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REVIEW ARTICLE

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]

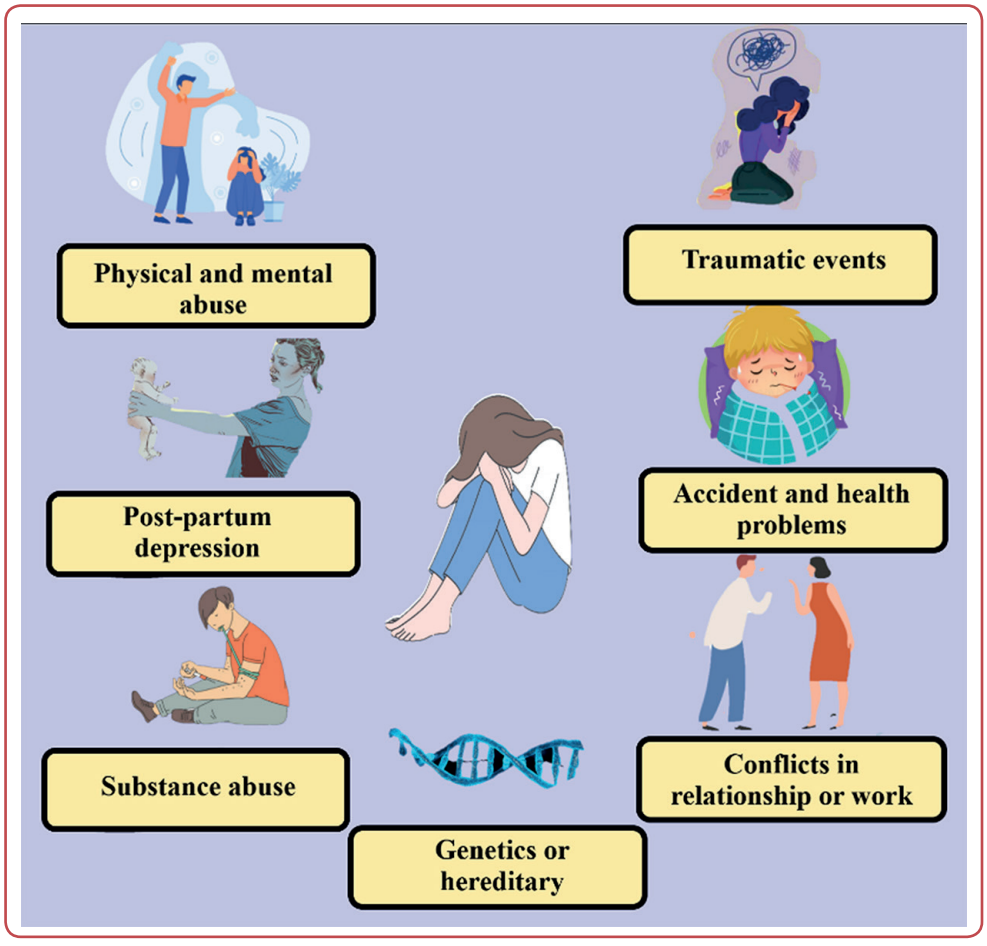

Figure 1: Causes of depression

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 bout 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 associates 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 covert 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-

