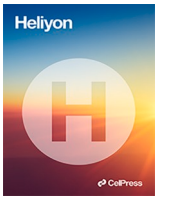
Heliyon 10 (2024) e38986

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Medicinal plants and plant-based traditional medicine: Alternative treatments for depression and their potential mechanisms of action

Juwairiah Remali [a], Wan Mohd Aizat [b,*]

[a] Department of Pathology, Hospital Pulau Pinang, Jalan Residensi, 10450, George Town, Pulau Pinang, Malaysia
[b] Institute of Systems Biology (INBIOSIS), Universiti Kebangsaan Malaysia (UKM), 43600, Bangi, Selangor, Malaysia

ARTICLE INFO

Keywords:
Anti-depressant
Ayurveda
Natural products
Phytotherapy
Traditional Chinese medicine (TCM)

ABSTRACT

Background: Clinical depression is a serious public health issue that affects 4.7 % of the world's population and can lead to suicide tendencies. Although drug medications are available, only 60 % of the depressed patients respond positively to the treatments, while the rest experience side effects that resulted in the discontinuation of their medication. Thus, there is an urgent need for developing a new anti-depressant with a distinct mode of action and manageable side effects. One of the options is using medicinal plants or plant-based traditional medicine as alternative therapies for psychiatric disorders.

Objectives: Therefore, the objective of this review was twofold; to identify and critically evaluate anti-depressant properties of medicinal plants or those incorporated in traditional medicine; and to discuss their possible mechanism of action as well as challenges and way forward for this alternative treatment approach.

Methods: Relevant research articles were retrieved from various databases, including Scopus, PubMed, and Web of Science, for the period from 2018 to 2020, and the search was updated in September 2024. The inclusion criterion was relevance to antidepressants, while the exclusion criteria included duplicates, lack of full-text availability, and non-English publications.

Results: Through an extensive literature review, more than 40 medicinal plant species with antidepressant effects were identified, some of which are part of traditional medicine. The list of the said plant species included *Albizia zygia* (DC.) J.F.Macbr., *Calculus bovis* Sativus, *Celastrus paniculatus* Willd., *Cinnamomum* sp., *Erythrina velutina* Willd., *Ficus platyphylla* Delile, *Garcinia mangostana* Linn., *Hyptis martiusii* Benth, and *Polygonum multiflorum* Thunb. Anti-depressant mechanisms associated with those plants were further characterised based on their modes of action such as anti-oxidation system, anti-inflammation action, modulation of various neurotransmitters, neuroprotective effect, the regulation of hypothalamic-pituitary-adrenal (HPA) axis and anti-depressant mechanism. The challenges and future outlook of this alternative and complementary medicine are also explored and discussed.

Conclusion: This pool of identified plant species is hoped to offer health care professionals the best possible alternatives of anti-depressants from natural phytocompounds that are efficacious, safe and affordable for applications in future clinical settings.

* Corresponding author.
E-mail address: wma@ukm.edu.my (W.M. Aizat).

https://doi.org/10.1016/j.heliyon.2024.e38986
Received 29 September 2024; Accepted 3 October 2024
Available online 5 October 2024

1. Introduction

Depression is among the most common psychiatric disorders that adversely impact more than 264 million people worldwide, and it has become highly prevalent in recent decades [1]. Depression is curently one of the main leading cause of death in the world due to the high incidence of suicide (15 %) and other complications related to depression and mental health [2]. Depression is a complex disorder that is caused by multifactorial pathophysiology factors together with genetic and environmental factors [3]. Depression is accompanied by negative mood, lack of passion or enjoyment, exhaustion, feeling guilty, feeling useless and hopeless, sleep and appetite impairment, difficulty in concentrating and suicidal ideation (https://www.who.int/news-room/fact-sheets/detail/depression). Furthermore, psychological symptoms of anxiety or panic attacks often come with depression. These situations can be either chronic or repetitive leading to a significant dysfunction or poor functioning of an individual to meet the needs of their daily responsibilities at work, school or with families [4]. Depression has caused significant personal distress and also loss of productivity resulting in massive economic loss [5,6].

To lessen this complicated health and social pressure, multiple therapeutic tools have been implemented to achieve effective medications for mental illnesses. Currently, several psychiatric medications are used in therapy including monoamine oxidase inhibitors (MAOIs) such as isocarboxazid, moclobemide and tranylcypromine, norepinephrine serotonin reuptake inhibitors (NSRIs) such as duloxetine, levomilnacipran and venlafaxine, tricyclic anti-depressants (TCAs) such as amitriptyline, desipramine, and imipramine as well as selective serotonin reuptake inhibitors (SSRIs) such as escitalopram, fluoxetine and paroxetine [7]. Despite the availability of these drugs, nearly half of the patients did not respond well to medication leading to an inadequacy of the primary therapy for the existing drugs [8]. For instance, conventional anti-depressant medicines have a slow-onset progressive effect, which typically takes at least two to eight weeks to achieve desirable therapeutic impact. In addition, anti-depressants have major side effects that involve gastrointestinal effects (constipation, dry mouth, increase/loss of appetite), central nervous system (CNS) side effects (anxiety, insomnia, sedation, nightmares), trouble getting to sleep, cardiotoxicity, neurotoxicity, ortho-static hypotension, and sexual dysfunction [9–13]. Approximately half of depressed patients has started reducing the dosage of anti-depressant drugs or even quit accepting psychiatric medications because of severe side effects [13]. These effects, along with the expensive price for drugs, have influence the interest of people in using alternatives that involve medicinal plant species [14].

Phytotherapy and traditional medicine including Traditional Chinese Medicine (TCM) and Ayurveda have long been used to promote wellness and general health [15–20]. In developing countries, rural communities are heavily dependent on traditional herbal medicine due to limited access to allopathic medicine [18]. In fact, plants are regarded as one of the most important resources for modern drugs where more than 80 % of nineteenth century's medicine have been derived or originated from plants [19–21]. Medicinal plant species have demonstrated their therapeutic role in the treatment of many psychological conditions including mental illnesses with relatively lower costs and lesser side effects compared to conventional drugs [22–24]. For example, numerous phytochemical compounds isolated from natural origins such as α-pinene [14], α-mangostin [25], myrsinoic acid [26], and Mogroside V [27] have been identified as potential new anti-depressants or at least provided an alternative to enhance the current treatment of depression [3]. Therefore, it is important to comprehend the potential mechanism of action from medicinal herbs that have been verified to have such biological effects [28].

There are evidence regarding pathophysiological mechanisms of depression that includes hypothalamus-pituitary axis (HPA) dysregulation [29], a rise in oxidative stress which is also associated with an increase in inflammatory mediators [30], and a reduction in neurotrophic factors [31]. Besides that, the pathophysiology of depression also has been hypothesised to be caused by monoamine imbalances such as serotonin (5-HT), noradrenaline (NA), and/or dopamine (DA) [32] as well as hypofunction of N-methyl--D-aspartate receptors (NMDAR) [33–35]. While there are various review papers on anti-depressants, most of them only discuss specific plant species rather than covering the majority of potential plant species or extracts available worldwide with their respective mode of action [3,36,37]. Thus, the aim of this review is to identify and compile a comprehensive list of medicinal plant species, including those used in traditional and alternative medicine, that possess potential antidepressant properties. Additionally, the review discusses the possible roles of various bioactive compounds and herbal products in their modes of action, including antioxidant, anti-inflammatory, neurotransmitter modulation, neuroprotective effects, regulation of the HPA axis, and other antidepressant mechanisms. Furthermore, this review seeks to highlight the potential use of these alternative and complementary medicines in the treatment of depression, with the goal of identifying a new antidepressant agent that is effective, safe, and affordable.

2. Methodology

Research articles were collected from various databases, including Scopus, PubMed, and Web of Science, using the keywords (plant* OR herb* OR botanical) AND (schizophrenia OR 'borderline personality disorder' OR 'bipolar mood disorder' OR 'major depressive disorder') for the period from 2018 to 2020. An additional search was conducted in September 2024 to gather more recent articles, and the review was updated accordingly. Relevant papers were identified through a critical assessment of their antidepressant significance, which served as the main inclusion criterion. Conversely, exclusion criteria include duplicates, irrelevant or non-full text articles, and non-English publications. Key information from each plant was extracted and simplified, as shown in Table 1. All plants were characterized and discussed based on their modes of action.

Table 1
Identified medicinal plant species and/or active phytocompounds with anti-depressant properties.

No.	Plant(s) and/or phytocompound(s)	Dosage of plant extract	Positive control/ placebo	Mental illness/ symptoms	Route of Adminis-tration	Period of treatment (days/weeks)	Experimental stress model	Effects	References
(1)	α-pinene (commercial source; naturally exists in *Pinus* spp.)	2 mL of α-Pinene (no information on concentration used)	Not applicable	Schizophrenia	Inhalation	60 min	MK-801 induced schizophrenia in mice	• Behavioural impairments are alleviated by α-pinene.	[14]
(2)	*Albizia zygia* (DC.) J.F. Macbr.	30, 100 and 300 mg/kg	Haloperidol (1 mg/kg) & Clozapine (10 mg/kg)	Schizophrenia	Oral gavage	7 days	Ketamine-induced schizophrenia in mice	• Demonstrated an anti-psychotic activity in mice by alleviating the positive, negative and cognitive symptoms of schizophrenia.	[249]
(3)	*Apocynum venetum* L.	30, 60, and 125 mg/kg	Fluoxetine (10 mg/kg)	MDD	Oral gavage	4 weeks	Chronic unpredictable mild stressed (CUMS) on mice	• Exerted anti-depressant-effects through anti-oxidative stress, increase BDNF level, and regulate HPA-axis	[24]
(4)	Berberine (commercial source; naturally exists in *Berberis* spp.)	20 mg/kg	Not applicable	Schizophrenia	Intraperitoneal injection	60 min	MK-801 induced schizophrenia in rats	• BBR treatment reduces cell death and increases neuronal differentiation in the hippocampus.	[205]
(5)	Brahma vati (BV) (Ayurvedic polyherbal formulation) *Bacopa monnieri* (L.) Wettst. • Bacoside A	32.5 mg/kg 32.5 mg/kg	Diazepam (4 mg/kg) & Piracetam (200 mg/kg)	Schizophrenia	Oral gavage	7 days	Amphetamine-induced schizophrenia, scopolamine-induced memory loss, and pentyleneterazol-induced convulsions in mice	• BV demonstrated antioxidant activity (↑GPx & ↓ MDA). • Improve cholinergic activity (↑ ACh levels).	[93]
(6)	*Calculus bovis sativus* (CBS)	50, 100, 150 mg/kg	Haloperidol (1.4 mg/kg)	Schizophrenia	Oral gavage	7 days	MK-801 induced schizophrenia in rats	• Combination of CBS with haloperidol resulted in a synergistic effect in alleviating abnormal behavioral.	[252]
(7)	*Cannabis indica* Lam.	Self-administered as any use for 6 months	Not applicable	Schizophrenia and Bipolar	Oral	24 weeks	Patients with schizophrenia or bipolar	• Cannabis self-administration caused sgp130 (anti-inflammation) markedly elevated in schizophrenia patients.	[117]
	Cannabis sativa L. • Cannabidiol (CBD)	15, 30, and 60 mg/kg	Clozapine (1 mg/kg)	Schizophrenia	Intraperitoneal injection	7 days	MK-801 induced schizophrenia in mice	• CBD reversed the behavioral impairments by activating serotonin receptors (5-HT1A).	[140]
(8)	*Celastrus paniculatus* Willd. • 3-(3,4-dimethoxy phenyl)-1-4(methoxy phenyl)prop-2-en-1-one (DPMPP)	40 mg/kg	Clozapine (10 mg/kg)	Schizophrenia	Oral gavage	15 days	Ketamine-induced schizophrenia in rats	• Anti-schizophrenic activity through normalising monoamine neurotransmitters. • The activity level of ATPases were restored to normal.	[143,206]
(9)	*Chrysanthellum americanum* L. Vatke	100 mg/kg	Not applicable	Anxiety and depression	Oral gavage	6 days	Psychological stress-induced rat model of irritable bowel syndrome (IBS)	• The extract increased anti-oxidant enzyme specific activity in the brain such as SOD and GPx and decreased MDA levels.	[61]
(10)	*Cinnamomum burmannii* (Nees & T.Nees) Blume	50, 100, 200 mg/kg	Haloperidol (0.5 mg/kg)	Psychosis	Oral gavage	28 days	Ketamine induced psychosis-like behaviour in rats	• The extract in combination with haloperidol can prevent neuronal cell death by	[65]

(*continued on next page*)

Table 1 (*continued*)

No.	Plant(s) and/or phytocompound(s)	Dosage of plant extract	Positive control/ placebo	Mental illness/ symptoms	Route of Adminis-tration	Period of treatment (days/weeks)	Experimental stress model	Effects	References
								inhibiting active caspase-3 activation in rats.	
	Cinnamomum zeylanicum Blume	50, 100, 200, and 400 mg/kg	Fluoxetine (0.5 mg/kg)	MDD	Intraperitoneal injection	60 min	Reserpine-induced depression in mice	• Has potent anti-oxidant activity with the anti-depressant effect was equal to fluoxetine.	[63]
	Cinnamomum tamala (Buch.-Ham.) T.Nees & Eberm.	500 g/day	Sertraline (200 mg/day)	MDD	Oral	6 weeks	Patients with MDD	• Significant improvement in treating MDD.	[64]
(11)	CocoaVia® (Flavanol rich cocoa preparation (FRP))	8, 40, 200, and 500 mg/kg	Not applicable	MDD	Oral gavage	2 weeks	Repeated social defeat stress (RSDS) mouse model	• Cocoa consumption attenuate depression through significant reduction of IL-6.	[103]
(12)	CPT herbal complex extract contained; *Clematis chinensis* Osbeck., *Prunella vulgaris* L., & *Trichosanthes kirilowii* Maximowicz.	30, 100 or 300 mg/kg	Aripiprazole (1 mg/kg)	Schizophrenia	Oral gavage	60 min	MK-801 induced schizophrenia in mice	• The extract ameliorates MK-801-induced dysfunctions by modulating the Akt/GSK-3b signalling pathways.	[212]
(13)	*Crocus sativus* L. (saffron)	60 mg/day	Sertraline (100 mg/day)	Major depressive disorder (MDD)	Oral	6 weeks	Patients with MDD	• Saffron and sertraline both reduced depressive symptoms in the elderly.	[258]
		30 mg/day	Placebo	MDD	Oral	6 weeks	Patients with MDD	• Saffron has the ability to improve hot flashes and depression symptoms in healthy females after menopause.	[259]
		30 mg/day	Fluoxetine (40 mg/day)	Depression and anxiety symptoms	Oral	6 weeks	Patients with Irritable Bowel Syndrome (IBS)	• Saffron has anti-depressive and anxiolytic activity which its effectiveness is equivalent as fluoxetine in IBS patients.	[260]
(14)	*Cuscuta chinensis* Lam.	500 mg/day	Fluoxetine (20 mg/day)	MDD	Oral	6 weeks	Patients with MDD	• *C. chinensis* has higher anti-depressant activity than fluoxetine with fewer side effects.	[267]
	Cuscuta epithymum (L.) L.	1000 mg/day	Placebo	Schizophrenia	Oral	8 weeks	Patients with schizophrenia	• *C. epithymum* improved cognitive disabilities in schizophrenia patients.	[268]

(*continued on next page*)

Table 1 (*continued*)

No.	Plant(s) and/or phytocompound(s)	Dosage of plant extract	Positive control/ placebo	Mental illness/ symptoms	Route of Adminis-tration	Period of treatment (days/weeks)	Experimental stress model	Effects	References
	Cuscuta chinensis Lam & *Lavandula angustifolia* Mill. (formulated herbal syrup)	2150 mg/5 ml	Citalopram (20 mg/day)	MDD	Oral	6 weeks	Patients with MDD	• The herbal syrup showed effective supplement for treating MDD with anxious distress.	[270]
(15)	*Daniellia oliveri* (Hutch. & Dalz.)	100, 200, and 300 mg/kg	Piracetam (150 mg/kg)	Amnesia	Intraperitoneal injection	2 weeks	Diazepam-induced amnesia in mice	• Neuroprotection by reducing oxidative damage (↑GPx & ↓ MDA).	[66]
(16)	*Echium amoenum* Fisch. & C. A.Mey., *Melissa officinalis* L., & *Crocus sativus* L. (combination called EACS)	30 ml/day syrup (3 g of *E. amoenum*, 1.5 g *M. officinalis*, & 150 mg C. *sativus*)	Citalopram (20 mg/day)	MDD	Oral	8 weeks	Patients with MDD	• EACS effectiveness has been demonstrated to be significantly more effective than citalopram with less side effects.	[285]
(17)	*Erythrina velutina* Willd. • Erythrine	100, 200 or 400 mg/kg	Olanzapine (1 mg/kg)	Schizophrenia	Oral gavage	7 days	Ketamine-induced schizophrenia in mice	• The extract possesses anti-oxidant activity by improving GPx and decreasing MDA concentration in brain.	[67]
		200 or 400 mg/kg	Olanzapine (2 mg/kg)	Schizophrenia	Oral gavage	7 days	Ketamine-induced schizophrenia in mice	• Extract reverted schizophrenia-like symptoms in mice.	[68]
(18)	*Ficus platyphylla* Delile	12.5, 25.0, 100 mg/kg	Amphetamine 9.0 mg/kg	Schizophrenia	Oral gavage	30 min	Electric foot shock or amphetamine induced hypothermia in mice	• *F. platyphylla* exhibited anti-psychotic properties, possibly due to dopaminergic neuron regulation.	[149]
(19)	*Galphimia glauca* Cav. (GgMeOH) Galphimine-Rich Fraction (GRF) Galphimines G-A Galphimines G-B Galphimines G-E	25 mg/kg 5 mg/kg 5 mg/kg 5 mg/kg 5 mg/kg	Haloperidol (1.0 mg/kg) & Olanzapine (1 mg/kg)	Schizophrenia	Oral gavage Oral gavage Oral gavage Oral gavage Oral gavage	20 days	Haloperidol induced catalepsy and ketamine induced schizophrenia in mice	• *G. glauca* activity is due to the interaction of its bioactive compounds with the dopaminergic and glutamatergic systems *in vivo*.	[151,152]
(20)	*Garcinia mangostana* Linn.	50, 150 and 200 mg/kg	Imipramine (20 mg/kg)	MDD	Oral gavage	14 days	Flinders Sensitive Line (FSL) rat (model depression in rat)	• Modulate the neurotransmitter by increasing noradrenergic and serotonergic processes, and reverse lipid peroxidation.	[77]
	Garcinia mangostana Linn. • α-mangostin	50 mg/kg 20 mg/kg	Haloperidol (2 mg/kg)	Schizophrenia	Oral gavage	14 days	LPS induced depressive-like behaviors in rats	• Decreased lipid peroxidation and reduced elevated plasma IL-6 levels and/or TNF-α levels.	[25]

(*continued on next page*)

Table 1 (*continued*)

