zhang M, Jiang YM, et al. Saikosaponin D exerts antidepressant effect by regulating Homer1 mGluR5 and mTOR signaling in a rat model of chronic unpredictable mild stress. *Chin Med.* 2022 May 24;17(1):60. doi: 10.1186/s13020-022-00621-8.
120. Wu YN, Wen SH, Zhang W, Yu SS, Yang K, Liu D, et al. *Gastrodia elata* Bl.: a comprehensive review of its traditional use, botany, phytochemistry, pharmacology, and pharmacokinetics. *Evid Based Complement Alternat Med.* 2023;2023:5606021. doi: 10.1155/2023/5606021.
121. Mancuso C, Santangelo R. *Panax ginseng* and *Panax quinquefolius*: from pharmacology to toxicology. *Food Chem Toxicol.* 2017 Sep;107:362–72. doi: 10.1016/j.fct.2017.07.019.
122. Kim S, Kim N, Jeong J, Lee S, Kim W, Ko SG, et al. Anti cancer effect of *Panax ginseng* and its metabolites: from traditional medicine to modern drug discovery. *Processes.* 2021 Jul 30;9(8):1344. doi: 10.3390/pr9081344.
123. Kim JH. Pharmacological and medical applications of *Panax ginseng* and ginsenosides: a review for use in cardiovascular diseases. *J Ginseng Res.* 2018 Jul;42(3):264–9. doi: 10.1016/j.jgr.2017.10.004.
124. Jin Y, Cui R, Zhao L, Fan J, Li B. Mechanisms of *Panax ginseng* action as an antidepressant. *Cell Prolif.* 2019 Nov;52(6):e12696. doi: 10.1111/cpr.12696.
125. Xu C, Wang W, Wang B, Zhang T, Cui X, Pu Y, et al. Analytical methods and biological activities of *Panax notoginseng* saponins: recent trends. *J Ethnopharmacol.* 2019 May;236:443–65. doi: 10.1016/j.jep.2019.02.035.
126. Ghosh S, Roy K, Pal C. Terpenoids against infectious diseases. In: Roy DN, editor. *Terpenoids Against Human Diseases*. CRC Press; 2019. p.187–208. doi: 10.1201/9781351026703-8.
127. Zhao M, Chen L, Yang J, Han D, Fang D, Qiu X, et al. BDNF Val66Met polymorphism, life stress and depression: a meta-analysis of gene–environment interaction. *J Affect Disord.* 2018 Feb;227:226–35. doi: 10.1016/j.jad.2017.10.024.
128. Xie W, Meng X, Zhai Y, Zhou P, Ye T, Wang Z, et al. *Panax notoginseng* saponins: a review of its mechanisms of antidepressant or anxiolytic effects and network analysis on phytochemistry and pharmacology. *Molecules.* 2018 Apr 17;23(4):940. doi: 10.3390/molecules23040940.
129. Fahad FI, Barua N, Islam MdS, Sayem SAJ, Barua K, Uddin MJ, et al. Investigation of the pharmacological properties of *Lepidagathis hyalina* Nees through experimental approaches. *Life (Basel).* 2021 Feb 25;11(3):180. doi: 10.3390/life11030180.
130. Islam S, Fahad FI, Sultana A, Sayem SAJ, Roy SB, Islam MN, et al. Evaluation of antioxidant, cytotoxic, anti inflammatory, antiarthritic, thrombolytic, and anthelmintic activity of methanol extract of *Lepidagathis hyalina* Nees root. *Evid Based Complement Alternat Med.* 2022 Feb 15;2022:2515260. doi: 10.1155/2022/2515260.
131. Hewawansa UHAJ, Houghton MJ, Barber E, Costa RJS, Kitchen B, Williamson G. Flavonoids and phenolic acids from sugarcane: distribution in the plant, changes during processing, and potential benefits to industry and health. *Compr Rev Food Sci Food Saf.* 2024 Mar;23(2):e13307. doi: 10.1111/1541-4337.13307.