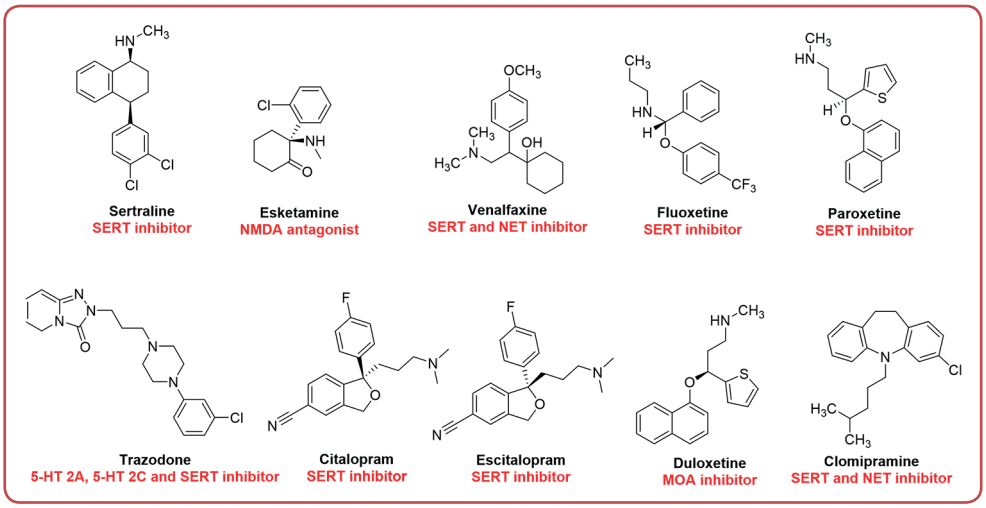

Figure 2: Different marketed anti-depressant with their structures

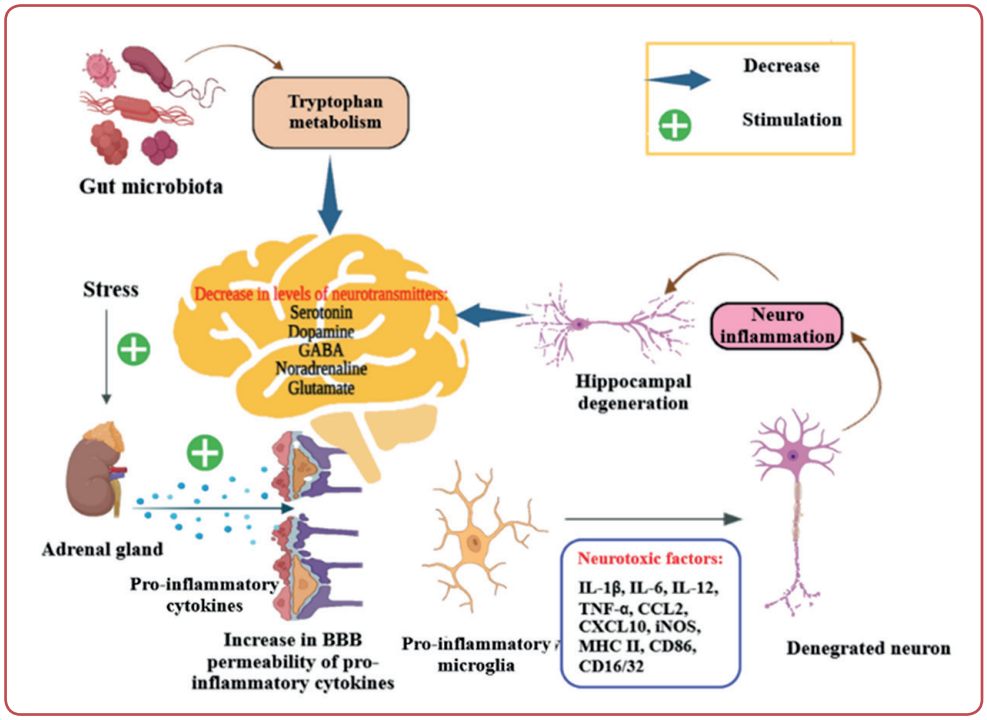

Figure 3: Different mechanism of causing depression

TNF-α: tumour necrosis factor-alpha; BBB: blood brain barrier; IL-12: interleukin 12; IL-6: interleukin 6; IL-1β: interleukin 1β, 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 serotoninergic 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 anti-depressants. 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 effects[43-49]

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 action[57-70]

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

11	*Tecoma stans (Yellow bells)*	*Bignoniaceae*	Tetradecanoic acid	Anti-oxidant
12	*Melissa officinalis (Lemon balm)*	*Lamiaceae*	Geranial, neral, urosolic acid, rosamarinic acid	Locomotion activity
13	*Cucurbita pepo (Zucchini)*	*Curcurbitaceae*	Protocatechuric acid, vanillic acid, feulic acid, luteolin	Reduction in caspase and glial fibrillary acidic protein (GFAP)
14	*Alafia multiflora (Alafia malouetiodies)*	*Apocynaceae*	Flavonoids, polyphenols, glycosides, triterpens, saponins, tannis	Non-adrenergic system
15	*Eicchornea crasspies (Pontederia crasspies)*	*Pontederiaceae*	Linolenic, hexadecenoic, myristic, stearic acids	Block reuptake of serotonin in presynaptic neuron
16	*Bacopa monnieri (Brahmi)*	*Plantaginaceae*	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]

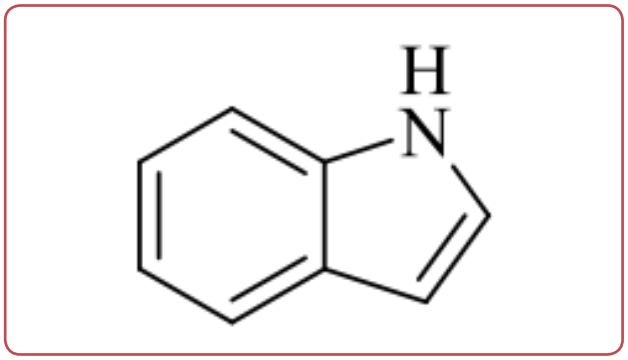

Figure 4: Chemical structure of indole

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]