No.	Plant(s) and/or phytocompound(s)	Dosage of plant extract	Positive control/ placebo	Mental illness/ symptoms	Route of Adminis-tration	Period of treatment (days/weeks)	Experimental stress model	Effects	References
(21)	*Gastrodia elata* Blume	250, 500 and 1000 μg/ml	Not applicable	Depression	*In vitro*	48 h	CORT-induced apoptosis in PC12 cells	• *G. elata* reduced ROS level, maintain membrane integrity and downregulated apoptosis pathway, and neuroprotective effect.	[96]
(22)	*Ginkgo biloba* L.	300 mg/kg	Paroxetine (30 mg/kg)	MDD	Oral gavage	4 weeks	CUMS on mice	• The extracts increase serotonin and dopamine concentration in multiple parts of brain.	[157]
		160 mg/day	Not applicable	Schizophrenia	Oral	1 week	Patients with schizophrenia	• *Ginkgo biloba* may cause mood dysregulation in patients.	[158]
(23)	*Hyptis martiusii* Benth. • 1,8-cineole (eucalyptol)	25, 50, 100 and 200 mg/kg 50 mg/kg	Diazepam (1, 2 or 5 mg/kg)	Psychosis	Intraperitoneal injection	30 min	Ethyl ether-induced sleeping time, pentylenetetrazole-induced seizure, haloperidol-induced catalepsy and ketamine-induced hyperkinesia in mice	• Anti-psychotic-like properties possibly due to regulation of glutamatergic and dopaminergic neurotransmission in mice.	[161]
(24)	Kai-Xin-San (KXS) formulae contained; *Panax ginseng* C.A.Mey. *Polygala tenuifolia* Willd. *Acorus tatarinowii* Schott.& *Poria cocos* (Schw.) Wolf.	3000–10000 mg/kg	Fluoxetine (4 mg/kg)	MDD	Intragastric	6 weeks	CUMS on mice	• KXS formulae in mice was able to suppress HPA activation (CRH, ACTH, corticosterone) and lowering of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α).	[122]
(25)	Mahuang- Fuzi-Xixin decoction formulae (MFX); *Aconitum carmichaeli* Debeaux, *Ephedra sinica* Stapf, and *Asarum sieboldii* Miq.	2.5, 12.5, and 25 g/kg	Escitalopram (10 mg/kg)	MDD	Intraperitoneal injection	7 days	LPS-induced depressive-like behaviours in mice	• MFX reduced expression IL-1β, suppressed the NLRP3 inflammation activation and promote the neurogenesis in the hippocampus.	[124]
(26)	*Milicia excelsa* (Welw.) C.C. Berg • Aqueous (AF) • Ethanol (EME) • Hexane (HF) • Ethyl acetate (EAF) • Butanol (BF)	250, 500 and 1000 mg/kg of the extract and fraction (s)	Haloperidol (1–2 mg/kg)	Schizophrenia	Oral gavage	60 min	Ketamine-induced hyperlocomotion in mice	• The extract fractions contain anti-psychotic ingredients that are physiologically active. • The activity of the fractions showed with the order EME > EAF > AF > HF > BF.	[276]
(27)	PAPZ formulation; *Panax ginseng* C.A.Mey., *Angelica sinensis* (Oliv.) Diels, *Polygala tenuifolia* Willd., *and Ziziphus jujuba* Mill.	1000 mg/kg	Not applicable	MDD	Oral gavage	3 weeks	Corticosterone treated in mice	• PAPZ increase protein expression BDNF and improve the anti-oxidation in brain (↑SOD & ↓ MDA).	[78]
(28)	*Pinus pinaster* Aiton • Pycnogenol	50 mg/day	Escitalopram	MDD	Oral	16 weeks	Patients with MDD	• Pycnogenol supplementation was able to reduce the anti-	[284]

(*continued on next page*)

Table 1 (*continued*)

No.	Plant(s) and/or phytocompound(s)	Dosage of plant extract	Positive control/ placebo	Mental illness/ symptoms	Route of Adminis-tration	Period of treatment (days/weeks)	Experimental stress model	Effects	References
								depressant adverse effect on sexual function.	
(29)	*Polygonum multiflorum* Thunb. • 2,3,5,4′-Tetrahydroxystilbene-2-O-beta-D-glucoside (THSG)	10, 20, and 40 mg/kg	Fluoxetine (10 mg/kg)	MDD	Subcutaneous injection	15 days	Chronic restraint stress (CRS) on mice	• Reduced oxidative stress by reversing MDA contents. • Inhibit expression of proinflammatory factors such as TNF-α, IL-1β, and IL-6 in mice brain. • Increased astrocyte multiplication and neurogenesis in the hippocampal of CRS mice.	[90]
(30)	*Rapanea ferruginea* (Ruiz & Pav.) Mez (RF) • Myrsinoic acid A (MAA) • Myrsinoic acid B (MAB)	50, 100, 150, 300 mg/kg 5, 15, 30 mg/kg 3, 10, 30, 60 mg/kg	Imipramine (20 mg/kg)	MDD	Intraperitoneal injection	60 min	Treatment of mice with dopaminergic, serotoninergic, and noradrenergic antagonists.	• Anti-depressant effect of RF, MAA and MAB is mediated by the regulation of various neurotransmitter and reducing MAO-A activity.	[26]
(31)	*Rhodiola rosea* L. & *Crocus sativus* L. (combination)	154 mg of *R. rosea* L. and 15 mg of *C. sativus* L.	Not applicable	MDD	Oral	6 weeks	Patients with MDD	• Extract combination able to reduce depression level and improve anxiety symptoms.	[261]
	Rhodiola rosea L.	3 ml/kg (84, 8.4 and 0.84 mg extract/kg)	Not applicable	Psychosis	Intraperitoneal injection	15 min before the behavioural test	Prepulse inhibition in rats and mice (apomorphine and dizocilpine)	• *R. rosea* extract exerted anti-psychotic-like effects and robustly reverses prepulse inhibition deficits in rodents.	[266]
(32)	*Siraitia grosvenori* Swingle • Mogroside V (MogV) • 11-oxo-mogrol	2.5 or 5 mg/ml	Not applicable	Schizophrenia	Intraperitoneal injection	2 weeks	MK-801 induced schizophrenia in mice	• Protect neuronal damage by enhancing neurite development, preventing cell apoptosis, and reducing intracellular calcium release.	[27]
(33)	*Spinacia oleracea* L. (SOEE)	50, 100 and 200 mg/kg	Haloperidol (1 mg/kg) or Olanzapine (5 mg/kg)	Schizophrenia	Oral gavage	15 days	Ketamine-induced schizophrenia in mice	• SOEE increased GPx levels, lowering MDA, lowered serum TNF- α level, attenuated AChE activity and increased the GABA concentration in psychotic mice.	[85]
(34)	SuHeXiang (SHXW) (*Lipuidambar orientalis* Mill.)	2 ml of 10 % SHX essential oil for 10 and 30 min	Not applicable	Depression and anxiety	Inhalation	12 days (acute) and 28 days (chronic)	CUMS on mice	• SHX possess anti-depressant and anxiolytic activities, and decreased the levels of TPO, IL 6, and TNF-α in serum.	[127]
(35)	Unmadgajakesari (UGK) (formulation based on Ayuverda Indian practice without detail on herbs used)	100, 200 and 400 mg/kg	Haloperidol (1.5 mg/kg)	Schizophrenia	Oral gavage	8 days	Apomorphine, 5-HTP & MK-801 induced schizophrenia in mice	• UGK exhibited significant dopaminergic, serotonergic, and NMDA reducing activity.	[183]
(36)	*Viola odorata* L. • 5,7-Dihydroxy-3,6-dimethoxyflavone • 5,7,4′-trihydroxy-	1, 10 and 30 mg/kg	Fluoxetine (20 mg/kg)	MDD	Intraperitoneal injection	30 min before the behavioural test	pCPA, D1 antagonist, D2 antagonist or prazosin (α1 adrenergic antagonist) treated in mice.	• Isolated compounds 1–3 produced a significant increase in 5-HT concentrations in brain tissue.	[2]

(*continued on next page*)

Table 1 (*continued*)

No.	Plant(s) and/or phytocompound(s)	Dosage of plant extract	Positive control/ placebo	Mental illness/ symptoms	Route of Adminis-tration	Period of treatment (days/weeks)	Experimental stress model	Effects	References
	3′,5'dimethoxyflavone • 5,7,4′-trihydroxy-3′-methoxyflavone								
(37)	*Withania somnifera* (L.) Dunal (Ashwagandha)	500 mg/day (1st week), 1000 mg/ day (2nd week)	Placebo	Schizophrenia	Oral	12 weeks	Patients with schizophrenia	• The extract significantly reduced depression symptoms compared to placebo.	[282]
		1000 mg/day	Placebo	Schizophrenia	Oral	12 weeks	Patients with schizophrenia	• The extract was able to treat the depression and anxiety symptoms in schizophrenia.	[283]
(38)	Xiaoyaosan (composed of 8 TCM herbs)	250 mg/kg	Fluoxetine (2.6 mg/kg)	MDD	Intragastric gavage	21 days	CUMS on mice	• Demonstrated anti-depressant effect.	[179]
(39)	Xin-Ke-Shu (XKS) tablets containing; *Salvia miltiorrhiza* Bunge, *Pueraria montana* var. thomsonii (Benth.) M.R. Almeida, *Crataegus monogyna* Jacq., *Panax notoginseng* (Burkill) F.H.Chen and *Aucklandia costus* Falc.	12 tablets/day (4 tablets, three times a day) (concentration was not mentioned)	Placebo	Depression or anxiety symptoms	Oral	12 weeks	Depression and anxiety symptoms in patients with coronary artery disease (CAD)	• Inhibiting the development of pro-inflammatory cytokines and stimulate the production of anti-inflammatory cytokines.	[131]
(40)	Yueju-Ganmaidazao Decoction (YG)	1.0, 1.5, 2.0, 2.5 and 3.0 g/kg	Not applicable	MDD	Intragastric gavage	1 day (24 h)	CMS on mice	• Demonstrated anti-depressant-like effects by inhibiting NMDA/NO/cGMP signaling pathway.	[86]
(41)	Zhile capsuled (TCM formulated composed 16 herbs)	735, 2205 and 6615 mg/kg	Fluoxetine (10 mg/kg)	MDD	Oral gavage	5 weeks	CUMS on rats	• Zhile alleviated depression-like behaviours by the upregulation of monoamine neurotransmitters such NE, 5-HT, and DA and upregulating neuroprotective effects by increasing BDNF protein.	[184]

Abbreviations: Acetylcholine (ACh), Acetylcholinesterase (AChE) Adenosine Triphosphatase (ATPases), Adrenocorticotropic Hormone (ACTH), Arginine Vasopressin (AVP), Brain-Derived Neurotrophic Factor (BDNF), Catalase (CAT), Chronic Mild Stress (CMS), Chronic Unpredictable Mild Stress (CUMS), Central Nervous System (CNS), Coronary Artery Disease (CAD), Corticosterone (CORT), Corticotropin-Releasing Hormone (CRH), Cyclic Guanosine 3,5 Monophosphate (cGMP), Decreased (↓), Dizocilpine Hydrogen Maleate (MK-801), Dopamine (DA), Dopaminergic 1 antagonist (D1), Dopaminergic 2 antagonist (D2), Gamma-Aminobutyric Acid (GABA), Glucocorticoid (GC), Glutathione Peroxidase (GPx), Glycogen Synthase Kinase 3-beta (GSK-3b), Hypothalamic-Pituitary-Adrenal (HPA), Increase (↑), Interleukin 1 beta (IL-1β), Irritable Bowel Syndrome (IBS), Lipopolysaccharide (LPS), N-methyl-D-aspartic acid (NMDA), N-methyl-D-aspartate acid receptor (NMDAR), Nitric Oxide (NO), NLR family pyrin domain containing 3 (NLRP3), Norepinephrine (NE), Major Depressive Disorder (MDD), Malondialdehyde (MDA), Maternal Immune-Activation (MIA), Monoamine Oxidase-A (MAO-A), Serotonin (5HT), Serotonin Synthesis Inhibitor (pCPA), Soluble gp130 (sgp130), Superoxide Dismutase (SOD), Thrombopoietin (TPO), Interleukin 6 (IL 6), Traditional Chinese Medicine (TCM), Tumor Necrosis Factor α (TNF-α), Pentyleneterazol (PTZ), Protein Kinase B (Akt), Repeated Social Defeat Stress (RSDS).

3. Potential anti-depressant mechanisms from medicinal plants and traditional medicine

Table 1 presents findings in more than 40 identified medicinal plant species that possess anti-depressant properties, some of which are part of traditional medicine formulation. Those species include *Albizia zygia* (DC.) J.F.Macbr., *Calculus bovis* Sativus, *Celastrus paniculatus* Willd., *Cinnamomum* sp., *Erythrina velutina* Willd., *Ficus platyphylla* Delile, *Garcinia mangostana* Linn., *Hyptis martiusii* Benth, and *Polygonum multiflorum* Thunb, among others. The important information about each plant species was documented in terms of species name and(or) compound, dosage of plant extracts, positive control, type of mental illness, administration, treatment period, experimental stress model and effects of plant extract treatment. All the identified plant species were characterised based on their modes of action such as anti-oxidation system, anti-inflammation, modulation of various neurotransmitters, neuroprotective effect, regulation of hypothalamic-pituitary-adrenal (HPA) axis and anti-depressant mechanisms (Figs. 1 and 2). The following subsections discuss in detail all modes of action.

3.1. Antioxidant mechanism for anti-depressant effect

Oxidative stress is known to be essential in the pathogenesis of depression [38]. The involvement of genetic markers with environmental stimuli, particularly stress, is thought to be the source of depression [39]. Exposure to stress can be related to an increase in the generation of reactive oxygen species (ROS) [40]. An imbalance proportion of pro-oxidants and anti-oxidants causes oxidative stress, which in consequence increases the release of ROS and a disturbance of redox regulation and its signalling pathways [41,42]. These abnormalities have contributed to the formation of psychotic symptoms [43]. Increasing evidence from preclinical and human post-mortem findings confirmed the theory that oxidative stress plays a crucial role in the development of depression [44–46]. Besides that, a growing study of anti-depressant effect on oxidative stress indicates that anti-depressants may have a role as an anti-oxidant mechanism in relieving depression [46–49]. Furthermore, the central nervous system (CNS) is also extremely susceptible to oxidative stress, and elevated levels of oxidative stress eventually result in oxidative damage, which is mainly manifested by the pro-oxidant or anti-oxidant imbalance [50]. In addition, depressed patients have higher levels of malondialdehyde (MDA) in their blood compared to healthy people [51]. The MDA is a metabolite that serves as an indirect indicator for measuring lipid peroxidation damage whereby an increase of free radicals leads to increased MDA production [52]. The MDA is an important oxidative stress biomarker, and changes in MDA levels in biological systems are associated with a variety of diseases [53] including cancer [52], neurodegenerative diseases [54], and depression [46,55].

A rodent model of depression using chronic unpredictable mild stressed (CUMS) exposure can cause oxidative damage in rat brain

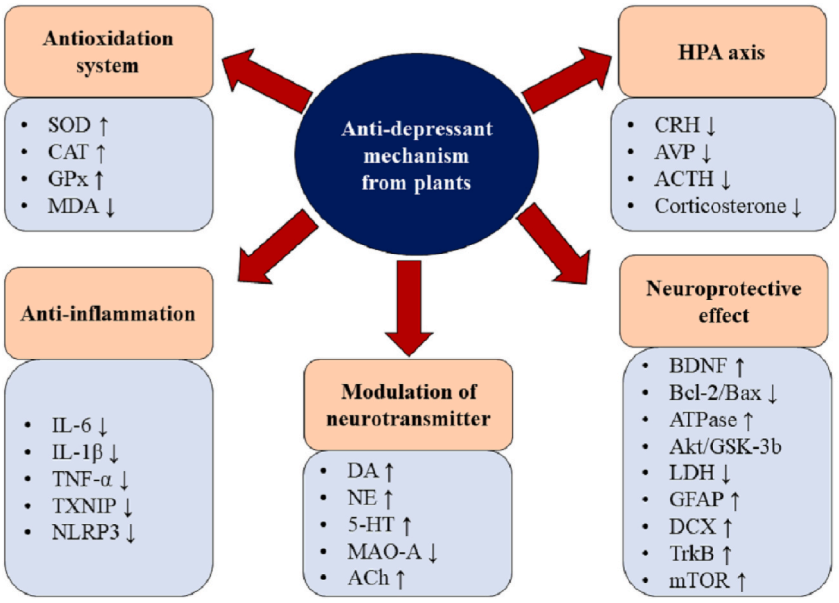


Fig. 1. Potential anti-depressant mechanisms from medicinal plants. The potential mechanisms have been characterised into five main modes of action, which are anti-oxidation system, anti-inflammation action, modulation of various neurotransmitters, neuroprotective effect as well as regulation of hypothalamic-pituitary-adrenal (HPA)-axis. Abbreviations: Adenosine Triphosphatase (ATPase), Acetylcholine (ACh), Adrenocorticotropic Hormone (ACTH), Arginine Vasopressin (AVP), B-cell lymphoma 2 ((Bcl-2)/Bax), Brain-Derived Neurotrophic Factor (BDNF), Catalase (CAT), Corticotropin-Releasing Hormone (CRH), Decreased (↓), Dopamine (DA), Doublecortin (DCX), Glial Fibrillary Acidic Protein (GFAP), Glutathione Peroxidase (GPx), Protein Kinase B (Akt), Glycogen Synthase Kinase 3-beta (GSK-3b), Increase (↑), Interleukin 1 beta (IL-1β), Interleukin 6 (IL-6), Lactate Dehydrogenase (LDH), NLR Family Pyrin Domain Containing 3 (NLRP3), Norepinephrine (NE), Malondialdehyde (MDA), Mechanistic Target of Rapamycin (mTOR), Monoamine Oxidase-A (MAO-A), Serotonin (5HT), Superoxide Dismutase (SOD), Tropomyosin-related Kinase Receptor B (TrkB), Tumor Necrosis Factor α (TNF-α).

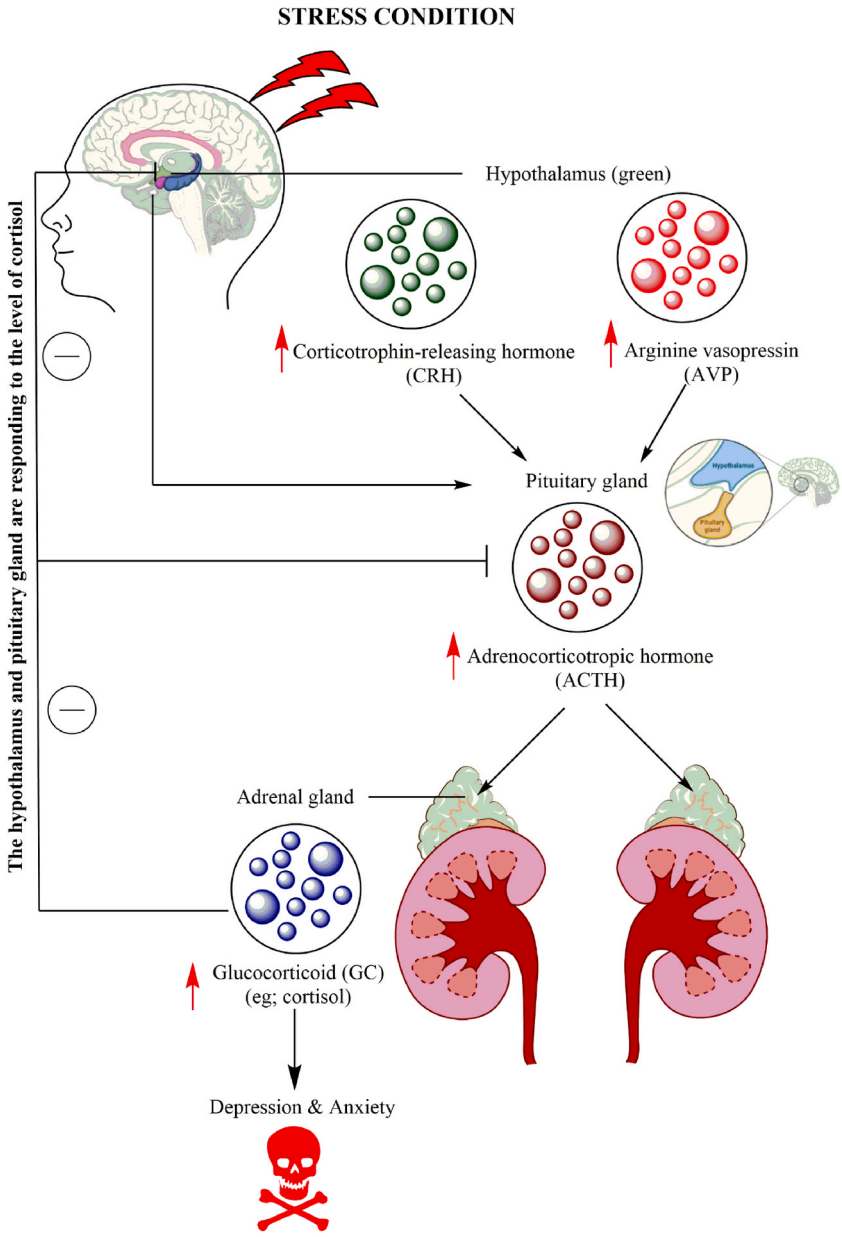


Fig. 2. Hypothalamic-pituitary-adrenal (HPA) axis. A complicated system of neurohormone featured by the HPA axis that connects the hypothalamus, pituitary gland, and adrenal glands. Over-stimulation of the HPA axis is one of the pathological hypotheses of depression. Hyperactivity of the HPA axis is characterised by the abnormal elevation of corticotropin-releasing hormone (CRH), arginine vasopressin (AVP), adrenocorticotropic hormone (ACTH), and cortisol that leads to the impairment of hippocampal neurons and cognitive ability in patients with depression. The figure has been created using ChemDraw and BioRender.

regions such as the hippocampus. This is evidenced by increased MDA levels and reduced anti-oxidant enzymes' superoxide dismutase (SOD) and catalase (CAT) activities. Meanwhile, prolonged anti-depressant therapy alleviates such abnormalities [56–58]. Interestingly, a natural product treatment using sword-leaf dogbane (*Apocynum venetum* L.) leaf extract (AVLE) was able to ameliorate the CUMS effects. This includes the increase in the expression levels of SOD, CAT, and glutathione peroxidase (GPx) [24] while reducing hydrogen peroxide (H_2O_2) [59], ROS production, and MDA levels in the rat hippocampus (Fig. 1 and Table 1) [24].