132. Winiarska Mieczan A, Kwiecień M, Jachimowicz Rogowska K, Donaldson J, Tomaszewska E, Baranowska Wójcik E. Anti inflammatory, antioxidant, and neuroprotective effects of polyphenols—polyphenols as

- an element of diet therapy in depressive disorders. *Int J Mol Sci.* 2023 Jan 23;24(3):2258. doi: 10.3390/ijms24032258.
133. Yahfoufi N, Alsadi N, Jambi M, Matar C. The immunomodulatory and anti-inflammatory role of polyphenols. *Nutrients.* 2018 Nov 2;10(11):1618. doi: 10.3390/nu10111618.
 134. Shakoor H, Feehan J, Apostolopoulos V, Platat C, Al Dhaheri AS, Ali HI, et al. Immunomodulatory effects of dietary polyphenols. *Nutrients.* 2021 Feb 25;13(3):728. doi: 10.3390/nu13030728.
 135. Winiarska Mieczan A, Baranowska Wójcik E, Kwiecień M, Grela ER, Sz wajgier D, Kwiatkowska K, et al. The role of dietary antioxidants in the pathogenesis of neurodegenerative diseases and their impact on cerebral oxidative balance. *Nutrients.* 2020 Feb 8;12(2):435. doi: 10.3390/nu12020435.
 136. Winiarska Mieczan A. Protective effect of tea against lead and cadmium induced oxidative stress—a review. *BioMetals.* 2018 Dec;31(6):909–26. doi: 10.1007/s10534-018-0153-z.
 137. Pannu A, Sharma PC, Thakur VK, Goyal RK. Emerging role of flavonoids as the treatment of depression. *Biomolecules.* 2021 Dec 3;11(12):1825. doi: 10.3390/biom11121825.
 138. Dias MC, Pinto DCGA, Silva AMS. Plant flavonoids: chemical characteristics and biological activity. *Molecules.* 2021 Sep 4;26(17):5377. doi: 10.3390/molecules26175377.
 139. Xu Z. Identification of anti-inflammatory mechanism of action and molecular targets of *Hypericum perforatum* in the treatment of major depression based on bioinformatics methods and machine learning [Internet]. In Review; 2023 [cited 2025 Jan 2]. Available from: <https://www.researchsquare.com/article/rs-2984434/v1>. doi: 10.21203/rs.3.rs-2984434/v1.
 140. Khalil HMA, Mahmoud DB, El Shiekh RA, Bakr AF, Boseila AA, Mehanna S, et al. Antidepressant and cardioprotective effects of self nanoemulsifying self nano-suspension loaded with *Hypericum perforatum* on post myocardial infarction depression in rats. *AAPS PharmSciTech.* 2022 Aug 26;23(7):243. doi: 10.1208/s12249-022-02387-6.
 141. Khan J, Asoom LIA, Sunni AA, Rafique N, Latif R, Saif SA, et al. Genetics, pathophysiology, diagnosis, treatment, management, and prevention of migraine. *Biomed Pharmacother.* 2021 Jul;139:111557. doi: 10.1016/j.biopha.2021.111557.
 142. Gerasimova A, Nikolova K, Petkova N, Ivanov I, Dincheva I, Tumbarski Y, et al. Metabolic profile of leaves and pulp of *Passiflora caerulea* L. (Bulgaria) and their biological activities. *Plants.* 2024 Jun 22;13(13):1731. doi: 10.3390/plants13131731.
 143. Rodríguez Landa JF, German Ponciano LJ, Puga Olgún A, Olmos Vázquez OJ. Pharmacological, neurochemical, and behavioral mechanisms underlying the anxiolytic and antidepressant like effects of flavonoid chrysin. *Molecules.* 2022 May 31;27(11):3551. doi: 10.3390/molecules27113551.
 144. Araujo SM, Poetini MR, Bortolotto VC, De Freitas Couto S, Pinheiro FC, Meichner LB, et al. Chronic unpredictable mild stress induced depressive like behavior and dysregulation of brain levels of biogenic amines in *Drosophila melanogaster*. *Behav Brain Res.* 2018 Oct;351:104–13. doi: 10.1016/j.bbr.2018.05.016.
 145. Zhang Y, Li L, Zhang J. Curcumin in antidepressant treatments: an overview of potential mechanisms, pre clinical/clinical trials and ongoing challenges. *Basic Clin Pharmacol Toxicol.* 2020 Oct;127(4):243–53. doi: 10.1111/bcpt.13455.