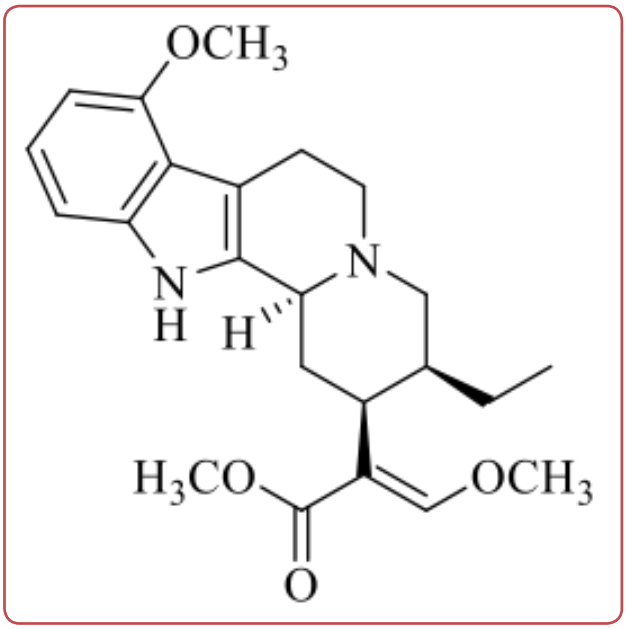

Figure 5: Chemical structure of mitragynine

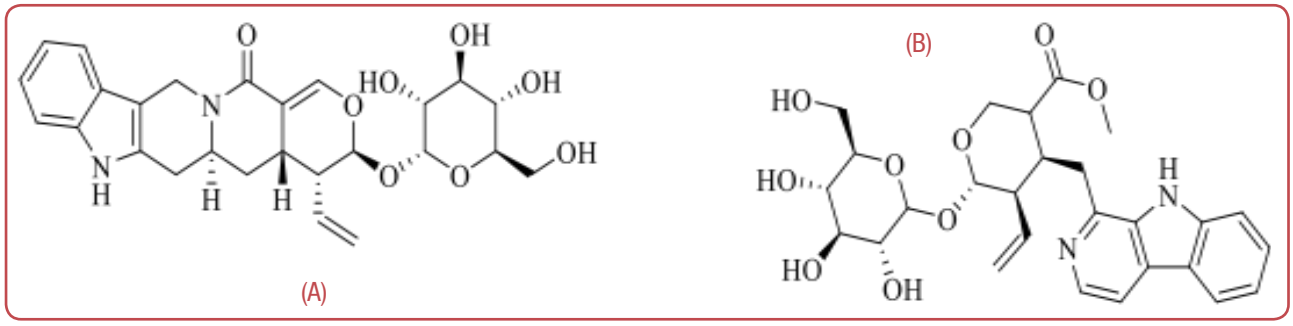

Figure 6: Chemical structure of A) lyaloside and B) strictosamide

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 ± 1.09 µg/mg of lyaloside and 132.5 ± 1.33 µg/mg of strictosamide. Their MAO-B inhibition activity examined at IC_{50} values of 306.6 ± 1.40 µg/mL for lyaloside and 162.8 ± 1.26 µg/mL for strictosamide.[83]

Psychotria umsbellate

P umbellate 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

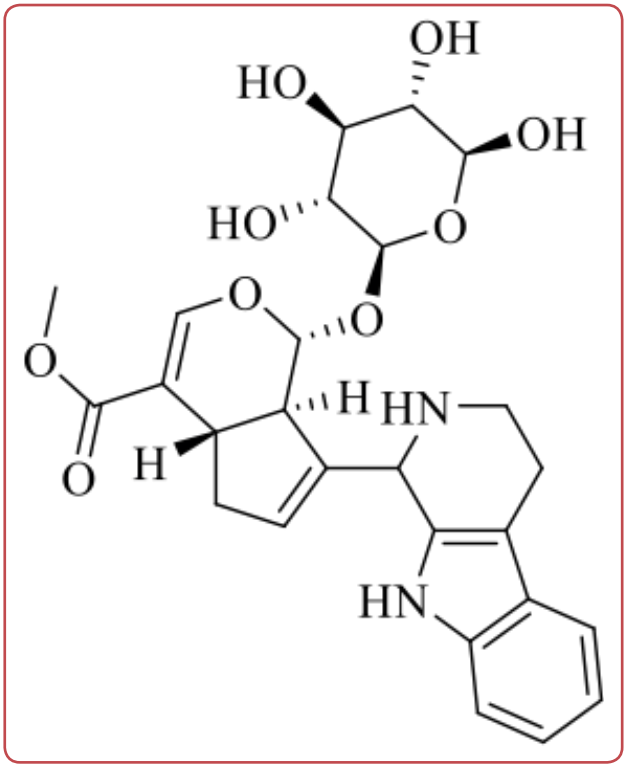

Figure 7: Chemical structure of psychollatine

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), butyrlcholinesterase (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 µm 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 contain β-carbonile 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 anticonvulsant.[92] The studies supported by Hsu, Lieh-Ching, et al for antidepressant action of *U gambir* active monoterpene indole alkaloid compound, corynoxeine (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]