Another plant-derived extract, *Chrysanthellum americanum* L. (Vatke), a Compositae-family medicinal plant used in west African [60] also possessed anti-depression effect with strong anti-oxidant activity in the psychologically stress-inducing rat model of irritable bowel syndrome (IBS) (Table 1) [61]. IBS is a severe functional gastrointestinal tract disruption that is characterised by immune and inflammatory-related abnormalities of CNS and peripheral intestinal systems and is frequently related to mood disorders such as depression and anxiety [62]. Administration of six-day oral gavage of the polyphenolic extract at a concentration of 100 mg/kg body

weight in stress-induced IBS rats presented noticeable anxiolytic and anti-depressant-like effects [61]. This was in conjunction with substantially enhanced antioxidant enzyme activities in the temporal lobe such as SOD and GPx and decreased MDA levels (Fig. 1 and Table 1) [61]. In addition, a linear regression analysis revealed strong associations between oxidative stress parameters and behavioural studies. This finding demonstrated that prescribing *C. americanum* polyphenolic extract could alleviate mood and cognitive abnormalities that are caused by stress-induced in an IBS rat model, which also can be associated with a reduction in the cerebral oxidative stress levels [61].

Cinnamomum plants have been documented in Asian medicine to treat various types of ailments such as diabetes and pain relief as well as depression [63–65]. In a study, *Cinnamomum zeylanicum* Blume extracts successfully reversed the depression effect in mice, similar to the positive control fluoxetine drug (Table 1) [63]. This extract also has potent anti-oxidant activity (IC50: 12.82 mg/ul) and has major anti-oxidant compounds such as phenolics (264.37 mg/g), flavonoid, (27.14 mg/g), and flavonol (26.25 mg/g). The anti-depressant activity of this extract may be due to its significant anti-oxidant properties (Table 1) [63]. Besides that, a clinical study using another *Cinnamomum* species, *C. tamala* (Buch.-Ham.) T.Nees and Eberm., has been shown to be an excellent adjuvant in the treatment of major depressive disorder (MDD) patients (Table 1) [64]. The use of *C. tamala* combination therapy with setraline also appeared to be generally safe and effective in this study with no significant side effect was identified (Table 1) [64]. Similarly to *C. zeylanicum*, *C. tamala* possesses a significantly high polyphenolic constituent that may exert anti-oxidative effects towards improving the pathophysiology of depression [64].

Another traditional herbal medicine utilising *Daniellia oliveri* (Hutch. & Dalz.), a native African plant known as copaiba balsam tree, has been implicated in treating anxiety and schizophrenia. A current study found that aqueous extracts of *D. oliveri* root bark at 100, 200, and 300 mg/kg BW dosages significantly improved memory processes in diazepam-induced amnesia (memory loss) in mice (Table 1) [66]. Such treatment might provide neuroprotection by reducing diazepam-induced oxidative damage as evidenced by the increase of GPx activity and the reduction in MDA concentrations in the hippocampus region of the extract-treated mice (Fig. 1 and Table 1) [66]. Additionally, a reduction in the hippocampal cell density as detected in the diazepam-untreated group was reversed by the pre-treatment of the herbal extract at a concentration of 300 mg/kg [66]. Therefore, these studies alluded that *D. oliveri* aqueous extract has potent antioxidant properties and could be effective in treating neurological conditions in amnesic patients.

Erythrina velutina Willd. or known as mulungu and is typically used in Brazilian traditional medicine also demonstrated their benefit in the treatment of mental disorders [67]. Administration of standardised extract from its leaves and erythrine, the bioactive compound, showed potential in reversing schizophrenia-like symptoms caused by repeated ketamine administration such as prepulse inhibition deficits, hyper-locomotive activity, and social behaviour deficits (Table 1) [67,68]. These results are comparable to those obtained with olanzapine, an anti-psychotic medication widely used in the psychiatric clinic (Table 1) [67]. The extract also possesses antioxidant activity by improving GPx concentration in the prefrontal brain cortex and striatum as well as decreasing MDA concentration in the ketamine-induced mice (Fig. 1 and Table 1) [67]. A previous study also found that *E. velutina* extract exhibits neuroprotective properties through *in vivo* and *in vitro* models of Parkinson's disease. This could be due to the anti-oxidant activity of the extract contributed by its high phenolic compounds [69,70]. Based on this evidence, *E. velutina* extract appears to be a valuable natural resource for the development of a future anti-schizophrenia drug.

Garcinia mangostana Linn., a tropical South East Asian plant, has been found to have a wide range of medicinal activities such as anti-cancer, anti-microbes, and anti-diabetes since it possess potent antioxidants of phenolic xanthone compounds [71–73]. These prenylated xanthones, especially α-mangostin and γ-mangostin, have also been shown to exert neuroprotective properties [71,74–76]. For instance, *G. mangostana* extract treatment in a depression rat model of Flinders Sensitive Line (FSL) was able to improve depressive-like behaviour through reversing the hippocampal lipid peroxidation (Table 1) probably via the antioxidative action of xanthones [77]. Another study has demonstrated that α-mangostin significantly decreased lipopolysaccharide (LPS)-induced lipid peroxidation in rat brain frontal cortex (Table 1), potentiating the development of a new adjunctive therapeutic alternative for people suffering from major depressive disorder (MDD) and schizophrenia [25].

Administration of a Chinese herbal remedy called "PAPZ" consisted of *Panax ginseng* C.A.Mey., *Angelica sinensis* (Oliv.) Diels, *Polygala tenuifolia* Willd., and *Ziziphus jujuba* Mill. improved the depression-like characteristics in the corticosterone (CORT) model (Table 1) [78]. Each herb in PAPZ has previously been shown to be useful for CNS disorders and is commonly used in Asian supplementation and also has various pharmacological effects including neuroprotection [79], depression [80], anti-psychotic [81], and sedative agent as well as an enhancer for memory and learning in mice [82]. PAPZ also exhibited a significantly decreased immobility time in tail suspension test (TST) and a significant increase in learning and memory capacity compared to a control group [78]. Besides that, PAPZ administration also enhanced the enzyme activity of SOD in the hippocampal tissues, correlating with a lower MDA level (Fig. 1 and Table 1) [78] suggesting that PAPZ may improve the cerebral antioxidant properties in depressed mice induced with CORT.

Spinacia oleracea L. (spinach) seeds have important pharmacotherapeutic effects such as anti-oxidant, anti-inflammatory, anti-epileptic, neuroprotective, and anti-Alzheimer effects [83,84]. Oral administration of *S. oleracea* seed extract (SOEE) at the doses of 50, 100, and 200 mg/kg has significantly minimised locomotor movement counts (hyperlocomotor activity represents positive symptoms of schizophrenia) after being induced by ketamine in mice as well as significantly reduced stereotypic behaviours such as the total number of falling and turn around in mice (Table 1). Besides that, oral administration of SOEE at the doses of 100 and 200 mg/kg also significantly reduce ketamine-induced immobility duration in the force swimming test (FST) (screening of anhedonia, a negative symptom of schizophrenia) and reversed the ketamine-induced cognitive deficit by enhancing learning and memory performance in mice (Table 1) [85]. Moreover, administration of ethanol extract of SOEE showed no toxicity effects up to 2000 mg/kg dose, thus would be safe for the development of anti-psychotic agent [85]. Furthermore, its beneficial role as anti-schizophrenia may be affiliated with its regulating effect as an anti-oxidant, anti-inflammation, and neurotransmitter modulation. SOEE has demonstrated free radical scavenging efficiency in an *in vitro* 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay indicating its anti-oxidant capacity.

Furthermore, SOEE was discovered to strengthen the anti-oxidant function by increasing GPx concentration in the brains of ketamine-induced schizophrenia in mice (Fig. 1 and Table 1) [85]. SOEE also was identified to minimise oxidative stress by reducing lipid peroxidation by lowering the MDA levels in the brains of mice at the doses of 100 and 200 mg/kg (Fig. 1 and Table 1) [85]. Anti-inflammation and modulation of neurotransmitter mode of action of SOEE will be discussed in the next subchapter.

Yueju-Ganmaidazao decoction (YG) is a traditional Chinese herbal medicine that is made up of Yueju (primarily *Atractylodes carlinoides* (Hand.-Mazz.) Kitam., *Cyperus absconditicoronatus* Bauters, Reynders & Goetgh., *Ligusticum acuminatum* Franch., *Gardenia jasminoides* J. Ellis, and "shenqu" (medicated leaf)) and Ganmaidazao (comprises of *Glycyrrhiza* sp., *Triticum aestivum* L., *Ziziphus jujuba* Mill) has been prescribed to treat depression and mood disorder. Administration of YG demonstrated anti-depressant potential of which a single dosage was sufficient to reverse the depression-like behaviours as early as 30 min and lasted for 7 days in chronically depressed or learned helpless (LH) mice. This highlights the rapid anti-depressant-like impact (Table 1) [86]. Moreover, a single dose of YG downregulated the over-expressions of NMDA receptor subunit 1 (NR1) and nitric oxide/cyclic guanosine monophosphate (NO/cGMP) [86]. In neuronal cultures, the activation of the NMDA receptor increases ROS production, which was mediated by NADPH oxidase through nitric oxide (NO), cyclic guanosine monophosphate (cGMP), and protein kinase G (PKG) [87]. Other *in vitro* research also revealed that inhibition of NMDA/NO/cGMP is typical among traditional anti-depressants including ketamine as described earlier [88,89].

Besides that, another compound called 2,3,5,4′-tetrahydroxystilbene-2-O-beta-D-glucoside (THSG) works through anti-oxidative stress mechanisms to reverse the stress-induced depression in mice [90]. THSG is one of the major compounds from *Polygonum multiflorum* Thunb. (known as Heshouwu in Chinese) and is being widely used as TCM [91]. It has been proven to exhibit anti-oxidant and anti-ageing properties as well as other benefits such as improving immunity, regulating blood lipids, preventing atherosclerosis, and enhancing learning and memory performances [92]. Peripheral administration of various THSG concentrations at 10 mg/kg, 20 mg/kg, and 40 mg/kg was able to counteract the depressive-like behaviours induced by chronic restraint stress (CRS) in mice as evaluated by TST, FST, and open-field test (OFT) (Table 1). Further experiments found that THSG treatment reduced oxidative stress by reversing MDA contents in the serum, hippocampus, and prefrontal cortex in CRS mice (Fig. 1 and Table 1) [90]. The finding of this study alludes to its effectiveness as an antioxidant in reversing depression-like phenotype as revealed from *in vitro* and *in vivo* experimentations.

Brahmi vati (BV) and *Gastrodia elata* Blume (orchid) also demonstrated anti-depressant activity through an anti-oxidant mode of action. BV has been shown to have anti-oxidant activity as administration of BV diminished MDA status and increased GPx levels in the brain (Fig. 1 and Table 1) [93]. BV is an Ayurvedic polyherbal mixture that has been used in India since the old days to treat seizures that are attributed to schizophrenia and memory problems. Oral administration of BV at a concentration of 32.5 mg/kg in mice has been identified to possess a significant anti-convulsant, memory-improving, and anti-schizophrenic properties compared to the negative control groups and Bacoside A (isolated from *Bacopa monnieri* (L.) Wettst. Plant which is an important ingredient of BV) at the same dose (Table 1) [93]. In addition, *G. elata* also demonstrated to have anti-depressant activity through anti-oxidant mode of action. *G. elata* is frequently used in TCM to cure a range of nervous conditions including sedative, anti-convulsant, headache, dizziness, tetanus, and epilepsy [94,95]. *G. elata* at concentrations of 250, 500, and 1000 μg/ml can significantly reverse the increased level of ROS generated in rat pheochromocytoma cell line (PC12) treated with corticosterone (CORT). This suggests the protective role of the natural product through oxidative stress inhibition (Table 1) [96].

3.2. Anti-inflammation mechanism for anti-depressant effect

Inflammation has been linked to a variety of diseases including neuropsychiatric disorders like depression. Depressive patients have been discovered to have a higher level of inflammatory cytokines, which is one of the main pathophysiology factors implicated in mental disease [97–100]. Besides that, inflammatory cytokines also serve an important role in synaptic plasticity (the capability of the brain to continue evolving, growing, and developing in response to life experiences) and abnormalities are often appeared in depressed patients [101,102]. Anti-depressant medication, on the other hand, has been associated with reductions in such inflammatory responses [97].

The development of CocoaVia® from flavanol-rich cocoa preparation (FRP) has demonstrated the potential to cure stress and anxiety disorders in humans [103]. Cocoa made from the dried seed of *Theobroma cacao* L., is an important source of polyphenolic compounds such as epicatechins [104,105]. It is highly effective in protecting against multiple metabolic, neurological and psychological disorders *in vivo*, primarily due to the modulation of synaptic function [106–109]. Published evidence also suggests cocoa product consumption such as chocolate to enhance cognitive function and is beneficial in modulating mood [110]. A recent study has identified that oral administration of FRP at a low dose (40 mg/kg) on a mouse model of social stress demonstrated its anti-inflammatory activity through significant reduction of interleukin-6 (IL-6) in rat plasma (Fig. 1 and Table 1) [103]. IL-6 has been verified to be the most frequently observed inflammatory cytokine that is strongly associated with MDD [111,112]. FRP that have a high content of phenolic acids such as epicatechin, catechin, proanthocyanidin B1 and B2, and gallic acid may contribute to its anti-inflammatory activity [103] to attenuate depression.

Besides that, the study also demonstrated the medicinal properties of *G. mangostana* Linn. and one of its dominant bioactive components, α-mangostin as an adjuvant therapy with haloperidol, a typical anti-psychotic on maternal immune activation (MIA)-induced schizophrenia-like behaviour in rats. MIA has been induced using lipopolysaccharide (LPS) (Table 1) [25]. Treatment with α-mangostin and raw *G. mangostana* pericarp extract in conjunction with haloperidol has been found to efficiently reverse MIA-induced depressive-like behaviour compared with haloperidol alone (Table 1) [25]. Furthermore, treatment with α-mangostin and *G. mangostana* alone was more effective than haloperidol in reversing depressive-like behaviour [25]. Apart from this, MIA-induced

deficits in sensorimotor gating were reversed by the combination of haloperidol and *G. mangostana* [25]. *G. mangostana* also substantially reversed depressive-like activities such as increased immobility and decreased active coping such as swimming and climbing in LPS-exposed offspring [25]. The finding is congruent with another previous study [77]. *G. mangostana* and α-mangostin also have anti-inflammatory properties in which both of these treatments were able to reduce elevated plasma interleukin-6 (IL-6) levels and/or tumour necrosis factor-α (TNF-α) levels (Fig. 1 and Table 1) [25]. α-mangostin previously has been documented to reduce inflammatory cytokines upon LPS induction [113], to inhibit interleukin-2 (IL-2) release [114], and to suppress IL-6 expression [115]. As a result, the potential benefits of *G. mangostana* supplementation may involve anti-inflammation mechanisms.

Besides that, *Cannabis indica* Lam. and *Cinnamomum burmannii* (Nees & T.Nees) Blume showed to have anti-depressant activity with an anti-inflammation mechanism. The psychopharmaceutical and medicinal properties of the *C. indica* plant, a species of the Cannabaceae family's Cannabis genus, have been acknowledged for thousands of years for their therapeutic benefit in ameliorating inflammation, injury, and rheumatic diseases [116]. A recent study has identified cannabis self-administration is attributed to a significant increase of soluble gp130 (sgp130) levels in schizophrenia patients (Table 1) [117]. Sgp130 is a decoy receptor that is able to bind to IL-6 or soluble IL-6-receptor (IL-6/sIL-6R) complex thus potently and selectively blocking inflammatory trans-signalling [118,119]. As a consequence, it can reduce the negative effects of IL-6 in the CNS [120]. Besides that, the combination of *C. burmannii* extract and haloperidol, an anti-psychotic medication, showed to have potent activity in controlling negative symptoms of psychosis. This combination was capable of preventing neuronal cell death by inhibiting active caspase-3 activation in Wistar rats exhibiting psychotic-like behaviour (Table 1) [65]. Caspase-3 is an endoprotease that regulates inflammation and apoptosis signalling networks resulting in the breakdown of cellular structures such as DNA fragmentation and cytoskeletal protein degradation [121]. Both of these plants showed an anti-inflammation effect, which links to the anti-depressant mechanism.

Several TCM such as Kai-Xin-San (KXS) and Mahuang-Fuzi-Xixin decoction (MFX) were able to ameliorate depression-like behaviours *in vivo* or clinical studies through inflammatory markers related to anti-depressant mechanisms. KXS that comprised of 4 herbal medicines (*Acorus tatarinowii* Schott., *Panax ginseng* C.A.Mey., *Polygala tenuifolia* Willd., and *Poria cocos* (Schw.) Wolf.) [122] was able to alleviate depression-like behaviours in CUMS mice by controlling gut microbiota, inflammation, and stress system (Table 1). KXS treatment significantly reduced the levels of LPS and pro-inflammatory cytokine expressions including interleukin 1 beta (IL-1β), IL-6, and TNF-α in the small intestines, serum, and in various parts of the brain of CUMS-exposed mice such as prefrontal cortex, hippocampus, and hypothalamus (Fig. 1 and Table 1) [122]. Whereas, MFX is efficient in the treatment of various diseases including mood disorders [123]. Administration of MFX at doses of 2.5, 12.5, and 25 g/kg also corrected the depressive-like behaviours in LPS-induced mice (Table 1). The anti-depressant effect of MFX is linked to the anti-inflammatory properties as it can significantly reduce the expression of IL-1β in the hippocampus of CUMS mice brain (Fig. 1 and Table 1) [124]. In MDD, the pro-inflammatory cytokine IL-1β has been shown to play a crucial role in inflammatory responses in the CNS and peripheral nervous systems [125]. MFX treatment also inhibited the activation of the inflammasome by NLR family pyrin domain containing 3 (NLRP3) in the LPS-induced mice (Fig. 1 and Table 1) [124]. Furthermore, MFX treatment also inhibited the increase of Trx-interacting protein (TXNIP) levels in the hippocampus, which was associated with the activation of NLRP3 in the LPS-induced mice (Fig. 1 and Table 1) [124]. These findings indicated that KXS and MFX could be used as a novel therapeutic approach for depression and stress-related disorders through anti-inflammation related to the anti-depressant mechanism.