 146. Corrêa Carvalho G, Marena GD, Gaspar Gonçalves Fernandes M, Ricci Leonardi G, Santos HA, Chorilli M. Curcuma longa: nutraceutical use and association with nanotechnology. *Adv Healthc Mater.* 2024 Sep;13(22):2400506. doi: 10.1002/adhm.202400506.
 147. Wu ZH, Fan H, Gao SY, Jin YF, Chen C, Jiang B, et al. Antidepressant like activity of oroxylin A in mice models of depression: a behavioral and neurobiological characterisation. *Front Pharmacol.* 2022 Jul 26;13:921553. doi: 10.3389/fphar.2022.921553.
 148. Limanaqi F, Biagioni F, Busceti CL, Polzella M, Fabrisi C, Fornai F. Potential antidepressant effects of *Scutellaria baicalensis*, *Hericium erinaceus* and *Rhodiola rosea*. *Antioxidants (Basel).* 2020 Mar 12;9(3):234. doi: 10.3390/antiox9030234.
 149. Gan Z, Fang X, Yin C, Tian Y, Zhang L, Zhong X, et al. Extraction, purification, structural characterisation, and bioactivities of the genus *Rhodiola* L. polysaccharides: a review. *Int J Biol Macromol.* 2024 Sep;276:133614. doi: 10.1016/j.ijbiomac.2024.133614.
 150. Li C, Wang F, Miao P, Yan L, Liu S, Wang X, et al. miR-138 increases depressive like behaviors by targeting SIRT1 in hippocampus. *Neuropsychiatr Dis Treat.* 2020 Apr;16:949–57. doi: 10.2147/NDT.S237558.
 151. Zhang X, Zhang Y, Li R, Zhu L, Fu B, Yan T. Salidroside ameliorates Parkinson's disease by inhibiting NLRP3 dependent pyroptosis. *Aging (Albany NY).* 2020 May 19;12(10):9405–26. doi: 10.18632/aging.103215.
 152. Butnariu M, Quispe C, Herrera Bravo J, Sharifi Rad J, Singh L, Aborehab NM, et al. The pharmacological activities of *Crocus sativus* L.: a review based on the mechanisms and therapeutic opportunities of its phytoconstituents. *Oxid Med Cell Longev.* 2022 Feb 14;2022:8214821. doi: 10.1155/2022/8214821.
 153. Matias JN, Achete G, Campanari GS, Guiguer ÉL, Araújo AC, Buglio DS, et al. A systematic review of the antidepressant effects of curcumin: beyond monoamines theory. *Aust N Z J Psychiatry.* 2021 May;55(5):451–62. doi: 10.1177/0004867421998795.
 154. Askary M, Behdani MA, Mollaei H, Fallahi HR, Azarmi Atajan F, Mokhtari Macinaei H. Bioactive compounds and apoptotic effects of saffron (*Crocus sativus* L.) in different fertiliser conditions. *Biochem Syst Ecol.* 2024 Jun;114:104806. doi: 10.1016/j.bse.2024.104806.
 155. Siddiqui SA, Ali Redha A, Snoeck ER, Singh S, Simal Gandara J, Ibrahim SA, et al. Anti depressant properties of crocin molecules in saffron. *Molecules.* 2022 Mar 23;27(7):2076. doi: 10.3390/molecules27072076.
 156. Constantinou CS, Andreou P, Nikitara M, Papageorgiou A. Cultural competence in healthcare and healthcare education. *Societies.* 2022 Nov 29;12(6):178. doi: 10.3390/soc12060178.
 157. Hasheminasab FS, Azimi M, Raeiszadeh M. Therapeutic effects of saffron (*Crocus sativus* L.) on female reproductive system disorders: a systematic review. *Phytother Res.* 2024 Jun;38(6):2832–46. doi: 10.1002/ptr.8186.
 158. Chrobak AA, Siwek M. Drugs with glutamate based mechanisms of action in psychiatry. *Pharmacol Rep.* 2024 Dec;76(6):1256–71. doi: 10.1007/s43440-024-00656-8.