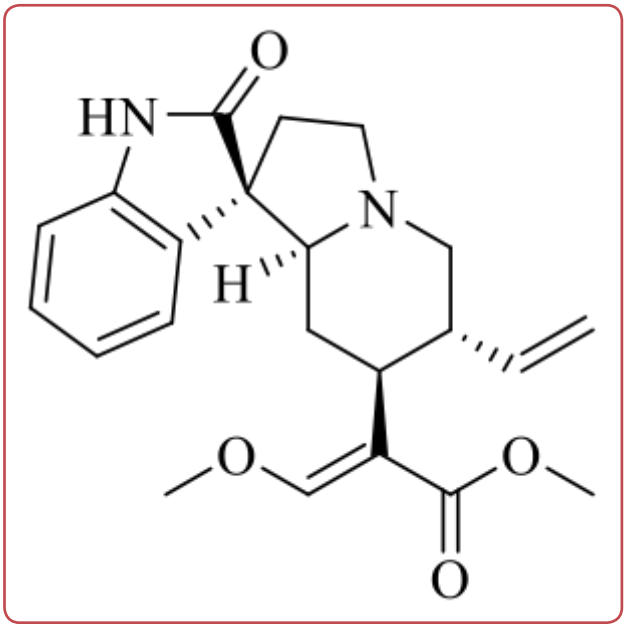

Figure 10: Chemical structure of corynoxeine

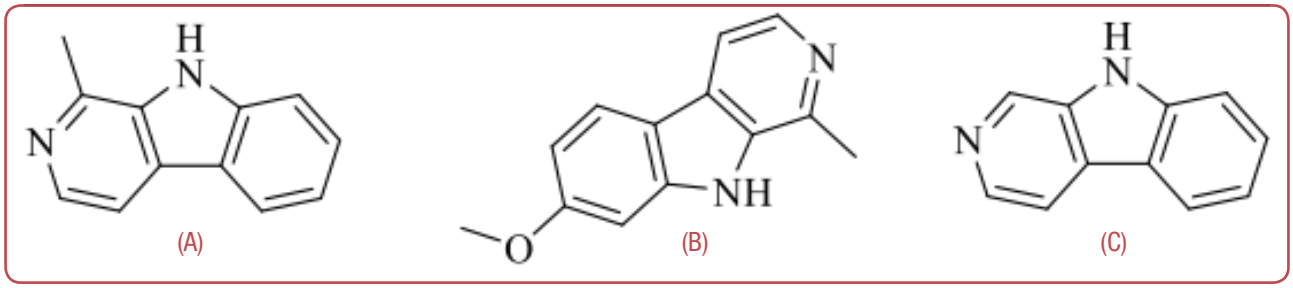

Figure 9: Chemical structure of A) harmane, B) harmine and C) harmaline

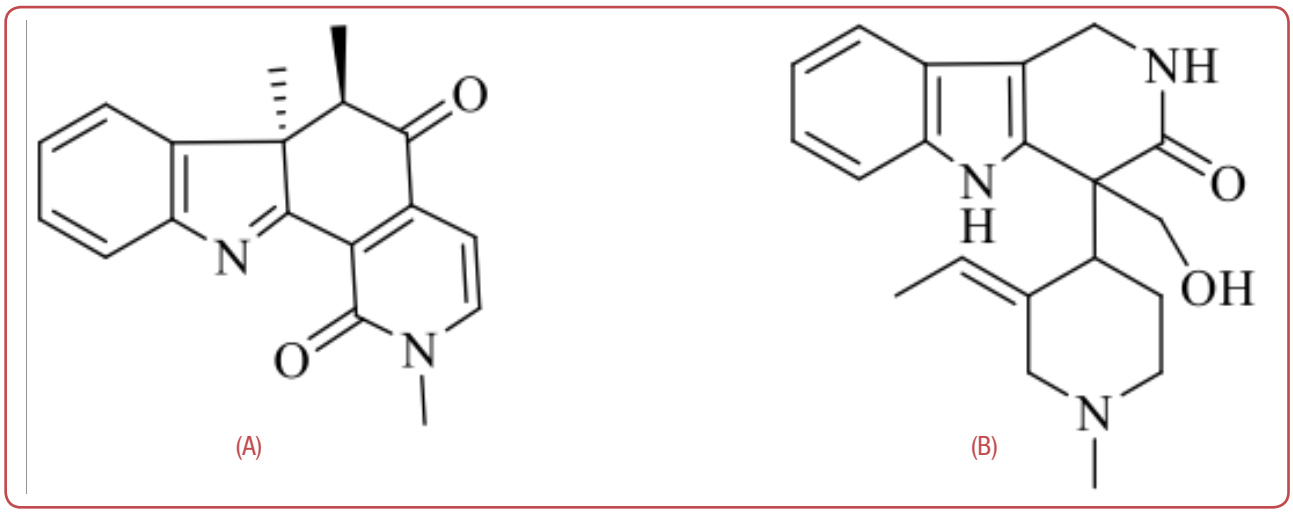

Figure 11: Chemical structure of A) alstoscholarisine F and B) alstoscholarisine G

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 monoterpenoid 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]

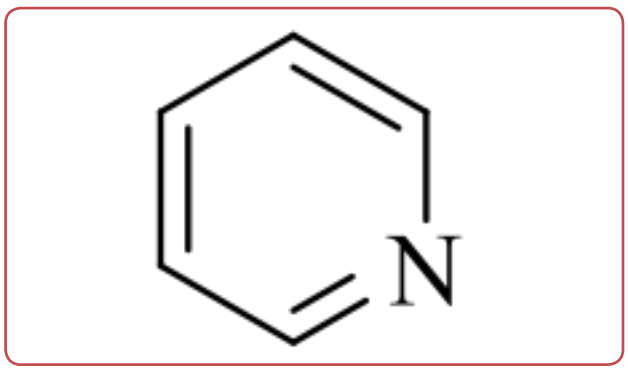

Figure 12: Chemical structure of pyridine

Areca catechu nut

It is an evergreen tree belonging to genus *Areca* of the palm family, *Arecacea.* 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]

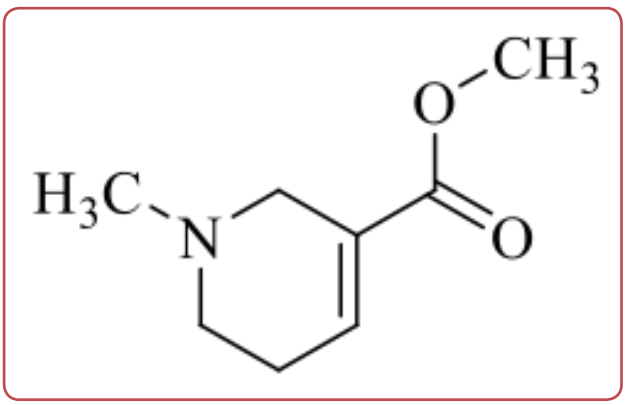

Figure 13: Chemical structure of arecoline

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 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 sapogenin (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 *Aspargoideae 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 Pharmacopoeias.[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]