Besides that, SuHeXiangWan (SHXW) and Xin-Ke-Shu (XKS) are also prominent Chinese traditional medicines that have been used to treat depression or coronary artery diseases (CAD), respectively. SHXW essential oil, which is derived from the trunk resin of the *Lipuidambar orientalis* Mill tree, is commonly used to treat epilepsy, infantile spasms, involuntary unconsciousness, and paralysis [126]. A study has identified repeated inhalation of SHX possessed significant anti-depressant and anxiolytic properties in CUMS induced-depression model in mice (Table 1) [127]. These effects might be facilitated by the modulation of the inflammatory response as it was able to reduce IL-6, TNF-α, and thrombopoietin (TPO) in CUMS mice serum (Fig. 1 and Table 1) [127]. Whereas, XKS has been used for the treatment of CAD in China [128] in which more than 30 % of CAD patients experienced depressive symptoms [129] and anxiety [130]. XKS tablet comprises of 5 medicinal plants or extracts including *Salvia miltiorrhiza* Bunge, *Pueraria montana* var. thomsonii (Benth.) M.R.Almeida, *Crataegus monogyna* Jacq., *Panax notoginseng* (Burkill) F.H.Chen, and *Aucklandia costus* Falc [131]. Oral ingestion of 4 XKS tablets 3 times a day for 12 weeks can effectively treat anxiety and depression symptoms in patients with CAD probably by inhibiting the development of pro-inflammatory cytokines and stimulating the production of anti-inflammatory cytokines (Fig. 1 and Table 1) [131]. These improvements have been correlated with anti-inflammatory cytokines changes in the peripheral blood, particularly trappin-2, adiponectin, IL-1β, TPO, activated leukocyte cell adhesion molecule (ALCAM), neurotrophin-3 (NT-3), and transferrin [131]. Due to its anti-depressant properties, these herbal extracts could be used as a natural remedy for depression.

THSG and SOEE also possess anti-inflammatory activity. The administration of THSG was effective in reducing the expression of pro-inflammatory factors including TNF-α, IL-1β, and IL-6 in the hippocampal and prefrontal cortex tissues of CRS mice (Fig. 1 and Table 1) [90]. Besides that, the anti-inflammatory activity of SOEE oral administration at doses of 50, 100, and 200 mg/kg was found effective against ketamine-induced neuroinflammation by lowering the TNF-α serum level in mice (Fig. 1 and Table 1) [85]. This finding showed that THSG and SOEE exhibit anti-depressant effects through their capability in modulating anti-inflammatory activity.

3.3. Modulation of neurotransmitter

The "monoamine hypothesis" was introduced in the 20th century as a major contribution to depression, thus paving the way for today's anti-depressant medication. According to the hypothesis, depression is caused by the reduced release and lesser amount of norepinephrine (NE), serotonin (5-HT), and dopamine (DA) in the CNS synaptic space [132]. Monoamine neurotransmitters such as NE, 5-HT, and DA are essential chemical substances in the CNS that participated in a variety of bodily functions such as emotion,

learning, and memory [133]. NE is involved in the brain reward system as well as learning and memory control. It also plays a vital role in regulating arousal. The amount of NE in the hypothalamus that is significantly reduced implies that the central NE deficiency is associated with depression [133]. Whereas, impairment of 5-HT is connected with anxiety, low mood, movement restriction, decreased appetite, sleep disturbances, and other depression symptoms [134]. Motivation, determination, pleasure, and attention are all controlled by DA, and all of these functions are prone to be affected in depressed patients. Prior studies also have reported that depression is frequently followed by a hypodopaminergic condition [135]. As a result, it is well established that many anti-depressant medications that are currently used showed their effects by manipulating the reuptake and metabolic balance of monoamine neurotransmitters [132] such as MAOIs, NSRIs, TCAs, and SSRIs [7].

Cannabidiol (CBD), a phytocannabinoid isolated from *Cannabis sativa* L., exhibits therapeutic benefits for a variety of human ailments such as neuropsychiatric disorders, neurodegeneration, and neuropathic allodynia [136–139]. The intraperitoneal administration of CBD at concentrations of 15, 30, and 60 mg/kg were able to improve cognitive function such as social interaction and novel object recognition tests through a behavioural test on MK-801-induced schizophrenia in mice (Table 1) [140]. Besides that, CBD activates serotonin 1A receptors (5-HT1A) that resulted in anti-psychotic-like effects (Fig. 1 & Table 1) [140]. CBD treatment also alleviates convulsive syndrome induced by N-methyl-D-aspartate (NMDA) and decreased the infarct size in schizophrenic mice [141]. Besides that, CBD has been identified to exhibit antagonist-like activity towards sigma 1 receptor (σ1R) [141] attributed to a number of pathogenesis in mental disorders including depression, schizophrenia, motor abnormalities, drug addiction, and attention deficit disorders [142].

A biologically active compound derived from *Celastrus paniculatus* Willd. (black oil plant), known as 3-(3,4-dimethoxy phenyl)-1-(4-methoxyphenyl) prop-2-en-1-one (DPMPP), appears to be a valuable therapeutic target for schizophrenia and other associated neuropsychiatric conditions (Table 1) [143]. *In vivo* study has demonstrated that this bioactive compound is capable of mitigating monoaminergic disturbances associated with neurological impairment via regulation of the CNS monoamine neurotransmitter system [143]. The levels of monoamine neurotransmitters such as DA, NE, 5-HT, and monoamine oxidase (MAO) activity were restored to normal following treatment with DPMPP, similarly to the treatment of a reference drug clozapine (Fig. 1 & Table 1) [143]. Furthermore, DPMPP also demonstrated to have the highest binding score against all of the dopamine receptors (D1, D2, D3 and D4) and 5-HT2A (serotonin receptor) with the lowest inhibition constant values compared to clozapine in rats [143]. In addition, DPMPP also exhibited the best dock score against all tested genes associated with schizophrenia such as tyrosine hydroxylase (TH), DOPA decarboxylase (DDC), NMDA, the regulator of G protein signalling 4 (RGS4), neuregulin-1 (NRG1), catechol O-methyltransferase (COMT), protein kinase B (AKT1), and dystrobrevin binding protein 1 (DTNBP1) compared to clozapine [144]. Thus, DPMPP could be implemented as a promising therapeutic candidate in the treatment of schizophrenia through the modulation of various neurotransmitters in the CNS [144].

Previous research studies have also indicated that certain psychotic disorders are associated with an imbalance of a neurotransmitter known as dopamine [145–147]. Neuroleptic medications work by blocking dopamine receptors in the brain, thus decreasing dopamine overactivity and therefore, reducing psychosis symptoms [148]. *Ficus platyphylla* Delile has been proposed to have an anti-depressant effect by modulating the dopaminergic pathway. The plant is used in Nigeria's traditional medicine to cure a wide range of mental diseases such as insomnia, psychotic symptoms, depression, epilepsy, pain, and inflammation [149]. Oral administration of *F. platyphylla* in mice confirms that this plant has neuroleptic-like effects probably via modulation of dopaminergic neurons based on the conditioned avoidance reaction (CAR) test (Table 1) [149].

Galphimia glauca Cav., also known as Calderona Amarilla, has been used in Latin American traditional medicine for many decades to treat mental illnesses including anxiety, nervousness, and tension [150]. The methanolic extract from *G. glauca*, the galphimine-rich fraction (GRF), and the pure galphimines (Galphimines A, Galphimines B, Galphimines C) were reported to interact with the dopaminergic and glutamatergic system to modify behavioural responses [151,152]. This includes potentiating the cataleptic effect induced by haloperidol and inhibiting the behaviour activity induced by ketamine in mice that has been subjected to OFT and FST (Table 1) [151,152]. Furthermore, the *G. glauca* extract and GRF were found to be responsible for suppressing positive and cognitive symptoms associated with ketamine (a glutamatergic drug)-induced psychosis evaluated by Passive Avoidance Test (PAT) (Table 1) [151,152].

G. mangostana Linn. is also able to modulate the neurotransmitter by increasing noradrenergic and serotonergic processes (Table 1). The *G. mangostana* extract (50 mg/kg dose) displayed prominent anti-depressant-like effects in FSL rats, a genetic animal model of depression (Table 1) [77]. Besides reversing hippocampal tissue damage, *G. mangostana* also has notable neuroreceptor activities, especially 5-HT (Fig. 1 & Table 1) [77,153]. The fruit extract also displayed a putative noradrenergic mode of action in the FST as shown by increased climbing activity and elicited a serotonergic-related mechanism (Table 1) [77]. This finding is in accordance with regional brain monoamine examination that revealed an elevation of main metabolites of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), in the hippocampus and also an increase in 5-HT turnover (serotonin substitution) across the frontal lobe and hippocampus of FSL rats treated with the extract (Fig. 1 and Table 1) [77].

Ginkgo biloba L. (ginkgo) is often used in China for countless generations as a popular herbal supplement [154]. It is commonly used to cure a variety of disorders including memory impairment and dementia-like Alzheimer's disease [155,156]. A study has demonstrated that natural water-soluble polysaccharide extracted from *G. biloba* L. leaves was found to reverse the depression-related gut dysbiosis and improve *Lactobacillus* sp. richness, which has been shown to be a path for the treatment of depression [157]. *G. biloba* L. leaves, which has been identified to have the same effect with paroxetine drug, substantially decreased immobility periods in TST, FST, and anxiety-like symptoms in the OFT (Table 1) [157]. *G. biloba* L. treatment could improve density reductions in serotonin-positive and dopamine-positive cells by increasing the levels of 5-HT and DA throughout various regions of the brain such as in the cerebral cortex, hippocampus, and olfactory bulb, contrary to the mice that were only exposed to CUMS (Fig. 1 and Table 1) [157]. As a result of

this discovery, the polysaccharide extracted from *Ginkgo biloba* L. leaves appears to be a potential pharmacotherapeutic candidate for the treatment of depression through the modulation of neurotransmitters. Even though *G. biloba* L. is commonly considered harmless, further attention should be given to the negative consequences while conducting treatments with this herb. This is because a case report found that a 50-year-old female with persistent schizophrenia developed cognitive problems presented with mood dysfunction with manifestations of impatience, trouble managing frustration, anxiety, and agitation following the herb treatment (Table 1) [158].

Hyptis martiusii Benth. (Lamiaceae), known as cidreira brava, is native and abundantly available in Northeastern Brazil. The plant has been documented to have therapeutic properties in the CNS such as having anti-depressant activity [159] and anti-convulsant activity [160]. Intraperitoneal injection of the *H. martiusii* leaf essential oil (OEHM) at concentrations of 25, 50, 100, and 200 mg/kg and its main component, 1,8-cineole (eucalyptol) at a concentration of 50 mg/kg increased sleep time after being induced by pentobarbital and ethyl ether in mice (Table 1) [161]. Besides that, OEHM and 1,8 cineole were also found to have an anti-convulsive profile and prolonged death latency in the pentylenetetrazole (PTZ)-induced convulsion model (Table 1) [161]. PTZ is a powerful CNS stimulant owing to its $GABA_A$ receptor inhibition capacity that produces significant excitotoxicity processes regulated by glutamate thus causing alterations in the CNS, which are primarily exhibited as generalised tonic-clonic seizures (a form of seizure that affects the entire body) [162–164]. Besides that, ketamine-induced hyperkinesia (excessive abnormal movements) in mice has been reversed by OEHM (200 mg/kg dose) and 1,8-cineole (50 mg/kg) (Table 1) [161]. This finding is similar to haloperidol, a dopaminergic antagonist, that caused a decrease in animal locomotor activity [165]. Therefore, this suggests that OEHM and 1,8-cineole possess an anti-psychosis effect by regulating dopaminergic neurotransmission. Throughout this study, the oil showed anti-convulsive, hypnotic-sedative, and anti-psychotic-like properties thus implying that these results could be due to eucalyptol-mediated regulation of glutamatergic and dopaminergic neurotransmission in mice (Table 1) [161].

Rapanea ferruginea Mez. which is popularly known as "Capororoca", was used in traditional Brazilian medicine to manage several illnesses such as skin, liver, and urinary diseases [166]. It has major compounds such as myrsinoic acid A (MAA) and myrsinoic acid B (MAB) (Table 1) [167]. Mice acutely administered with a hydroalcoholic extract derived from barks of *R. ferruginea* (HEBRF) at 100, 150, and 300 mg/kg presented a dose-dependent anti-depressant-like effect by decreasing the immobility time when introduced to the TST (Table 1) [26]. Moreover, MAA at a dose of 5 mg/kg and MAB at a dose of 3 mg/kg also have anti-depressant-like effects and anti-anhedonic effects in mice (Table 1) [26]. In addition, HEBRF possesses an anti-depressant-like effect through the modulation of various neurotransmitters including 5-HT, DA, and NE (Fig. 1 andTable 1) [26]. Besides that, HEBRF inhibited the monoamine oxidase A (MAO-A) [26], a flavoenzyme that degrades the neurotransmitters such as 5-HT, DA, and NE [168] in the hippocampus (HIP) and prefrontal cortex (PFC) of mice (Fig. 1 and Table 1) [26]. Therefore, these findings suggest that HEBRF exerted an anti-depressant-like effect through the modulation of monoaminergic as well as lowering the MAO-A activity in mice.

A neurochemical analysis demonstrated that pre-treatment with SOEE significantly inhibited the ketamine-induced dopamine hyperactivity, attenuate ketamine-induced acetylcholinesterase (AChE), and increase the GABA concentration in psychotic mice (Table 1) [85]. Dopamine concentration at abnormally high levels in certain regions of the brain can generate harmful reactions on physiological and psychological aspects such as violent behaviour, hallucinations, and delusions [169]. In addition, Acetylcholine (ACh), a neurotransmitter that is essential in learning and memory [170] is degraded by the enzyme Acetylcholinesterase (AChE), which also contribute to the pathology of neurodegenerative disorders [171]. Biochemical analysis revealed that ketamine-induced mice had a significantly increased AChE activity, which may result in the reduction of ACh concentrations while a decrease in AChE activity has been identified following pre-treatment of SOEE in mice (Fig. 1 and Table 1) [85]. The reduction of AChE activity by SOEE leads to an increase of ACh level at synaptic cleft, thus making ACh function normally throughout the CNS (Fig. 1 and Table 1) [170] as well as parasympathetic nervous systems such as smooth muscles contraction, blood vessels dilation, body fluids improvement, and heart rate reduction [172]. A similar finding has been identified in Brahma Vati (BV)-treated group in which the activity of AChE was significantly lower compared to the control group (Table 1) [93]. Reduced AChE activity caused by BV treatment is thought to improve cholinergic activity by raising the ACh levels, thus preserving and enhancing cognitive functions (Fig. 1 and Table 1) [93]. Furthermore, the anti-psychotic effect may be related to the existence of flavonoids and polyphenols in SOEE, both of which are considered to have GABA agonist properties. This is confirmed by previous studies regarding the GABA agonists agent that contributes to the higher GABA levels in the brain that might prevent or delay schizophrenia progression [173,174].

Xiaoyaosan is a classic Chinese compound that has been used to treat mental illnesses for thousands of years, dating back to the Song dynasty that began from 960 to 1279 [175]. This formula consisted of 8 Chinese herbs including *Bupleurum chinense* DC., *Paeonia lactiflora* Pall., *Angelica sinensis* (Oliv.) Diels, *Poria cocos* F.A.Wolf, *Atractylodes macrocephala* Koidz., *Glycyrrhiza acanthocarpa* (Lindl.) J. M.Black, *Zingiber officinale* Roscoe, and *Mentha alaica* Boriss. This formulation has been found to be safe and beneficial in the treatment of a variety of conditions associated with mental illnesses such as anti-depressant [176–178]. Administration of both treatments of Xiaoyaosan suspension (250 mg/kg) and fluoxetine (2.6 mg/kg) exhibited the anti-depression properties in CUMS-induced mice with depressive-like features such as increase of sucrose preference and reversed the anhedonia in the CUMS rats (Table 1) [179]. Xiaoyaosan and its positive control, fluoxetine, also alleviate the depression effect by reducing hyperlocomotor activity in the OFT [179]. In addition, treatment with Xiaoyaosan significantly enhanced the contents of 5-HT and DA in CUMS hippocampus rats (Fig. 1) [180]. This could explain the mechanism of Xiaoyaosan in alleviating depression effects through modulating the monoamine neurotransmitter.

Viola odorata L., is a tiny perennial herb also referred to as sweet violet, Gule-Banafsh or English violet and has been traditionally used as an analgesic, anti-pyretic, anti-inflammatory, anti-oxidant, anti-helminthic. It is also being used to treat several neurological disorders such as depression and anxiety [181,182]. A study also revealed the anti-depressant activity of novel flavonoids derivatives such as 5,7-Dihydroxy-3,6-dimethoxyflavone, 5,7,4′-trihydroxy-3′,5'dimethoxyflavone, and 5,7,4′-trihydroxy-3′-methoxyflavone isolated from the herb (Table 1) [2]. Intraperitoneal administration of these 3 compounds at a concentration of 1–30 mg/kg significantly

reduced the immobility period in TST and FST in mice (Table 1) [2]. Furthermore, additional studies using mice pre-treated with 5HT, DA, and adrenergic antagonists inhibitors revealed that these 3 novel compounds produced a significant increase in 5-HT concentrations in the brain tissue (Fig. 1 and Table 1) [2]. These compounds could also interact with several serotonin receptors such as 5HT1A, 5HT2A, and 5HT3 according to molecular docking findings [2]. This finding indicates that these compounds have anti-depressant-like properties that are regulated through the serotonergic system.

Unmadgajakesari (UGK) is a herb-mineral formulation that has been used to treat depression by modulating various neurotransmitters [183]. UGK is prescribed for the treatment of psychosis and epilepsy in Ayurveda practitioners in India [183]. UGK appears to be a novel medication that modulates multiple neurotransmitters at different times resulting in the regulation of the multireceptor profile. For example, UGK exhibited significant dopaminergic, serotonergic, and NMDA reducing activities in several animal models that have been subjected to apomorphine-induced climbing (dopamine), 5-HTP induced head twitches (serotonin), and antagonism of MK-801-induced hyperlocomotion (NMDA), respectively in mice (Fig. 1 & Table 1) [183]. This study thus validated the theory in Ayurveda that UGK is effective in the treatment of depression.

ZL is a traditional Chinese medicinal complex formula comprised of 16 different herbs including *Schisandra chinensis* (Turcz.) Baill., *Ziziphus abyssinica* Hochst. ex A.Rich., *Codonopsis affinis* Hook.f. & Thomson, *Cinnamomum cassia* (L.) J.Presl, *Rehmannia glutinosa* (Gaertn.) DC., *Dioscorea polystachya* Turcz., *Paeonia suffruticosa* var. papaveracea (Andrews) A. Kern., *Gardenia jasminoides* J.Ellis, *Cassia abbreviata* Oliv., *Inula japonica* Thunb., *Polygonum multiflorum* Thunb., *Trichosanthes kirilowii* Maxim., *Bambusa tuldoides* Munro, *Lophatherum gracile* Brongn., *Ophiopogon japonicus* (Thunb.) Ker Gawl., and *Zingiber officinale* Roscoe. This formulation exhibited anti-depressant-like effects on rats exposed to CUMS (Table 1) [184]. Treatment with ZL enhanced body weight and improved sucrose intake while decreasing the immobility period in FST and TST [184]. ZL also possessed anti-depressant effects through the upregulation of monoamine neurotransmitters such as NE, 5-HT, and DA in the hippocampus of CUMS rats (Fig. 1 and Table 1) [184]. Interestingly, ZL has been identified to have a similar anti-depressant-like activity to fluoxetine, a currently available medication for anti-depressant (Fig. 1 and Table 1) [184].

3.4. Neuroprotective effects and regulation of the biochemical pathway

Neurogenesis is an important form of neuroplasticity that occurs in the adult brain and play essential roles in learning, memory, and emotional control. Thus, depression highly depends on the growth and survival of new neurons in the hippocampus [185]. The most essential neurotrophic factor in the brain, known as a brain-derived neurotrophic factor (BDNF), contribute to the survival, growth, and maintenance of neurons [186]. BDNF also regulates synaptic plasticity and neural integrity in neuronal networks in which its low level is associated with the development of depression [187,188]. A growing body of evidence suggests that BDNF and oxidative stress are involved in the pathogenesis of MDD and bipolar disorder [186]. There was additional evidence whereby a decrease in BDNF expression was linked to other neurodegenerative disorders such as schizophrenia [189,190]. Previous research has also found that BDNF blood level is lower in depressive patients compared to healthy people, while anti-depressant treatment increases its levels [191–193]. In this review, we have identified several plants and compounds that act as an anti-depressant through the modulation of BDNF level as well as other neuroprotective mechanisms.

For example, AVLE has been shown to increase hippocampal BDNF expression and decreased hippocampus cell apoptosis by altering the B-cell lymphoma 2 (Bcl-2)/Bax pathways in rats exposed to CUMS (Fig. 1 and Table 1) [24]. Bcl-2 and Bax family proteins play critical roles in regulating apoptosis and cell survival in reaction to various apoptotic stimuli [194]. Given the reduction in BDNF caused by oxidative stress, it has been postulated that AVLE administration could protect the BDNF system from the negative effects of oxidative stress following CUMS exposure, therefore, alleviating depressive symptoms [24]. This study revealed that AVLE exhibited anti-depressant-like effects in CUMS through elevation of hippocampus BDNF levels as well as regulation of Bcl-2/Bax pathways.

Berberine chloride hydrate (BBR) is an isoquinoline alkaloid discovered in the root of *Coptis chinensis* Franch. (goldenthread) extract offered multiple pharmacological effects such as anti-bacterial, anti-inflammatory, and anti-ischemic properties [195] as well as neuroprotective activity [196]. Studies indicate that BBR appears to attenuate neuronal damage in animal models of Parkinson's disease, brain ischaemia, stroke, and encephalomyelitis [197–200]. Previous research also has attempted to demonstrate that BBR treatment reduces cell death and increases neuronal differentiation in the hippocampus, a crucial learning and memory centre in the brain [195]. BBR has also been shown to promote the survival of NMDA receptor-expressing neural cells [201]. NMDA receptor signalling is one of the most important pathways that is involved in cognitive, locomotor, synaptic plasticity, learning, and memory [202,203] and its impairment in several brain regions, particularly the prefrontal cortex (PFC), produces schizophrenia-like symptoms [204]. In addition, BBR exerts a neuroprotective effect in rats subjected to MK-801 that induced behavioural impairment (Table 1) [205]. Intraperitoneal administration of BBR (20 mg/kg) in rats with MK-801-induced schizophrenia revealed that BBR treatment improved balance disturbances, locomotor agitation, and spatial learning problems. This implies that BBR treatment may be useful in MK-801-related cognitive abnormalities (Table 1) [205]. Altogether, it is hypothesised that BBR administration could be used as a treatment for schizophrenic patients via the neuroprotective effect mechanism.

The activity level of 3 adenosine triphosphatase (ATPases) was restored to a normal level in the hippocampus (HC), cerebellum (CB), and cerebral cortex (CC) after pre-treatment with bioactive compound DPMPP on ketamine-induced schizophrenic rats (Fig. 1 & Table 1) [206]. These ATPases such as sodium–potassium adenosine triphosphatase (Naþ/Kþ-ATPase), magnesium-importing adenosine triphosphatase (Mg2þ ATPase), and calcium adenosine triphosphatase (Ca2þ ATPase) play a critical role in maintaining the excitability of neurons, transmitting ion gradients, signalling pathways for neurotransmitter as well as an energy transducer through the interaction of ATP hydrolysis with bioenergetic processes. ATPase abnormalities have been documented to include numerous neurological disorders such as Alzheimer's disease [207], bipolar mood disorder [208], seizures [209,210], and spongiform

encephalopathy, which is a progressive degenerative brain disorder characterised by multiple tiny holes in the brain tissue that give the brain an appearance like a 'sponge' [211]. The activity levels of all 3 ATPases were restored to their original state after pre-treatment with the DPMPP indicating that energy loss that happened during ketamine-induced schizophrenia in rats has been recovered. This is comparable to the reference compound treatment of clozapine (Fig. 1 and Table 1) [206]. In addition, the molecule DPMPP showed robust interaction and had the highest binding energies against all 3 ATPases (Naþ/Kþ-ATPase, Mg2þ ATPase, and Ca2þ ATPase) while having the lowest inhibition constant value compared to clozapine (Fig. 1 and Table 1) [206]. The findings of this study clearly show that the DPMPP has a considerable neuroprotective effect through modifying bioenergy pathways that were disrupted during the induction of schizophrenia [206].

Oral administration of herbal complex extract (CPT) consisted of *Clematis chinensis* Osbeck (Ranunculaceae), *Prunella vulgaris* Linne (Lamiaceae), and *Trichosanthes kirilowii* Maximowicz (Cucurbitaceae) at concentrations of 100 or 300 mg/kg alleviated the abnormal behaviours induced by MK-801 in mice such as sensorimotor deficits as well as social or object recognition memory deficits in mice (Table 1) [212]. In addition, CPT was able to reduce expression levels of phosphorylated-Akt (p-Akt) as well as glycogen synthase kinase 3 beta (GSK-3b) in the prefrontal cortex that has been induced in the MK801-mice model (Fig. 1 and Table 1) [212]. The Akt/GSK-3b signalling pathway is one of the most recognised pathways associated with schizophrenia [213] and is important in the pathophysiology and treatment of psychiatric disorders [214]. The level of phosphorylation of Akt and GSK-3b has been altered after injection of MK-801 [215,216], however, these changes were reversed by CPT (Fig. 1 and Table 1) [212]. These findings suggest that CPT improves MK-801-induced dysfunction in sensorimotor deficits, social interactions, and cognitive performance, in part via modulating the Akt/GSK-3b signalling pathways.

G. elata demonstrated a neuroprotective activity against CORT-induced apoptosis in PC12 cells [96], a cell line originated from rat pheochromocytoma, which is an adrenal medullary tumour [217] that is widely used in neuroscience research [218]. Pre-treatment with *G. elata* at different concentrations ranging from 250, 500, and 1000 μg/ml resulted in a significant increase in PC12 cell survival rates, thus demonstrating that *G. elata* alleviates the harmful effect of CORT treatment (Table 1) [96]. Besides that, *G. elata* was also able to alleviate lactate dehydrogenase (LDH) leakage in CORT-induced PC12 cells (Fig. 1 and Table 1) [96] indicating that the treatment promotes cell membrane integrity [96,219]. Furthermore, *G. elata* markedly alleviated the endoplasmic reticulum (ER) stress-mediated apoptotic pathways induced by CORT through the downregulation of several protein expression levels such as glucose-regulated protein 78 (GRP78), X-box binding protein 1 (XBP-1), growth arrest and DNA damage 153 (GADD153), caspase 9, and caspase 12 in the PC12 cells (Table 1) [96]. As a result, *G. elata* may have the potential as a novel therapeutic agent for depression that acts through neuroprotective effects.

THSG treatment was able to accelerate astrocyte multiplication and neurogenesis in the hippocampal of CRS-treated mice (Table 1) [90]. The THSG treatment also upregulated neurogenesis-related protein, known as doublecortin (DCX) expression in the mice hippocampus, of which long-term CRS exposure significantly decreased its expression (Fig. 1 and Table 1) [90]. This study also demonstrated the effect of THSG treatment on the upregulation of glial fibrillary acidic protein (GFAP) expression in MDD mice hippocampal tissue (Fig. 1 and Table 1) [90]. GFAP expression that was considered as a glial cell biomarker was significantly downregulated in depressed individual hippocampus tissues [220]. THSG also improved the Akt signalling pathway, which is associated with neuroprotection, by upregulating the expression of the p-Akt protein in the brains of the CRS-treated mice (Fig. 1 and Table 1) [90]. Overall, the neuroprotective effect of THSG is mediated by a number of complex mechanisms including *in vivo* anti-oxidative mechanism, anti-inflammatory effects, and neurogenesis stimulation.

Mogroside V (MogV) from Siraitia grosvenori Swingle (monkfruit) demonstrated a wide range of pharmacological properties such as anti-oxidant [221], anti-cancer [222,223], and anti-inflammatory [224]. A recent study has demonstrated that Mogroside V and its bioactive component, called 11-oxo-mogrol, have neuroprotective properties against MK801-induced neuronal damages (Table 1) [27]. Besides that, MK-801-induced prepulse inhibition impairments and social withdrawal were also alleviated by MogV treatment in behavioural experiments (Table 1) [27]. Furthermore, MogV administration also alleviated the cellular and neurochemical alterations caused by MK-801 induction in the medial prefrontal cortex (mPFC) in mice (Table 1) [27]. Moreover, an *in vitro* examination of primary neuronal culture revealed that the treatment with MogV and 11-oxo-mogrol protected MK-801-induced neuronal damage by enhancing neurite development, preventing cell apoptosis, and reducing intracellular calcium [Ca^{2+}] release (Table 1) [27] while excessive calcium will mediate excitotoxicity in the neurons [225]. In addition, 11-oxo-mogrol restored MK801-induced inactivation of phosphorylation levels of Akt and mechanistic target of rapamycin (mTOR) (Fig. 1) [27]. The Akt pathway plays an essential part in neuronal cell survival [226], whereas the mTOR pathway plays a crucial role in the neural network development and suppressing apoptotic processes [227]. 11-oxo-mogrol could prevent MK801-induced neuronal apoptosis by activating the Akt/mTOR pathway (Fig. 1 and Table 1) [27]. These findings imply that MogV may have therapeutic potential for schizophrenia due to its neuroprotective properties.

Xiaoyaosan also possesses neuroprotective properties by controlling the imbalance of excitatory or inhibitory amino acids in the brain of CUMS mice (Table 1) [179]. The changes in the ratio of excitatory and inhibitory amino acids in the brain have a significant impact on the incidence of depression [228]. Excitatory neurotransmitters such as glutamic acid (Glu) and aspartic acid (Asp) enhance the transmission of brain impulses and increase the activity of the nervous system. Meanwhile, inhibitory neurotransmitters such as gamma-aminobutyric acid (GABA) and taurine (Tau) inhibit the transmission of brain impulses and thereby, reduce the activity of the nervous system. The significant increase of excitatory amino acids such as Glu and Asp level is closely associated with depression [229], whereas a significant decrease of GABA and Tau has been identified in depressed patients [230]. Xiaoyaosan has significantly reduced the amounts of Glu and Asp in the hippocampus implying that it may prevent excitatory neurotoxicity that is induced by the accumulation of glutamate and aspartate in the hippocampus of depressive rats [180].

Furthermore, several herbal formulations such as MFX, PAPZ, and ZL showed a neuroprotective effect on an animal model. For

example, treatment of MFX could stimulate neurogenesis by increasing the level of DCX, BDNF, and tropomyosin-related kinase receptor B (TrkB) in the hippocampal of LPS-induced mice (Fig. 1 and Table 1) [124]. Whereas, continuous PAPZ treatment was able to enhance BDNF protein expression in the hippocampus tissue in mice (Fig. 1 and Table 1) [78]. In addition, ZL also has anti-depressant-like effects through the BDNF signalling pathway (Fig. 1 and Table 1) [184]. The BDNF protein and mRNA levels in the CUMS rat hippocampus increased significantly following treatment with the ZL formula compared to the control group (Fig. 1 and Table 1) [184]. Besides that, other important neurotrophins that are involved in the BDNF signalling pathway such as p-CREB/CREB level was significantly increased after the administration of ZL [184]. Moreover, cAMP that can upregulate CREB phosphorylation also was found to be increased after the ZL treatment on CUMS rats [184]. All of these findings suggest the therapeutic potential of MFX, PAPZ, and ZL as an anti-depressant through neuroprotective effects.

3.5. Hypothalamic-pituitary-adrenal (HPA) axis-related anti-depressant mechanisms

The hypothalamic-pituitary-adrenal (HPA) axis is a fundamental component of the stress-response systems, which include the neurological and endocrine systems [231]. In a normal condition, the hypothalamus secreted corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which were delivered into the corticotroph cells in the anterior pituitary gland. They then synergistically induce the secretion of adrenocorticotropic hormone (ACTH) into the blood circulation. The secretion of ACTH will stimulate the adrenal gland to produce glucocorticoids (GC) such as cortisol (Fig. 2) [232]. In the 1970s, researchers discovered that the HPA axis is one of the pathological hypotheses of depression [233,234]. MDD is one of the mental illnesses that has been characterised by hyperactivity of the HPA axis that is associated with an abnormally high release of CRH, ACTH, and elevated GC production such as cortisol (or corticosterone (CORT) in rodents). The release of these mediators could contribute to the hippocampal neurons impairment and reduction of cognitive function in depressed patients (Fig. 2) [235–237] while chronic administration of anti-depressants could attenuate or reversed this problem.

CUMS is known to increase the levels of CORT, CRH, and ACTH in both plasma and the hypothalamus of rats accompanied by depressive-like changes in behaviour, thus proving that hyperactivity of the HPA axis is linked to the pathophysiology of depression (Fig. 2) [180]. Animal models subjected to CUMS also showed long-term changes in behavioural coping, motivational states, anhedonia (a diminished ability to enjoy pleasure), and other emotional and cognitive symptoms similar to those seen in depressed individuals [238,239]. A natural product AVLE treatment at concentrations of 30, 60, and 125 mg/kg was shown to have anti-depressant-like effects in CUMS-exposed rats that is equivalent to positive control fluoxetine at 10 mg/kg (Table 1) [24]. AVLE treatment was also shown to reduce the activity of the HPA axis in CUMS rat model by modulating ACTH and CORT serum levels (Table 1, Figs. 1 and 2) [24].

KXS and Xiaoyaosan formulae also have been identified to exhibit anti-depressant activity through the regulation of the HPA axis. For example, 6 weeks intervention of KXS formulae in mice was able to suppress HPA activation by reducing stress-related hormone levels in the serum and organs such as CRH in the hypothalamus, ACTH in the pituitary gland, and corticosterone in the adrenal gland compared to the CUMS group (Table 1, Figs. 1 and 2) [122]. Besides that, another study also demonstrated that Xiaoyaosan could significantly reduce the levels of CRH, AVP, ACTH, and CORT in the plasma and hypothalamus hence indicating that anti-depressant effects demonstrated by Xiaoyaosan were due to its ability to suppress the HPA axis hyperactivity (Figs. 1 and 2) [180]. This finding further suggested that chemicals from the Xiaoyaosan prescription may be useful for treating depression owing to their positive effects on depressive-like behaviours in CUMS-mice possibly via the HPA axis regulation [179].

3.6. Anti-depressant effect with unknown mechanism

Several plants possessed significant anti-depressant activity, however, their mechanism of action remains undiscovered. For example, aromatherapy, a complementary medicine that employs medicinal plants, is frequently used to prevent various illnesses including depression, anxiety, insomnia, bipolar disorder, and stress-related conditions [15,240]. Through inhalation of essential oils, signals are transmitted from the olfactory system to the brain, and thus the brain is responsible for regulating depression and mood disorders through the secretion of neurotransmitters such as serotonin and dopamine [15]. Recent behavioural experiments that have been carried out on dizocilpine (MK-801)-induced schizophrenia in mice has demonstrated that inhalation of α-pinene substantially decreased abnormal behaviour in treated mice such as hyperactivity and anxiety-like behaviours (Table 1) [14]. α-pinene is a naturally occurring terpene compound found in the oil of coniferous trees and as well as in rosemary (*Rosmarinus officinalis* L.) oil, *Eucalyptus abdita* Brooker & Hopper oil, *Bupleurum fruticescens* L., and *Opuntia humifusa* (Raf.) Raf., which are also widely used as food-additive. Inhalation of α-pinene previously has been identified to cause accumulation of α-pinene in the brain [241]. Therefore, α-pinene, which acts on the CNS, may be used as a therapeutic agent for psychoneurotic disorders such as schizophrenia [14]. Apart from that, α-pinene is also thought to have other physiological impacts on humans [242,243] such as anti-inflammatory [244], anti-convulsant [245], anti-oxidant [246], and anti-nociceptive effects [247].

Besides that, hydro-ethanolic extract of the roots of deciduous tree, *Albizia zygia* (DC.) J.F. Macbr., has long been used across Africa to treat infertility, pain, and malaria [248]. The extract also exhibited anti-psychotic-like behaviour in mice with the ability to reduce schizophrenia symptoms including positive (excess or impairment of normal function such as hallucinations and delusions), negative (normal function deterioration such as loss of motivations, social withdrawal, and lack of emotion), and cognitive indicators (impaired to organise, impair memory, and attention as well as poor decision making) (Table 1) [249]. Furthermore, the extract that has been given through oral gavage at concentrations of 30, 100, and 300 mg/kg was found to significantly decrease ketamine-induced hyperlocomotion, immobility, apomorphine-induced climbing behaviour, and object recognition in mice (Table 1). In addition, at

the lowest dose of 30 mg/kg, the extract also significantly reduced haloperidol-induced catalepsy in mice (Table 1) [249]. *A. zygia* also possesses various pharmacological activities such as anti-nociceptive, anti-oedemic, anti-pyretic, and anti-oxidant properties [250,251].

In addition, *Calculus bovis* Sativus (CBS) improved the anti-schizophrenic effectiveness of haloperidol by increasing its bioavailability [252]. CBS, also known as 'niu-huang' in China, is one of the TCM that has been traditionally used to treat neurological problems [253]. Oral co-administration of CBS (50, 100, 150 mg/kg) with haloperidol (1.4 mg/kg) for 7 days resulted in a synergistic effect after treating with MK-801-induced schizophrenia rats (Table 1) [252]. Compared to the treatment with haloperidol alone, the combination of haloperidol and CBS demonstrated stronger inhibition of psychosis-like symptoms such as decreased locomotor activity and anxiety [252]. The data proposed that the combination of haloperidol and CBS may have a synergistic impact on haloperidol pharmacodynamics due to changes in haloperidol intestinal absorption (Table 1) [252]. Human trials should be performed to determine the clinical significance of the synergistic effects of haloperidol and CBS, as well as their mechanism of action [252].

Crocus sativus L., (saffron) also has a long history of usage in traditional medicine [254]. The plant possesses major compounds such as crocins, crocetin, picrocrocin, and safranal [255] that are known to relieve depression [256,257]. In a group of older people with MDD, intervention with *Crocus sativus* 60 mg/day for 6 weeks had the same effects in alleviating depression symptoms as the positive control of sertraline (Table 1) [258]. The study was conducted using randomised, medication-controlled and double-blind design and the depression symptoms were measure using the Hamilton Depression Rating Score [258]. Furthermore, MDD patients with post-menopausal hot flashes who were given *C. sativus* (30 mg/day) for 6 weeks have successfully improved their conditions (Table 1) [259]. As the plant extract may have fewer side effects, this could provide a non-hormonal and alternate herbal medicine in the treatment of MDD in older women (Table 1) [259]. In addition, Irritable Bowel Syndrome (IBS) patients that are characterised by recurrent abdominal pain accompanied by depression and anxiety can be ameliorated by consuming *C. sativus* at 30 mg/day for 6 weeks and can be as efficient as fluoxetine (40 mg/day) drug (Table 1) [260].

According to preliminary findings, the combination of rhodiola (*Rhodiola rosea* L.) and saffron (*C. sativus* L.) was also effective in treating depression and anxiety disorders in MDD patients (Table 1) [261]. Rhodiola, also known as golden root, has been used for centuries to boost physical and mental toughness [262,263] as well as showing anti-depressant activity in preclinical and clinical studies [262,264,265]. Additionally, pre-treatment with the plant extract substantially improved apomorphine and dizocilpine-induced prepulse inhibition deficits in mice and rats (Table 1) [266]. Prepulse inhibition is a well-known method in the measurement of sensorimotor gating, which is disrupted in schizophrenia and other psychotic disorders [266]. However, additional investigation is required to determine the pharmacological mechanisms and current compounds that underpin the anti-depressant impact of *R. rosea* and *C. sativus*.