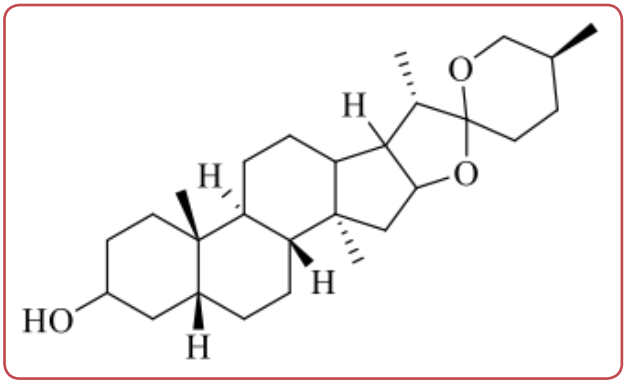

Figure 14: Chemical structure of sarsasapogenin

Bupleurum falcatum

Bupleri radix is the dried roots of *B falcatum* which belongs to *umbelliferae,* used mainly in China, Korea and Japan. Bupleri radix contain 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

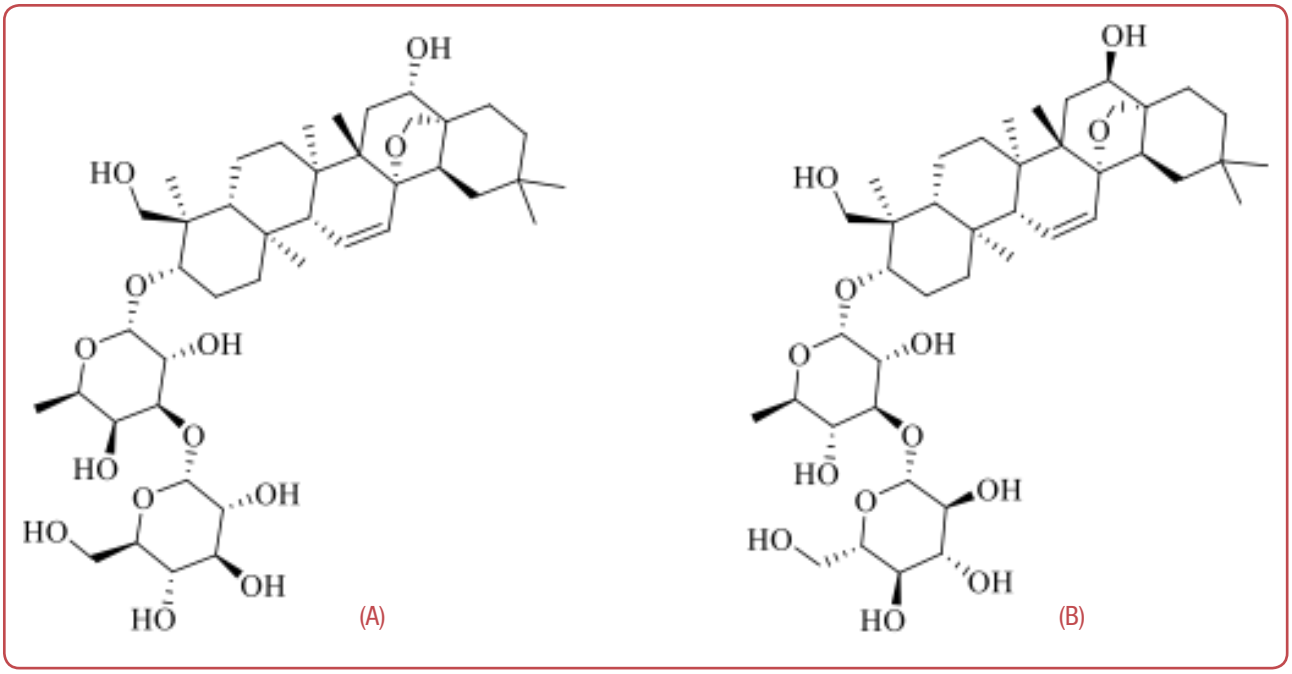

Figure 15: Chemical structure of A) saikosaponin A and B) saikosaponin B

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

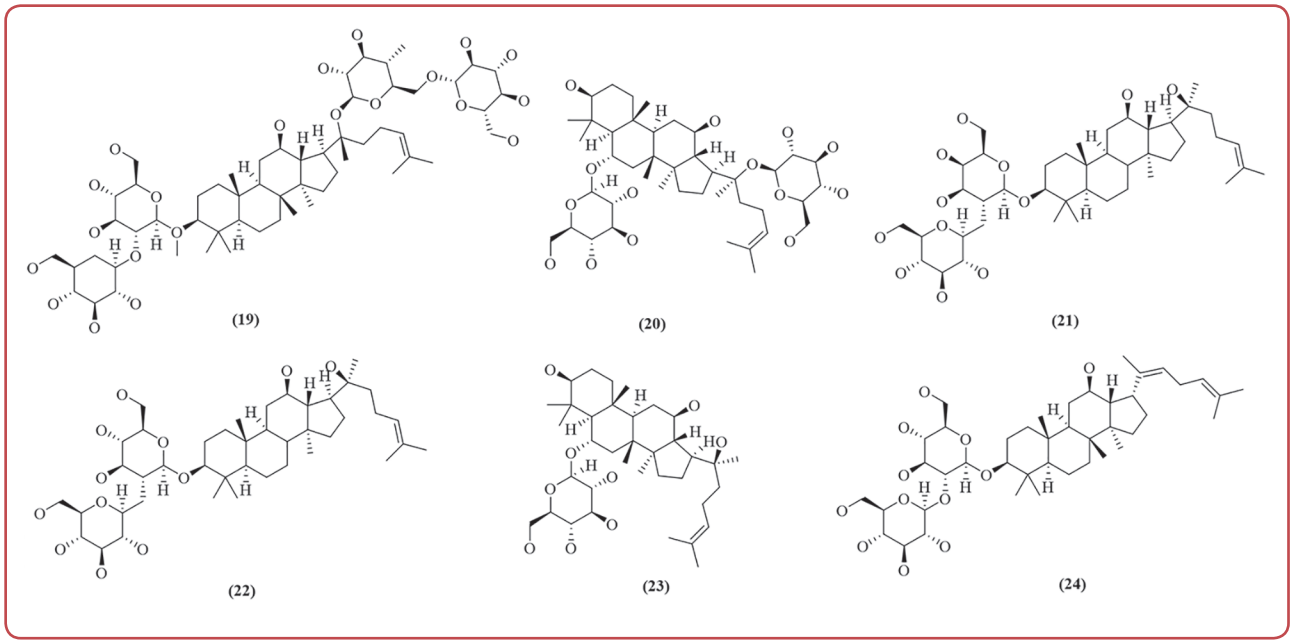

Figure 16: Chemical structure of six bioactive ginsenosides

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 consider as "The Lord of the herbs".[120] *P ginseng* contains secondary metabolite, ginsenosides that exerts several pharmacological effect on nervous system and immune system.[121] Ginsenosides are triterpene saponin with 30 carbon atom skeletons, classified into two primary groups: dammarane-possess four rings carbon skeleton and oleanane-containing five ring carbon skeleton.[122] The studies revel the six bioactive ginsenosides which shows 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 neurotropic factors, have anti-inflammatory action and also regulating the function of HPA axis.