Cuscuta species such as *Cuscuta chinensis* Lam (Convolvulaceae) and *Cuscuta epithymum* (L.) L. (dodder) are important herbs and are traditionally used by the Persians for treating neurologic and psychotic disorders including depression [267,268]. The *Cuscuta* sp. is rich in flavonoids exhibiting pharmacological properties such as anti-viral, anti-cancer, anti-proliferative, anti-oxidant, anti-inflammatory, anti-microbial, and anxiolytic activity [269]. Patients that receive *C. chinensis* at 500 mg/day for 6 weeks showed a significant improvement in their depressive symptoms compared to fluoxetine treatment (Table 1) [267]. Besides that, some adverse effects were noticeably lowered in the *C. chinensis* groups such as reduction of sexual dysfunction, palpitation, dry mouth, decreased appetite, and abdominal discomfort compared to the fluoxetine group (Table 1) [267]. Furthermore, schizophrenia patients that received a total dose of 1000 mg C. epithymum per day demonstrated that it safely improved cognitive disabilities with no serious side effects (Table 1) [268]. A double-blind randomised trial also demonstrated that the formulated herbal syrup consisting of *C. chinensis* and lavender (*Lavandula angustifolia* Mill.) were found to be beneficial as citalopram in treating depression and had markedly stronger anxiolytic properties compared to the standard drug of citalopram (20 mg/day) (Table 1) [270]. Considering these plants have been traditionally used for patients with anxiety and depression disorders, further study should be performed to determine the plant bioactive compounds that are responsible for the anti-depressant effect and their mechanisms of action.

Milicia excelsa (Welw.) C.C. Berg, also known as the Iroko tree or African teak, is a species of native tree in Africa [271]. This plant is used in African traditional medicines for the treatment of anaemia [272], sexual dysfunction [273], as well as mental illnesses [274,275]. Oral administration of ethanol leaf extract of *M. excelsa* (EME), aqueous fractions (AF), and ethyl acetate fractions (EAF) at different doses of 250, 500, and 1000 mg/kg showed that the duration of grooming behaviour in mice decreased significantly in swim-induced grooming behaviour experiment compared to the control group (Table 1) [276]. Previous studies revealed that stress-induced grooming such as cleaning of skin and fur is associated with high anxiety levels [277,278] related to depression [279]. Besides that, in ketamine-induced hyperlocomotion, EME, and all fractions (aqueous (AF), butanol (BF), ethyl acetate (EAF), and (hexane (HF)) also significantly inhibited hypermotility, while AF has greater ataxia reducing effect compared to the standard anti-psychotic medication of haloperidol (Table 1) [276]. Besides that, EME and EAF also significantly reduced climbing behaviour in mice suggesting that the extract and fraction were able to alleviate depressive symptoms in apomorphine-treated mice [276]. The median lethal dose (LD_{50}) of EAF and AF was found to be greater than 5000 mg/kg in mice indicating that the fractions are potentially safe to be implemented in humans [276].

Withania somnifera (L.) Dunal (Ashwaganda) is a medicinal herb that has been long exploited in Ayurvedic medicine. Several clinical trials suggest that the extracts of this plant could be beneficial in the treatment of mental illnesses such as depression or anxiety [280,281]. The oral intake of *W. somnifera* extract at doses of 250 mg twice daily for the first week and 500 mg of *W. somnifera* extract twice daily for the second week improved schizophrenia conditions (Table 1) [282] including anxiety and depression symptoms [283]. All these patients took part in a randomised, double-blind, and placebo-controlled clinical trial study in which neither the patients nor the researchers were aware of the respective treatments [283]. Although such studies hinted at the use of these phytocompounds in clinical settings, further research is still required to identify its potential mechanism as an anti-depressant agent.

Lastly, herbal syrup combination called EACS syrup (containing *Echium amoenum* Fisch. & C.A.Mey., *Melissa officinalis* L., and *Crocus sativus* L.) and pycnogenol also showed to have anti-depressant activity (Table 1) [284,285]. MDD patients that were randomly selected to receive EACS syrup for 8 weeks also demonstrated fewer side effects compared to citalopram control (Table 1) [285]. Whereas, oral pycnogenol supplementation at a concentration of 50 mg on MDD patients for 16 weeks showed improvement of depressive symptoms and resulted in attenuation adverse effect of sexual dysfunction induced by escitalopram (Table 1) [284]. Pycnogenol is a bark extract from the *Pinus pinaster* Aiton tree and has been traditionally used to decrease blood sugar levels, improve vascular permeability, reduce oxidative damage, and suppress inflammatory reaction [284,286] as well as improvement of erectile dysfunction [287]. Pycnogenol supplementation can be used as a complementary therapy for anti-depressant-induced sexual dysfunction. However, further assessments should be done to enhance our knowledge regarding the effect and mechanisms of EACS as well as pycnogenol as an anti-depressant.

4. Challenges and future perspective of medicinal plants and traditional medicine in the treatment of depression

Although natural products and traditional medicine are valued for their natural origins and medicinal potential, particularly in the context of antidepressant effects as mentioned earlier, they are not without limitations. Several challenges and shortcomings need to be addressed to elevate the efficacy and safety of these alternative treatments for human health.

One of the most critical challenges is ensuring quality control of herbal and traditional medicine products. As many are traditionally produced or locally sourced, maintaining consistent quality and standards can be a significant hurdle. For example, the standardization of bioactive compounds can be difficult due to non-standardised procedures, sourcing from various regions and farmers, variations in processing, and limited access to modern technology for traditional practitioners or producers. The inclusion of multiple herbs in a single formulation further complicates the identification of the active ingredients responsible for therapeutic effects [288]. Without proper standardization, these products may not be as effective as claimed and could result in batch-to-batch variability. Worse, they may contain adulterants or contaminants that could pose health risks. Therefore, stringent standardization and quality control measures are essential to ensure the reproducibility and consistency of treatment outcomes [288]. Achieving this may require close collaboration between practitioners, research institutions, universities, and government agencies to develop rigorous standard operating procedures (SOPs) for traditional and alternative medicinal products. Recently, artificial intelligence (AI) has been utilised alongside technologies like hyperspectral imaging and high-throughput omics approaches to enhance quality control of these products [289–291], and this could be revolutionary for the future of alternative and complementary medicine.

Another major challenge in traditional and alternative medicine is ensuring consumer safety. The potential toxicity of herbal products must be thoroughly considered [292], but the lack of standardization, as discussed earlier, makes this task more difficult. Two major markers of toxicity in medicinal products are nephrotoxicity and hepatotoxicity, which lead to kidney and liver damage, respectively [292,293]. In addition, research has documented other forms of toxicity, such as effects on reproduction [294], the cardiovascular system [295], and the nervous system [296]. For herbal products, this is further complicated by variations in response and dose independence across different populations and individuals [297]. The potential long-term side effects of these traditional medicines and possible interactions with conventional antidepressants are also significant concerns. As a result, future regulations for herbal and traditional medicine products should include clear, methodical, and instructive guidelines for commercial approval, ensuring their safety before entering the market. Furthermore, these products must move beyond pre-clinical studies and pharmacopoeial evidence, with high-quality randomised controlled trials (RCTs) being essential to demonstrate their safety and efficacy. This will require coordinated support from both government and industry to secure proper funding and streamline the approval process.

Finally, the complex relationship between traditional and Western medicinal practices is another critical factor in the future adoption of alternative medicine for depression treatment. Traditional healers may lack the knowledge and expertise in modern psychological approaches to treating depression, leading to a mismatch between traditional practices and systematic care [298,299]. Conversely, while most healthcare professionals are trained in modern psychiatric treatments, integrating alternative and traditional practices may require further familiarization and understanding [300]. Patient acceptance of these alternative treatments may also depend on cultural and personal beliefs, making it crucial for practitioners and clinicians to navigate these differences sensitively [301]. Moreover, unlike conventional medications that typically target specific molecular pathways, traditional and alternative approaches often consider a broader scope, addressing the patient's physical, spiritual, and emotional well-being [301,302]. While this holistic approach has its merits, it complicates the prediction of treatment outcomes based solely on biological markers, leading to varying degrees of efficacy across individuals. Therefore, engaging both traditional and mainstream medical practitioners in discussions and research on best practices for traditional and alternative medicine is essential to ensure that all potential avenues for depression treatment are fully explored and utilised.

5. Conclusion

Complementary and alternative medicine plays an essential role in the treatment of psychiatric disorders such as depression. There is no exception even in this research as each plant species has demonstrated its targeting effect as an anti-depressant while being fairly safe with few side effects, if any. For example, *C. americanum*, *E. velutina*, and *G. mangostana* may act due to their potent anti-oxidant activity. Whereas, *Cinnamomum* sp. (*C. burmannii,* C. *zeylanicum* and *C. tamala),* TCM such as KXS and SHXW and MFX, as well as SOEE demonstrated to act as anti-inflammation substances to ameliorate depression pathology. Furthermore, several plants or compounds act through the modulation of neurotransmitters such as *F. platyphylla, G. glauca,* cannabidiol, and DPMPP. Besides that, several plants possess neuroprotective effects such as *G. elata*, BBR, THSG, and *P. cocos*. In addition, AVLE, KXS, and Xiaoyaosan may reverse the

hypothalamic-pituitary-adrenal (HPA) axis dysfunction. Last but not least, there are several plants that have significant anti-depressant effects such as *A. zygia*, *M. excelsa*, *R. rosea*, and *W. somnifera*, however, their mechanism of action remains undiscovered. In future, key compounds in these plant extracts or other formulations should be identified and elucidated to pinpoint their exact mode of action in ameliorating depression. Furthermore, toxicology testing, bioavailability studies, pharmacokinetic evaluation as well as systematic clinical trials must be performed to make sure their safety and effectiveness (efficacy) in the treatment of human depression. Challenges and future perspectives of traditional and alternative medicine are also discussed to unravel key points to potentially advance their development and adoption in mainstream depression treatment. Overall, this review is hoped to offer health care professionals the best possible alternatives of anti-depressants from natural phytocompounds that are efficacious, safe and affordable, with minimal or no side effects. This may also assist scientists and physicians in understanding and better evaluating specific plant extracts possessing bioactive compounds with potential to act as anti-depressants for applications in clinical settings.

Sources of funding

This study was funded by the UKM Research University grant (GUP-2023-063 and GP-K019471).

Declaration of generative AI in scientific writing

None.

CRediT authorship contribution statement

Juwairiah Remali: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Wan Mohd Aizat:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Wan Mohd Aizat reports financial support was provided by Universiti Kebangsaan Malaysia (UKM). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

References

[1] S.L. James, D. Abate, K.H. Abate, et al., Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, Lancet (2018).
[2] L. Dobrek, K. Głowacka, Depression and its phytopharmacotherapy—a narrative review, Int. J. Mol. Sci. (2023).
[3] Y. Zhang, L. Li, J. Zhang, Curcumin in antidepressant treatments: an overview of potential mechanisms, pre-clinical/clinical trials and ongoing challenges, Basic Clin. Pharmacol. Toxicol. (2020).
[4] H. Sivertsen, G.H. Bjørkløf, K. Engedal, G. Selbæk, A.S. Helvik, Depression and quality of life in older persons: a review, Dement. Geriatr. Cognit. Disord. (2015).
[5] A.J. Ferrari, A.J. Somerville, A.J. Baxter, et al., Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature, Psychol. Med. (2013).
[6] Z. Hussain, E. Wegmann, H. Yang, C. Montag, Social networks use disorder and associations with depression and anxiety symptoms: a systematic review of recent research in China, Front. Psychol. (2020).
[7] Q. Cheng, J. Huang, L. Xu, et al., Analysis of time-course, dose-effect, and influencing factors of antidepressants in the treatment of acute adult patients with major depression, Int. J. Neuropsychopharmacol. (2020).
[8] A.J. Rush, M.H. Trivedi, S.R. Wisniewski, et al., Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report, Am. J. Psychiatr. (2006).
[9] A.M. Reid, J.P.H. McNamara, T.K. Murphy, et al., Side-effects of SSRIs disrupt multimodal treatment for pediatric OCD in a randomized-controlled trial, J. Psychiatr. Res. (2015).
[10] S. Ulrich, R. Ricken, P. Buspavanich, P. Schlattmann, M. Adli, Efficacy and adverse effects of tranylcypromine and tricyclic antidepressants in the treatment of depression: a systematic review and comprehensive meta-analysis, J. Clin. Psychopharmacol. (2020).
[11] X. Zhong, G. Harris, L. Smirnova, et al., Antidepressant paroxetine exerts developmental neurotoxicity in an iPSC-derived 3D human brain model, Front. Cell. Neurosci. (2020).
[12] S. Ilgin, V. Kilic, M. Baysal, et al., Evidence for cardiotoxicity associated with sertraline in rats, Toxicology Research (2018).
[13] E.A. Khawam, G. Laurencic, D.A. Malone, Side effects of antidepressants: an overview, Cleve. Clin. J. Med. (2006).
[14] H. Ueno, A. Shimada, S. Suemitsu, et al., Attenuation effects of alpha-pinene inhalation on mice with dizocilpine-induced psychiatric-like behaviour, Evid. base Compl. Alternative Med. (2019).
[15] X. Lv, Z. Liu, H. Zhang, C. Tzeng, Aromatherapy and the central nerve system (CNS): therapeutic mechanism and its associated genes, Curr. Drug Targets (2013).
[16] J. Remali, W.M. Aizat, A review on plant bioactive compounds and their modes of action against coronavirus infection, Front. Pharmacol. (2021).
[17] M.A.M. Noordin, M.M. Noor, W.M. Aizat, The Impact of Plant Bioactive Compounds on Aging and Fertility of Diverse Organisms: A Review, Mini-Reviews in Medicinal Chemistry, 2020.

[18] M.A. Aziz, M. Adnan, A.H. Khan, et al., Traditional uses of medicinal plants practiced by the indigenous communities at mohmand agency, FATA, Pakistan, J. Ethnobiol. Ethnomed. (2018).
[19] R. Ullah, A.S. Alqahtani, O.M.A. Noman, et al., A review on ethno-medicinal plants used in traditional medicine in the Kingdom of Saudi Arabia, Saudi J. Biol. Sci. (2020).
[20] A.S. Alqahtani, GC-MS analysis, heavy metals, biological, and toxicological evaluation of reseda muricata and marrubium vulgare methanol extracts, Evid. base Compl. Alternative Med. (2022).
[21] Z.K. Shinwari, M. Qaiser, Efforts on conservation and sustainable use of medicinal plants of Pakistan, Pakistan J. Bot. (2011).
[22] R. Bahramsoltani, M.H. Farzaei, M.S. Farahani, R. Rahimi, Phytochemical constituents as future antidepressants: a comprehensive review, Rev. Neurosci. (2015).
[23] M.S. Farahani, R. Bahramsoltani, M.H. Farzaei, M. Abdollahi, R. Rahimi, Plant-derived natural medicines for the management of depression: an overview of mechanisms of action, Rev. Neurosci. (2015).
[24] X. Li, T. Wu, Z. Yu, et al., Apocynum venetum leaf extract reverses depressive-like behaviors in chronically stressed rats by inhibiting oxidative stress and apoptosis, Biomed. Pharmacother. (2018).
[25] J. Lotter, M. Möller, O. Dean, M. Berk, B.H. Harvey, Studies on haloperidol and adjunctive α-mangostin or raw *Garcinia mangostana* Linn pericarp on bio-behavioral markers in an immune-inflammatory model of schizophrenia in male rats, Front. Psychiatr. (2020).
[26] P.L. Zimath, A.P. Dalmagro, T.C. Ribeiro, et al., Antidepressant-like effect of hydroalcoholic extract from barks of *Rapanea ferruginea*: role of monoaminergic system and effect of its isolated compounds myrsinoic acid A and B, Behav. Brain Res. (2020).
[27] P. Ju, W. Ding, J. Chen, et al., The protective effects of Mogroside V and its metabolite 11-oxo-mogrol of intestinal microbiota against MK801-induced neuronal damages, Psychopharmacology (2020).
[28] D.P. De Sousa, P. De Almeida Soares Hocayen, L.N. Andrade, R. Andreatini, A systematic review of the anxiolytic-like effects of essential oils in animal models, Molecules (2015).
[29] Y. Wang, G. Chen, S. Zhong, et al., Association between resting-state brain functional connectivity and cortisol levels in unmedicated major depressive disorder, J. Psychiatr. Res. (2018).
[30] D. Lindqvist, F.S. Dhabhar, S.J. James, et al., Oxidative stress, inflammation and treatment response in major depression, Psychoneuroendocrinology (2017).
[31] J. Keller, R. Gomez, G. Williams, et al., HPA axis in major depression: cortisol, clinical symptomatology and genetic variation predict cognition, Mol. Psychiatr. (2017).
[32] J.J. Schildkraut, The catecholamine hypothesis of affective disorders: a review of supporting evidence, Am. J. Psychiatr. (1965).
[33] A.M. Fineberg, L.M. Ellman, Inflammatory cytokines and neurological and neurocognitive alterations in the course of schizophrenia, Biol. Psychiatr. (2013).
[34] J.T. Coyle, NMDA receptor and schizophrenia: a brief history, Schizophr. Bull. (2012).
[35] J. Frohlich, J.D. Van Horn, Reviewing the ketamine model for schizophrenia, J. Psychopharmacol. (2014).
[36] N. Zirak, M. Shafiee, G. Soltani, M. Mirzaei, A. Sahebkar, *Hypericum perforatum* in the treatment of psychiatric and neurodegenerative disorders: current evidence and potential mechanisms of action, J. Cell. Physiol. (2019).
[37] M. Shafiee, S. Arekhi, A. Omranzadeh, A. Sahebkar, Saffron in the treatment of depression, anxiety and other mental disorders: current evidence and potential mechanisms of action, J. Affect. Disord. (2018).
[38] T. Maria Michel, D. Pulschen, J. Thome, The role of oxidative stress in depressive disorders, Curr. Pharmaceut. Des. (2012).
[39] G. Guidotti, F. Calabrese, C. Anacker, et al., Glucocorticoid receptor and fkbp5 expression is altered following exposure to chronic stress: modulation by antidepressant treatment, Neuropsychopharmacology (2013).
[40] D.C. Andersson, J. Fauconnier, T. Yamada, et al., Mitochondrial production of reactive oxygen species contributes to the β-adrenergic stimulation of mouse cardiomycytes, J. Physiol. (2011).
[41] D.P. Jones, Redefining oxidative stress, Antioxidants Redox Signal. (2006).
[42] B. Harwell, Biochemistry of oxidative stress, Biochem. Soc. Trans. (2007).
[43] E. Asevedo, A. Gadelha, C. Noto, et al., Impact of peripheral levels of chemokines, BDNF and oxidative markers on cognition in individuals with schizophrenia, J. Psychiatr. Res. (2013).
[44] T.M. Michel, S. Frangou, D. Thiemeyer, et al., Evidence for oxidative stress in the frontal cortex in patients with recurrent depressive disorder-a postmortem study, Psychiatr. Res. (2007).
[45] T.M. Michel, S. Camara, T. Tatschner, et al., Increased xanthine oxidase in the thalamus and putamen in depression, World J. Biol. Psychiatr. (2010).
[46] P. Gałecki, J. Szemraj, M. Bieńkiewicz, A. Florkowski, E. Gałecka, Lipid peroxidation and antioxidant protection in patients during acute depressive episodes and in remission after fluoxetine treatment, Pharmacol. Rep. (2009).
[47] M. Bilici, H. Efe, M.A. Köroğlu, et al., Antioxidative enzyme activities and lipid peroxidation in major depression: alterations by antidepressant treatments, J. Affect. Disord. (2001).
[48] G.A. Behr, J.C.F. Moreira, B.N. Frey, Preclinical and clinical evidence of antioxidant effects of antidepressant agents: implications for the pathophysiology of major depressive disorder, Oxid. Med. Cell. Longev. (2012).
[49] M. Hu, W. Zou, C.Y. Wang, et al., Hydrogen sulfide protects against chronic unpredictable mild stress-induced oxidative stress in Hippocampus by upregulation of BDNF-TrkB pathway, Oxid. Med. Cell. Longev. (2016).
[50] I.M. Balmus, A. Ciobica, I. Antioch, R. Dobrin, D. Timofte, Oxidative stress implications in the affective disorders: main biomarkers, animal models relevance, genetic perspectives, and antioxidant approaches, Oxid. Med. Cell. Longev. (2016).
[51] T. Liu, S. Zhong, X. Liao, et al., A meta-analysis of oxidative stress markers in depression, PLoS One (2015).
[52] S. Gaweł, M. Wardas, E. Niedworok, P. Wardas, Malondialdehyde (MDA) as a Lipid Peroxidation Marker, Wiadomości lekarskie, 2004.
[53] J. Chen, L. Zeng, T. Xia, et al., Toward a biomarker of oxidative stress: a fluorescent probe for exogenous and endogenous malondialdehyde in living cells, Anal. Chem. (2015).
[54] E. Niedzielska, I. Smaga, M. Gawlik, et al., Oxidative stress in neurodegenerative diseases, Mol. Neurobiol. (2016).
[55] A.L. Lopresti, G.L. Maker, S.D. Hood, P.D. Drummond, A review of peripheral biomarkers in major depression: the potential of inflammatory and oxidative stress biomarkers, Prog. Neuro Psychopharmacol. Biol. Psychiatr. (2014).
[56] G. Lucca, C.M. Comim, S.S. Valvassori, et al., Increased oxidative stress in submitochondrial particles into the brain of rats submitted to the chronic mild stress paradigm, J. Psychiatr. Res. (2009).
[57] H.M. Abelaira, G.Z. Réus, K.F. Ribeiro, et al., Effects of lamotrigine on behavior, oxidative parameters and signaling cascades in rats exposed to the chronic mild stress model, Neurosci. Res. (2013).
[58] S. liu, T. Li, H. Liu, et al., Resveratrol exerts antidepressant properties in the chronic unpredictable mild stress model through the regulation of oxidative stress and mTOR pathway in the rat hippocampus and prefrontal cortex, Behav. Brain Res. (2016).
[59] B. Halliwell, Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment, Drugs Aging (2001).
[60] B. Oliver-Bever, Medicinal Plants in Tropical West Africa, Cambridge University Press, 1985.
[61] R. Cojocariu, A. Ciobica, I.M. Balmus, et al., Antioxidant capacity and behavioral relevance of a polyphenolic extract of Chrysanthellum americanum in a rat model of irritable bowel syndrome, Oxid. Med. Cell. Longev. (2019).
[62] H.Y. Qin, C.W. Cheng, X.D. Tang, Z.X. Bian, Impact of psychological stress on irritable bowel syndrome, World J. Gastroenterol. (2014).
[63] H. Ghaderi, M. Rafieian, H.R. Nezhad, Effect of hydroalcoholic Cinnamomum zeylanicum extract on reserpine-induced depression symptoms in mice, Pharmacophore (2018).
[64] S. Ghaffari, A. Ghobadi, A.H. Jamshidi, et al., Cinnamomum tamala as an adjuvant therapy in the treatment of major depressive disorder: a double-blind, randomized, placebo-controlled clinical trial with placebo control, Advances in Integrative Medicine (2020).

[65] R.U. Partan, R. Hidayat, M.I. Saleh, N. Parisa, N.S. Tanzil, Effect of supplementation kayu manis (*Cinnamomum burmannii*) extract in neuronal cell death protection in wistar rats lir-psychotic on haloperidol therapy, Asian J. Pharmaceut. Clin. Res. (2018).
[66] G.J. Beppe, L.B. Kenko Djoumessie, E. Keugong Wado, et al., Aqueous root bark extract of *Daniellia oliveri* (hutch. & Dalz.) (fabaceae) protects neurons against diazepam-induced amnesia in mice, Evid. base Compl. Alternative Med. (2020).
[67] K.C.F. Dias, J.C. de Almeida, L.C. Vasconcelos, et al., Standardized extract of *Erythrina velutina* Willd. attenuates schizophrenia-Like behaviours and oxidative parameters in experimental animal models, J. Pharm. Pharmacol. (2019).
[68] N.C. Ximenes, M.A. Dos Santos Júnior, G.S. Vasconcelos, et al., Ethanolic extract of *Erythrina velutina* Willd ameliorate schizophrenia-like behavior induced by ketamine in mice, J. Compl. Integr. Med. (2019).
[69] E.V.L. Da-Cunha, C. Dias, J.M. Barbosa-Filho, A.I. Gray, Eryvellutinone, an isoflavanone from the stem bark of *Erythrina vellutina*, Phytochemistry (1996).
[70] L.A. Rabelo, M. De Fátima Agra, E.V.L. Da-Cunha, M.S. Da Silva, J.M. Barbosa-Filho, Homohesperetin and phaseollidin from *Erythrina velutina*, Biochem. Systemat. Ecol. (2001).
[71] W.M. Aizat, I.N. Jamil, F.H. Ahmad-Hashim, N.M. Noor, Recent updates on metabolite composition and medicinal benefits of mangosteen plant, PeerJ 7 (2019) e6324.
[72] S.F. Mamat, K.A. Azizan, S.N. Baharum, N.M. Noor, W.M. Aizat, GC-MS and LC-MS analyses reveal the distribution of primary and secondary metabolites in mangosteen (*Garcinia mangostana* Linn.) fruit during ripening, Sci. Hortic. (2020).
[73] I.N. Marzaimi, W.M. Aizat, Current review on mangosteen usages in antiinflammation and other related disorders, in: Bioactive Food as Dietary Interventions for Arthritis and Related Inflammatory Diseases, 2019.
[74] P. Janhom, P. Dharmasaroja, Neuroprotective effects of alpha-mangostin on MPP+-induced apoptotic cell death in neuroblastoma SH-SY5Y cells, J. Toxicol. (2015).
[75] Y. Lee, S. Kim, Y. Oh, et al., Inhibition of oxidative neurotoxicity and scopolamine-induced memory impairment by γ-mangostin: in vitro and in vivo evidence, Oxid. Med. Cell. Longev. (2019).
[76] G.L. Pardo Andreu, N. Maurmann, G.K. Reolon, et al., Mangiferin, a naturally occurring glucoxilxanthone improves long-term object recognition memory in rats, Eur. J. Pharmacol. (2010).
[77] I. Oberholzer, M. Möller, B. Holland, et al., *Garcinia mangostana* Linn displays antidepressant-like and pro-cognitive effects in a genetic animal model of depression: a bio-behavioral study in the Flinders Sensitive Line rat, Metab. Brain Dis. (2018).
[78] H. Chen, Q. Huang, S. Zhang, et al., The Chinese herbal formula PAPZ ameliorates behavioral abnormalities in depressive mice, Nutrients (2019).
[79] G. Chen, X. Guo, Neurobiology of Chinese herbal medicine on major depressive disorder, Int. Rev. Neurobiol. (2017).
[80] J. Shen, J. Zhang, M. Deng, et al., The antidepressant effect of *Angelica sinensis* extracts on chronic unpredictable mild stress-induced depression is mediated via the upregulation of the BDNF signaling pathway in rats, Evid. base Compl. Alternative Med. (2016).
[81] Y. Hu, P. Liu, D.H. Guo, et al., Antidepressant effects of the extract YZ-50 from *Polygala tenuifolia* in chronic mild stress treated rats and its possible mechanisms, Pharmaceut. Biol. (2010).
[82] B. Li, Z. Fu, R. Hu, Y. Chen, Z. Zhang, *Semen ziziphi spinosae* and *Fructus gardeniae* extracts synergistically improve learning and memory of a mouse model, Biomedical Reports (2013).
[83] Y. Wang, C.F. Chang, J. Chou, et al., Dietary supplementation with blueberries, spinach, or spirulina reduces ischemic brain damage, Exp. Neurol. (2005).
[84] R. Sultana, M. Perluigi, D.A. Butterfield, Protein oxidation and lipid peroxidation in brain of subjects with Alzheimer's disease: insights into mechanism of neurodegeneration from redox proteomics, Antioxidants Redox Signal. (2006).
[85] M. Yadav, M. Parle, N. Sharma, et al., Protective effects of *Spinacia oleracea* seeds extract in an experimental model of schizophrenia: possible behavior, biochemical, neurochemical and cellular alterations, Biomed. Pharmacother. (2018).
[86] H. Zhang, Y. Sun, S. Qian, et al., Yueju-Ganmaidazao Decoction confers rapid antidepressant-like effects and the involvement of suppression of NMDA/NO/cGMP signaling, J. Ethnopharmacol. (2020).
[87] H. Girouard, G. Wang, E.F. Gallo, et al., NMDA receptor activation increases free radical production through Nitric Oxide and NOX2, J. Neurosci. (2009).
[88] M. Cunha, F. Pazini, F. Ludka, et al., The modulation of NMDA receptors and l-arginine/nitric oxide pathway is implicated in the anti-immobility effect of creatine in the tail suspension test, Amino Acids (2015).
[89] Y.F. Li, Y.Z. Zhang, Y.Q. Liu, et al., Inhibition of N-methyl-D-aspartate receptor function appears to be one of the common actions for antidepressants, J. Psychopharmacol. (2006).
[90] C.Y. Jiang, X.Y. Qin, M.M. Yuan, G.J. Lu, Y. Cheng, 2,3,5,4′-Tetrahydroxystilbene-2-O-beta-D-glucoside reverses stress-induced depression via inflammatory and oxidative stress pathways, Oxid. Med. Cell. Longev. (2018).
[91] L. Lin, B. Ni, H. Lin, et al., Traditional usages, botany, phytochemistry, pharmacology and toxicology of *Polygonum multiflorum* Thunb.: a review, J. Ethnopharmacol. (2015).
[92] S. Ling, J.W. Xu, Biological activities of 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside in antiaging and antiaging-related disease treatments, Oxid. Med. Cell. Longev. (2016).
[93] A. Mishra, A.K. Mishra, S. Jha, Effect of traditional medicine brahmi vati and bacoside A-rich fraction of *Bacopa monnieri* on acute pentylenetetrzole-induced seizures, amphetamine-induced model of schizophrenia, and scopolamine-induced memory loss in laboratory animals, Epilepsy Behav. 80 (2018) 144–151.
[94] L.M. Ojemann, W.L. Nelson, D.S. Shin, A.O. Rowe, R.A. Buchanan, Tian ma, an ancient Chinese herb, offers new options for the treatment of epilepsy and other conditions, Epilepsy Behav. (2006).
[95] W. Tang, G. Eisenbrand, W. Tang, G. Eisenbrand, *Gastrodia elata* bl, in: Chinese Drugs of Plant Origin, 1992.
[96] B. Zhou, J. Tan, C. Zhang, Y. Wu, Neuroprotective effect of polysaccharides from *Gastrodia elata* Blume against corticosterone-induced apoptosis in PC 12 cells via inhibition of the endoplasmic reticulum stress-mediated pathway, Mol. Med. Rep. (2018).
[97] A.H. Miller, V. Maletic, C.L. Raison, Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression, Biol. Psychiatr. (2009).
[98] A. Sluzewska, J. Rybakowski, E. Bosmans, et al., Indicators of immune activation in major depression, Psychiatr. Res. (1996).
[99] M. Maes, Major depression and activation of the inflammatory response system, in: Advances in Experimental Medicine and Biology, 1999.
[100] M. Maes, J. Lambrechts, E. Bosmans, et al., Evidence for a systemic immune activation during depression: results of leukocyte enumeration by flow cytometry in conjunction with monoclonal antibody staining, Psychol. Med. (1992).
[101] K. Kroenke, R.L. Spitzer, J.B.W. Williams, The PHQ-9: validity of a brief depression severity measure, J. Gen. Intern. Med. (2001).
[102] R.A. Khairova, R. MacHado-Vieira, J. Du, H.K. Manji, A potential role for pro-inflammatory cytokines in regulating synaptic plasticity in major depressive disorder, Int. J. Neuropsychopharmacol. (2009).
[103] J. Wang, D. Zhao, S. Tiano, et al., Prophylactic effect of flavanol rich preparation metabolites in promoting resilience to a mouse model of social stress, Transl. Psychiatry (2020).
[104] J.B. Blumberg, E.L. Ding, R. Dixon, G.M. Pasinetti, F. Villarreal, The science of cocoa flavanols: bioavailability, emerging evidence, and proposed mechanisms, Adv. Nutr. (2014).
[105] L. Dubner, J. Wang, L. Ho, L. Ward, G.M. Pasinetti, Recommendations for development of new standardized forms of cocoa breeds and cocoa extract processing for the prevention of Alzheimer's disease: role of cocoa in promotion of cognitive resilience and healthy brain aging, J. Alzheim. Dis. (2015).
[106] J. Wang, C. Tang, M.G. Ferruzzi, et al., Role of standardized grape polyphenol preparation as a novel treatment to improve synaptic plasticity through attenuation of features of metabolic syndrome in a mouse model, Mol. Nutr. Food Res. (2013).
[107] J. Wang, W. Bi, A. Cheng, et al., Targeting multiple pathogenic mechanisms with polyphenols for the treatment of Alzheimer's disease-experimental approach and therapeutic implications, Front. Aging Neurosci. (2014).
[108] P. Liu, L.J. Kemper, J. Wang, et al., Grape seed polyphenolic extract specifically decreases Aβ*56 in the brains of Tg2576 mice, J. Alzheim. Dis. (2011).
[109] J. Wang, L. Ho, W. Zhao, et al., Grape-derived polyphenolics prevent Aβ oligomerization and attenuate cognitive deterioration in a mouse model of Alzheimer's disease, J. Neurosci. (2008).

[110] A. Scholey, L. Owen, Effects of chocolate on cognitive function and mood: a systematic review, Nutr. Rev. (2013).
[111] M.B. Howren, D.M. Lamkin, J. Suls, Associations of depression with c-reactive protein, IL-1, and IL-6: a meta-analysis, Psychosom. Med. (2009).
[112] R. Haapakoski, J. Mathieu, K.P. Ebmeier, H. Alenius, M. Kivimäki, Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder, Brain Behav. Immun. (2015).
[113] S.H. Liu, L.T. Lee, N.Y. Hu, et al., Effects of alpha-mangostin on the expression of anti-inflammatory genes in U937 cells, Chinese Med J (2012).
[114] P. Kasemwattanaroj, P. Moongkarndi, K. Pattanapanyasat, et al., Immunomodulatory activities of α-mangostin on peripheral blood mononuclear cells, Nat. Prod. Commun. (2013).
[115] I. Yiemwattana, R. Kaomongkolgit, Alpha-mangostin suppresses IL-6 and IL-8 expression in *P. gingivalis* LPS-stimulated human gingival fibroblasts, Odontology (2015).
[116] E.B. Russo, History of cannabis and its preparations in saga, science, and sobriquet, Chem. Biodivers. (2007).
[117] A. Szabo, I.A. Akkouh, T. Ueland, et al., Cannabis use is associated with increased levels of soluble gp130 in schizophrenia but not in bipolar disorder, Front. Psychiatr. (2020).
[118] J.S. Silver, C.A. Hunter, gp130 at the nexus of inflammation, autoimmunity, and cancer, J. Leukoc. Biol. (2010).
[119] M. Narazaki, K. Yasukawa, T. Saito, et al., Soluble forms of the interleukin-6 signal-transducing receptor component gp130 in human serum possessing a potential to inhibit signals through membrane-anchored gp130, Blood (1993).
[120] I.L. Campbell, M. Erta, S.L. Lim, et al., Trans-signaling is a dominant mechanism for the pathogenic actions of interleukin-6 in the brain, J. Neurosci. (2014).
[121] D.R. McIlwain, T. Berger, T.W. Mak, Caspase functions in cell death and disease, CSH Perspectives in Biology (2013).
[122] C. Cao, M. Liu, S. Qu, et al., Chinese medicine formula Kai-Xin-San ameliorates depression-like behaviours in chronic unpredictable mild stressed mice by regulating gut microbiota-inflammation-stress system, J. Ethnopharmacol. (2020).
[123] Q. Zhu, Q. Yue, J. Li, W. Shi-Guo, The effects of ephedra monkshood asarum decoction for mood disorders on depression model rats model behavior, Neural Plast. (2016).
[124] W. Jing, S. Song, H. Sun, et al., Mahuang-fuzi-xixin decoction reverses depression-like behavior in LPS-induced mice by regulating NLRP3 inflammasome and neurogenesis, Neural Plast. (2019).
[125] A. Gadek-Michalska, J. Tadeusz, P. Rachwalska, J. Bugajski, Cytokines, prostaglandins and nitric oxide in the regulation of stress-response systems, Pharmacol. Rep. (2013).
[126] B. Karadeniz, Z. Ulker, L. Alpsoy, Genotoxic and cytotoxic effects of storax in vitro, Toxicol. Ind. Health (2013).
[127] M. Liang, Y. Du, W. Li, et al., Suhexiang essential oil inhalation produces antidepressant- and anxiolytic-like effects in adult mice, Biol. Pharm. Bull. (2018).
[128] Y.T. Liu, C. Zhou, H.M. Jia, X. Chang, Z.M. Zou, Standardized Chinese Formula Xin-Ke-Shu inhibits the myocardium Ca2+ overloading and metabolic alternations in isoproterenol-induced myocardial infarction rats, Sci. Rep. (2016).
[129] J.C. Huffman, C.M. Celano, S.R. Beach, S.R. Motiwala, J.L. Januzzi, Depression and cardiac disease: epidemiology, mechanisms, and diagnosis, Cardiovascular Psychiatry and Neurology (2013).
[130] S.L. Grace, S.E. Abbey, J. Irvine, Z.M. Shnek, D.E. Stewart, Prospective examination of anxiety persistence and its relationship to cardiac symptoms and recurrent cardiac events, Psychother. Psychosom. (2004).
[131] H. Ma, Y. Wang, Y.L. Xue, et al., The effect of Xinkeshu tablets on depression and anxiety symptoms in patients with coronary artery disease: results from a double-blind, randomized, placebo-controlled study, Biomed. Pharmacother. (2019).
[132] O. Berton, E.J. Nestler, New approaches to antidepressant drug discovery: beyond monoamines, Nat. Rev. Neurosci. (2006).
[133] D.H. Root, A.F. Hoffman, C.H. Good, et al., Norepinephrine activates dopamine d4 receptors in the rat lateral habenula, J. Neurosci. (2015).
[134] R. Goda, T. Otsuka, A. Iwamoto, et al., Serotonin levels in the dorsal raphe nuclei of both chipmunks and mice are enhanced by long photoperiod, but brain dopamine level response to photoperiod is species-specific, Neurosci. Lett. (2015).
[135] N. Takamura, S. Nakagawa, T. Masuda, et al., The effect of dopamine on adult hippocampal neurogenesis, Progress in Neuro-Psychopharmacology & Biological Psychiatry (2014).
[136] M. Machado Bergamaschi, R. Helena Costa Queiroz, A. Waldo Zuardi, J. Alexandre S. Crippa, Safety and side effects of cannabidiol, a *Cannabis sativa* constituent, Curr. Drug Saf. (2011).
[137] L.M. Borgelt, K.L. Franson, A.M. Nussbaum, G.S. Wang, The pharmacologic and clinical effects of medical cannabis, Pharmacotherapy (2013).
[138] A.J. Hill, C.M. Williams, B.J. Whalley, G.J. Stephens, Phytocannabinoids as novel therapeutic agents in CNS disorders, Pharmacology and Therapeutics (2012).
[139] A.W. Zuardi, Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action, Rev. Bras. Psiquiatr. (2008).
[140] N. Rodrigues da Silva, F.V. Gomes, A.B. Sonego, N.R. da Silva, F.S. Guimarães, Cannabidiol attenuates behavioral changes in a rodent model of schizophrenia through 5-HT1A, but not CB1 and CB2 receptors, Pharmacol. Res. (2020).
[141] M. Rodríguez-Muñoz, Y. Onetti, E. Cortés-Montero, J. Garzón, P. Sánchez-Blázquez, Cannabidiol enhances morphine antinociception, diminishes NMDA-mediated seizures and reduces stroke damage via the sigma 1 receptor 11 medical and health sciences 1109 neurosciences 11 medical and health sciences 1115 pharmacology and pharmaceutical scien, Mol. Brain (2018).
[142] X. Guitart, X. Codony, X. Monroy, Sigma receptors: biology and therapeutic potential, Psychopharmacology (2004).
[143] C. Venkataramaiah, B. Lakshmi Priya, W. Rajendra, Perturbations in the catecholamine metabolism and protective effect of '3-(3, 4-dimethoxy phenyl)-1-4 (methoxy phenyl) prop-2-en-1-one' during ketamine-induced schizophrenia: an in vivo and in silico studies, J. Biomol. Struct. Dyn. (2020).
[144] V. Chintha, R. Wudayagiri, Bioavailability and Neuroprotectivity of 3-(3, 4-dimethoxy phenyl)-1-4 (methoxy phenyl) prop-2-en-1-one against Schizophrenia: an in silico approach, J. Recept. Signal Transduction 39 (5–6) (2019) 392–398.
[145] M. Laruelle, A. Abi-Dargham, R. Gil, L. Kegeles, R. Innis, Increased dopamine transmission in schizophrenia: relationship to illness phases, Biol. Psychiatr. (1999).
[146] J.J. Weinstein, M.O. Chohan, M. Slifstein, et al., Pathway-specific dopamine abnormalities in schizophrenia, Biol. Psychiatr. (2017).
[147] A. Abi-Dargham, J. Rodenhiser, D. Printz, et al., Increased Baseline Occupancy of D2 Receptors by Dopamine in Schizophrenia, Proceedings of the National Academy of Sciences, 2000.
[148] P. Seeman, T. Lee, M. Chau-Wong, K. Wong, Antipsychotic drug doses and neuroleptic/dopamine receptors, Nature (1976).
[149] J. Sutter, B.A. Chindo, A. Becker, Effects of a methanol extract of *Ficus platyphylla* stem bark on a two-way active avoidance task and on body core temperature, Behav. Brain Res. (2019).
[150] J. Tortoriello, O. Romero, Plants used by Mexican traditional medicine with presumable sedative properties: an ethnobotanical approach, Arch. Med. Res. (1992).
[151] M.A. Santillán-Urquiza, M. Herrera-Ruiz, A. Zamilpa, et al., *Galphimia glauca* and natural galphimines block schizophrenia-like symptoms induced with apomorphine and MK-801 in mice, Evid. base Compl. Alternative Med. (2019).
[152] M.A. Santillán-Urquiza, M. Herrera-Ruiz, A. Zamilpa, et al., Pharmacological interaction of *Galphimia glauca* extract and natural galphimines with Ketamine and Haloperidol on different behavioral tests, Biomed. Pharmacother. (2018).
[153] Y.-W. Chin, A. Kinghorn, Structural characterization, biological effects, and synthetic studies on xanthones from mangosteen (*Garcinia mangostana*), a popular botanical dietary supplement, Mini-Reviews Org. Chem. (2008).
[154] R. Schmid, K. Kubitzki, K.U. Kramer, P.S. Green, The Families and Genera of Vascular Plants, vol. 1, Pteridophytes and Gymnosperms, Taxon, 1991.
[155] B. Vellas, N. Coley, P.J. Ousset, et al., Long-term use of standardised *Ginkgo biloba* extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial, Lancet Neurol. (2012).
[156] B.S. Oken, D.M. Storzbach, J.A. Kaye, The efficacy of *Ginkgo biloba* on cognitive function in Alzheimer disease, Arch. Neurol. (1998).
[157] P. Chen, M. Hei, L. Kong, et al., One water-soluble polysaccharide from *Ginkgo biloba* leaves with antidepressant activities via modulation of the gut microbiome, Food Funct. (2019).
[158] S.S. Rho, Y.S. Woo, W.M. Bahk, *Ginkgo biloba* induced mood dysregulation: a case report, BMC Complementary Medicine and Therapies (2018).