[124] The studies has demonstrated that the extract of *P ginseng* can reduces 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 traditionally used in treatment of cardiovascular diseases, immune system and also have been reported for anti-tumour and anti-atherosclerotic action.[125] The pharmacological determination situated 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 impression on locomotor activity in chronic mild stress model.[127] It also modulates the gamma-amino butyric acid (GABA), BDNF and its intra-cellular signalling pathways in the CNS, additionally also had anti-inflammatory, anti-oxidative, inhibitory neuronal apoptosis actions.[128]

Lepidagathis hyaline Nees

L hyaline is subtropical wild herbal plant of family *Acanthacear*, also known as curved *Lepiagathis*. The plant has been utilised in Ayurvedic practice to address coughs and cardiovascular aliments. The new studies found that the bioactive saponin constituent of *L hyaline* consist the antidepressant activity that has 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) isolated and evaluated for its

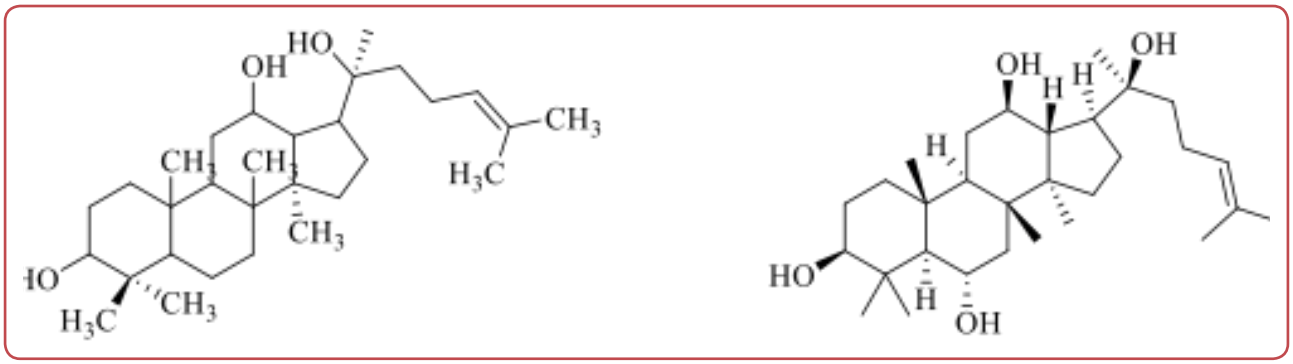

Figure 17: Chemical structure of A) 20(S)-protopanaxadiol and B) 20(S)-protopanaxatriol

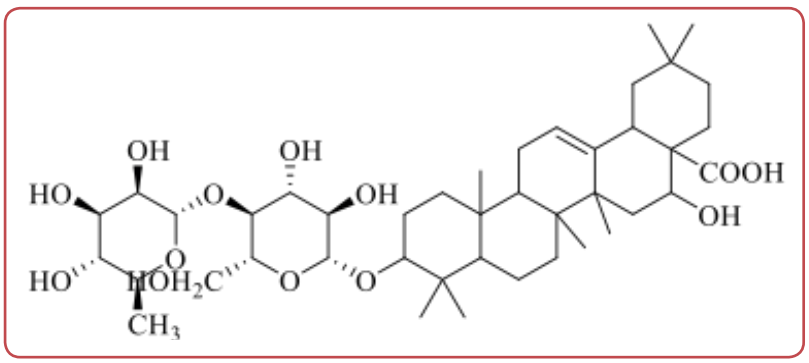

Figure 18: Chemical structure of bioactive triterpenoid saponin found in Lepidagathis hyaline Nees

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 officially 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

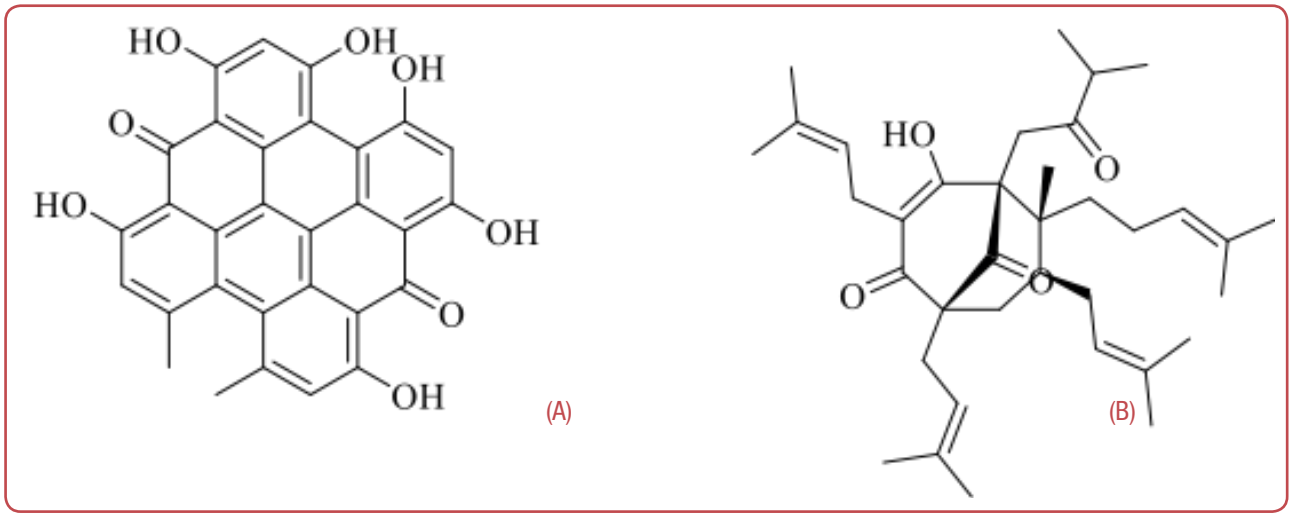

Figure 19: Chemical structure of A) hypericin and B) hyperforin

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]

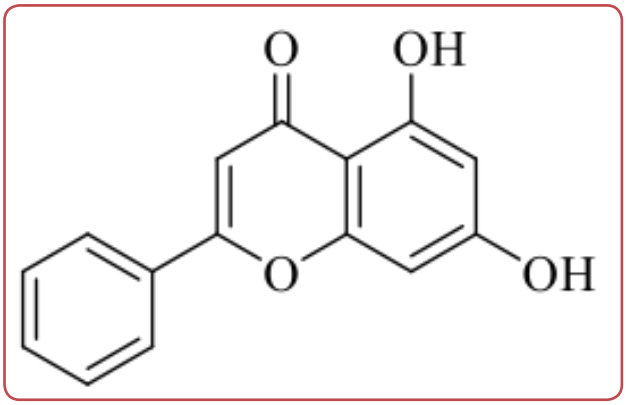

Figure 20: Chemical structure of chrysin (5,7-dihydroxyflavone)

Non-flavonoids

Curcuma longa

C longa (turmeric) and belongs to family *Zingiberacea.* 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

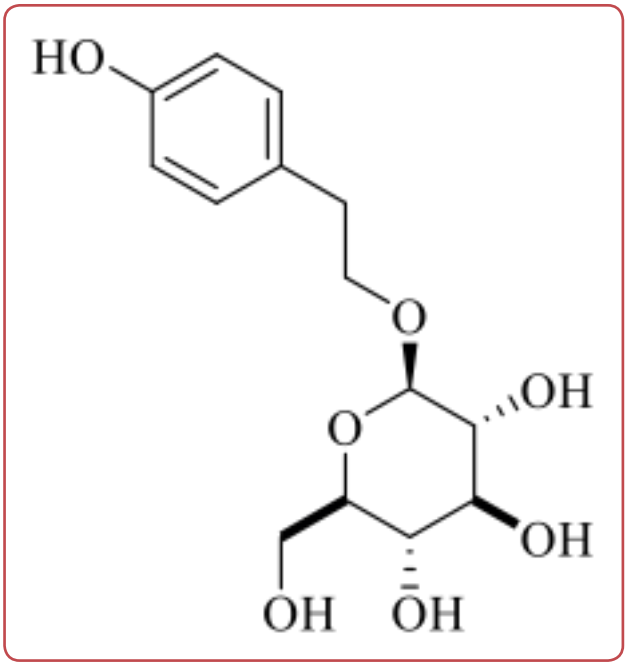

Figure 22: Chemical structure of glycone

while increasing the antioxidant enzymes activity, anti-immune inflammatory action by reducing the levels of inflammatory cytokines like TNF-α, IL-6, NF-$_{K}$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-

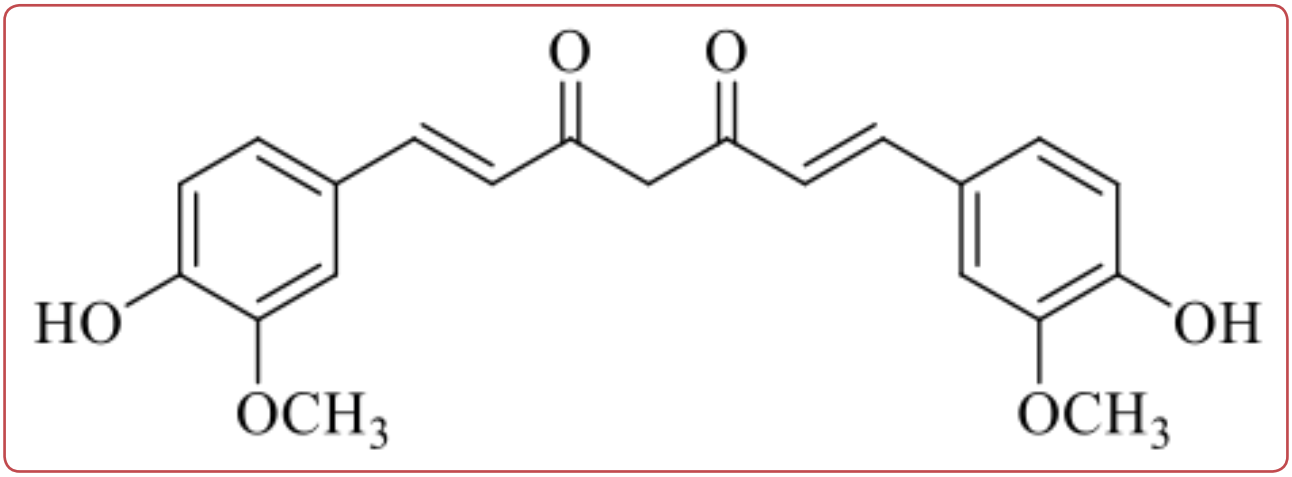

Figure 21: Chemical structure of curcumin

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 safranel, crocin, crocetin and picrocrocin exhibits the antidepressant like action (Figure 23).[153, 154]

The numerous *in vitro,* clinical tails 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]

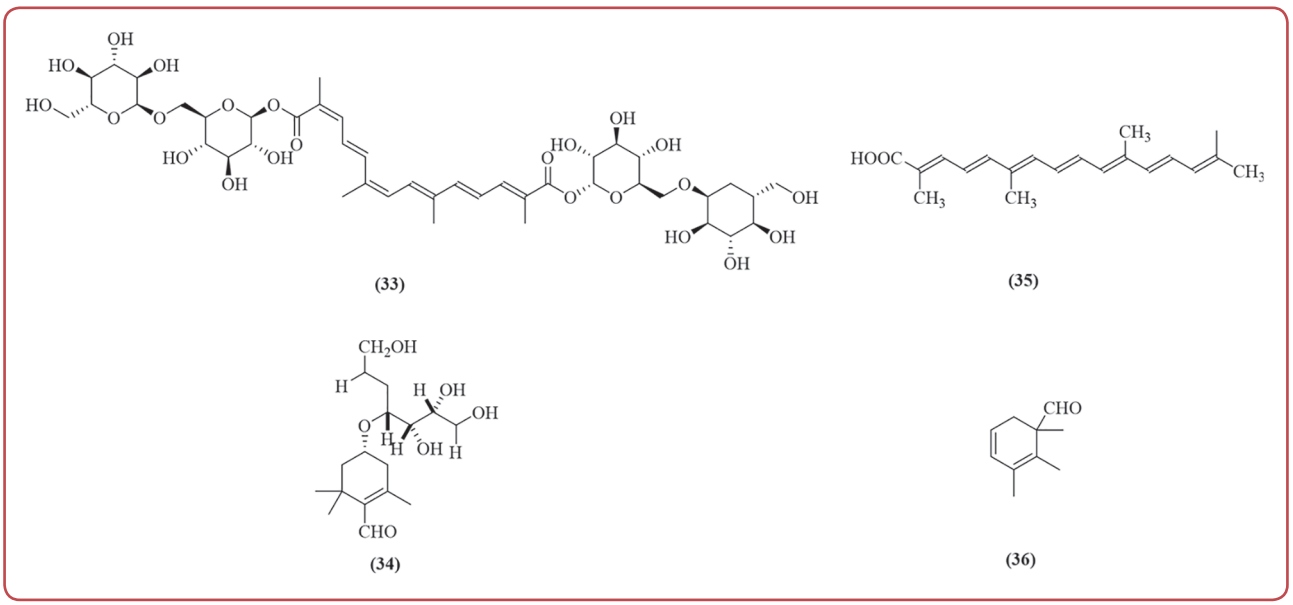

Figure 23: Chemical structure of 33) safranel, 34) crocin, 35) crocetin and 36) picrocrocin

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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Validation: TK
Formal analysis: HK, TK
Data curation: TK
Writing- original draft: HK, TK
Writing- review and editing: TK.

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