[159] A.X. Bueno, A.T.S. Moreira, F.T. Silva, C.S. Estevam, M. Marchioro, Effects of the aqueous extract from *Hyptis pectinata* leaves on rodent central nervous system, Revista Brasileira de Farmacognosia (2006).
[160] E.N. Bum, G.S. Taiwe, L.A. Nkainsa, et al., Validation of Anticonvulsant and Sedative Activity of Six Medicinal Plants, Epilepsy & Behavior, 2009.
[161] F.R. Sobreira Dantas Nóbrega de Figuêiredo, Á.B. Monteiro, I.R. Alencar de Menezes, et al., Effects of the *Hyptis martiusii* Benth. leaf essential oil and 1,8-cineole (eucalyptol) on the central nervous system of mice, Food Chem. Toxicol. (2019).
[162] W. Lasoñ, M. Chlebicka, K. Rejdak, Research advances in basic mechanisms of seizures and antiepileptic drug action, Pharmacol. Rep. (2013).
[163] J.A. Armijo, E.M. Valdizán, I. De las Cuevas, A. Cuadrado, Advances in the Physiopathology of Epileptogenesis: Molecular Aspects, Revista de Neurologia, 2002.
[164] R. Singh, R.J.M.K. Gardner, K.M. Crossland, I.E. Scheffer, S.F. Berkovic, Chromosomal abnormalities and epilepsy: a review for clinicians and gene hunters, Epilepsia (2002).
[165] A.J.J. Pijnenburg, W.M.M. Honig, J.M. Van Rossum, Inhibition of d-amphetamine-induced locomotor activity by injection of haloperidol into the nucleus accumbens of the rat, Psychopharmacologia (1975).
[166] J. Dal Mas, T. Zermiani, L.C. Thiesen, et al., Nanoemulsion as a carrier to improve the topical anti-inflammatory activity of stem bark extract of *Rapanea ferruginea*, Int. J. Nanomed. (2016).
[167] T. Zermiani, À. Malheiros, R.M.L. da Silva, H.K. Stulzer, T.M.B. Bresolin, Structural and physicochemical characterization and purity assessment of myrsinoic acids A and B, active compounds isolated from *Rapanea ferruginea* barks, Arab. J. Chem. (2016).
[168] V. Gupta, A.A. Khan, B.K. Sasi, N.R. Mahapatra, Molecular mechanism of monoamine oxidase A gene regulation under inflammation and ischemia-like conditions: key roles of the transcription factors GATA2, Sp1 and TBP, J. Neurochem. (2015).
[169] R.M.M. De Almeida, P.F. Ferrari, S. Parmigiani, K.A. Miczek, Escalated aggressive behavior: dopamine, serotonin and GABA, Eur. J. Pharmacol. (2005).
[170] M.E. Hasselmo, J.M. Bower, Acetylcholine and memory, Trends Neurosci. (1993).
[171] J. Micheau, A. Marighetto, Acetylcholine and memory: a long, complex and chaotic but still living relationship, Behav. Brain Res. (2011).
[172] Z.A. Al-Shareeda, R.A. Abramovich, O.G. Potanina, H.M. Alhejoj, Modification of choline derivatives and the study of the pharmacological activity, International Journal Quality Assurance (2020).
[173] M. Yadav, D.K. Jindal, M.S. Dhingra, et al., Protective effect of gallic acid in experimental model of ketamine-induced psychosis: possible behaviour, biochemical, neurochemical and cellular alterations, Inflammopharmacology (2018).
[174] S. Okuyama, T. Fukata, Y. Nishigawa, et al., Citrus flavonoid improves MK-801-induced locomotive hyperactivity: possible relevance to schizophrenia, J. Funct.Foods (2013).
[175] Z.Z. Meng, J.X. Chen, Y.M. Jiang, H.T. Zhang, Effect of xiaoyaosan decoction on learning and memory deficit in rats induced by chronic immobilization stress, Evid. base Compl. Alternative Med. (2013).
[176] X. Gao, X. Zheng, Z. Li, et al., Metabonomic study on chronic unpredictable mild stress and intervention effects of Xiaoyaosan in rats using gas chromatography coupled with mass spectrometry, J. Ethnopharmacol. (2011).
[177] P. Li, X.D. Tang, Z.X. Cai, et al., CNP signal pathway up-regulated in rectum of depressed rats and the interventional effect of Xiaoyaosan, World J. Gastroenterol. (2015).
[178] X.J. Li, Q.Y. Ma, Y.M. Jiang, et al., Xiaoyaosan exerts anxiolytic-like effects by down-regulating the TNF-α/JAK2-STAT3 pathway in the rat hippocampus, Sci. Rep. (2017).
[179] Z.Y. Yan, X.J. Li, X.F. Ding, Y.Y. Liu, J.X. Chen, Evaluating the anti-depression effect of xiaoyaosan on chronically-stressed mice, JoVE (2019).
[180] L.L. Wu, Y. Liu, C. Yan, et al., Antidepressant-like effects of fractions prepared from Danzhi-Xiaoyao-San decoction in rats with chronic unpredictable mild stress: effects on hypothalamic-pituitary-adrenal axis, arginine vasopressin, and neurotransmitters, Evid. base Compl. Alternative Med. (2016).
[181] K. Rizwan, S.A. Khan, I. Ahmad, et al., A comprehensive review on chemical and pharmacological potential of *Viola betonicifolia*: a plant with multiple benefits, Molecules (2019).
[182] N. Muhammad, M. Saeed, H. Khan, Antipyretic, analgesic and anti-inflammatory activity of *Viola betonicifolia* whole plant, BMC Complementary Medicine and Therapies (2012).
[183] R. Joseph, Evaluation of multitargeted antipsychotic activity of unmadgajakesari - a herbomineral formulation - an animal experimental study, International Journal of Pharceutical Sciences and Research (2019).
[184] J. Wu, T. Zhang, L. Yu, et al., Zhile capsule exerts antidepressant-like effects through upregulation of the BDNF signaling pathway and neuroprotection, Int. J. Mol. Sci. (2019).
[185] K.I. Erickson, D.L. Miller, K.A. Roecklein, The aging hippocampus: interactions between exercise, depression, and BDNF, Neuroscientist (2012).
[186] U.E. Lang, S. Borgwardt, Molecular mechanisms of depression: perspectives on new treatment strategies, Cell. Physiol. Biochem. (2013).
[187] C. Pittenger, R.S. Duman, Stress, depression, and neuroplasticity: a convergence of mechanisms, Neuropsychopharmacology (2008).
[188] I. Ninan, Synaptic regulation of affective behaviors; Role of BDNF, Neuropharmacology (2014).
[189] X.Y. Zhang, D.C. Chen, Y.L. Tan, et al., The interplay between BDNF and oxidative stress in chronic schizophrenia, Psychoneuroendocrinology (2015).
[190] S.S. Valvassori, C.O. Arent, A.V. Steckert, et al., Intracerebral administration of BDNF protects rat brain against oxidative stress induced by ouabain in an animal model of mania, Mol. Neurobiol. (2015).
[191] B.A.A. Bus, M.L. Molendijk, I. Tendolkar, et al., Chronic depression is associated with a pronounced decrease in serum brain-derived neurotrophic factor over time, Mol. Psychiatr. (2015).
[192] M.L. Molendijk, B.A.A. Bus, P. Spinhoven, et al., Serum levels of brain-derived neurotrophic factor in major depressive disorder: state-trait issues, clinical features and pharmacological treatment, Mol. Psychiatr. (2011).
[193] C. Zhou, J. Zhong, B. Zou, et al., Meta-analyses of comparative efficacy of antidepressant medications on peripheral BDNF concentration in patients with depression, PLoS One (2017).
[194] J.M. Adams, S. Cory, The Bcl-2 protein family: arbiters of cell survival, Science (1998).
[195] J.S. Lim, H. Kim, Y.S. Choi, et al., Neuroprotective effects of berberine in neurodegeneration model rats induced by ibotenic acid, Animal Cells System (2008).
[196] M. Ye, S. Fu, R. Pi, F. He, Neuropharmacological and pharmacokinetic properties of berberine: a review of recent research, J. Pharm. Pharmacol. (2009).
[197] X. Ma, Y. Jiang, A. Wu, et al., Berberine attenuates experimental autoimmune encephalomyelitis in C57 BL/6 mice, PLoS One (2010).
[198] F. Negahdar, M. Mehdizadeha, M.T. Joghataei, et al., Berberine chloride pretreatment exhibits neuroprotective effect against 6-hydroxydopamine-induced neuronal insult in rat, Iran. J. Pharm. Res. (IJPR) (2015).
[199] K.Y. Yoo, I.K. Hwang, B.O. Lim, et al., Berberry extract reduces neuronal damage and N-methyl-D-aspartate receptor 1 immunoreactivity in the gerbil hippocampus after transient forebrain ischemia, Biol. Pharm. Bull. (2006).
[200] X.Q. Zhou, X.N. Zeng, H. Kong, X.L. Sun, Neuroprotective effects of berberine on stroke models in vitro and in vivo, Neurosci. Lett. (2008).
[201] Y. Albayrak, K. Hashimoto, Beneficial effects of the sigma-1 agonist fluvoxamine for Tardive dyskinesia in patients with postpsychotic depressive disorder of schizophrenia: report of 5 cases, Prim. Care Companion J. Clin. Psychiatry (2012).
[202] J. Kocerh, M. Ali Faghihi, M.A. Lopez-Toledano, et al., MicroRNA-219 Modulates NMDA Receptor-Mediated Neurobehavioral Dysfunction, Proceedings of the National Academy of Sciences, 2009.
[203] C.G. Lau, R.S. Zukin, NMDA receptor trafficking in synaptic plasticity and neuropsychiatric disorders, Nat. Rev. Neurosci. (2007).
[204] A.R. Mohn, R.R. Gainetdinov, M.G. Caron, B.H. Koller, Mice with reduced NMDA receptor expression display behaviors related to schizophrenia, Cell (1999).
[205] S. Ghotbi Ravandi, M. Shabani, H. Bashiri, et al., Ameliorating effects of berberine on MK-801-induced cognitive and motor impairments in a neonatal rat model of schizophrenia, Neurosci. Lett. (2019).
[206] C. Venkataramaiah, Modulations in the ATPases during ketamine-induced schizophrenia and regulatory effect of '3-(3, 4-dimethoxy phenyl) -1- (4-methoxyphenyl) prop-2-en-1-one': an in vivo and in silico studies, J. Recept. Signal Transduction (2020).
[207] A.M. Rose, R. Valdes, Understanding the sodium pump and its relevance to disease, Clin. Chem. (1994).

[208] P.J. Christo, R.S. El-Mallakh, Possible role of endogenous ouabain-like compounds in the pathophysiology of bipolar Illness, Med. Hypotheses (1993).
[209] M.L. Brines, H. Tabuteau, S. Sundaresan, et al., Regional Distributions of Hippocampal Na+, K+-ATPase, Cytochrome Oxidase, and Total Protein in Temporal Lobe Epilepsy, Epilepsia, 1995.
[210] M.J.S. Fernandes, M.G. Naffah-Mazzacoratti, E.A. Cavalheiro, Na+K+ ATPase activity in the rat hippocampus : a study in the pilocarpine model of epilepsy, Neurochem. Int. (1996).
[211] K. Renkawek, W.O. Renier, J.H.H.M. de Pont, O.J.M. Vogels, F.J.M. Gabreëls, Neonatal Status Convulsivus, Spongiform Encephalopathy, and Low Activity of Na+/K+ -ATPase in the Brain, 1992. Epilepsia.
[212] B. Koo, H.J. Bae, N. Goo, et al., A botanical drug composed of three herbal materials attenuates the sensorimotor gating deficit and cognitive impairment induced by MK-801 in mice, J. Pharm. Pharmacol. (2020).
[213] E.S. Emamian, J.-M. Beaulieu, C. Bagni, A. Salahpour, AKT/GSK3 signaling pathway and schizophrenia, Front. Mol. Neurosci. (2012).
[214] R.S. Jope, C.J. Yuskaitis, E. Beurel, Glycogen synthase kinase-3 (GSK3): inflammation, diseases, and therapeutics, Neurochem. Res. (2007).
[215] M.S. Seo, S.H. Kim, Y.M. Ahn, et al., The effects of repeated administrations of MK-801 on ERK and GSK-3β signalling pathways in the rat frontal cortex, Int. J. Neuropsychopharmacol. (2007).
[216] D. Xi, Y.C. Li, M.A. Snyder, et al., Group II metabotropic glutamate receptor agonist ameliorates MK801-induced dysfunction of NMDA receptors via the Akt/GSK-3B pathway in adult rat prefrontal cortex, Neuropsychopharmacology (2011).
[217] L.A. Greene, A.S. Tischlert, S.W. Kuffler, Establishment of a noradrenergic clonal line of rat adrenal pheochromocytoma cells which respond to nerve growth factor (sympathetic neurons/cell culture/catecholamines/differentiation/neurites), Cell Biol. (1976).
[218] B. Wiatrak, A. Kubis-Kubiak, A. Piwowar, E. Barg, PC12 cell line: cell types, coating of culture vessels, differentiation and other culture conditions, Cells (2020).
[219] F. Bernuzzi, S. Recalcati, A. Alberghini, G. Cairo, Reactive oxygen species-independent apoptosis in doxorubicin-treated H9c2 cardiomyocytes: role for heme oxygenase-1 down-modulation, Chem. Biol. Interact. (2009).
[220] A. Surget, M. Saxe, S. Leman, et al., Drug-dependent requirement of hippocampal neurogenesis in a model of depression and of antidepressant reversal, Biol. Psychiatr. (2008).
[221] X.Y. Qi, W.J. Chen, L.Q. Zhang, B.J. Xie, Mogrosides extract from *Siraitia grosvenori* scavenges free radicals in vitro and lowers oxidative stress, serum glucose, and lipid levels in alloxan-induced diabetic mice, Nutr. Res. (2008).
[222] M. Takasaki, T. Konoshima, Y. Murata, et al., Anticarcinogenic activity of natural sweeteners, cucurbitane glycosides, from *Momordica grosvenori*, Cancer Lett. (2003).
[223] M. Ukiya, T. Akihisa, H. Tokuda, et al., Inhibitory effects of cucurbitane glycosides and other triterpenoids from the fruit of Momordica grosvenori on Epstein-Barr virus early antigen induced by tumor promoter 12-O-tetradecanoylphorbol-13-acetate, J. Agric. Food Chem. (2002).
[224] R. Di, M.T. Huang, C.T. Ho, Anti-inflammatory activities of mogrosides from *Momordica grosvenori* in murine macrophages and a murine ear edema model, J. Agric. Food Chem. (2011).
[225] J.Y. Hwang, Y.H. Kim, Y.H. Ahn, M.B. Wie, J.Y. Koh, N-methyl-D-aspartate receptor blockade induces neuronal apoptosis in cortical culture, Exp. Neurol. (1999).
[226] H. Dudek, S.R. Datta, T.F. Franke, et al., Regulation of neuronal survival by the serine-threonine protein kinase Akt, Science (1997).
[227] P. Curatolo, R. Moavero, J. van Scheppingen, E. Aronica, mTOR dysregulation and tuberous sclerosis-related epilepsy, Expert Rev. Neurother. (2018).
[228] G. Sanacora, R. Gueorguieva, C.N. Epperson, et al., Subtype-specific alterations of γ-aminobutyric acid and glutamate in patients with major depression, Arch. Gen. Psychiatr. (2004).
[229] G. Sanacora, G. Treccani, M. Popoli, Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders, Neuropharmacology (2012).
[230] X. Zhao, C. Wang, J.F. Zhang, et al., Chronic curcumin treatment normalizes depression-like behaviors in mice with mononeuropathy: involvement of supraspinal serotonergic system and GABAA receptor, Psychopharmacology (2014).
[231] N. Goel, J.L. Workman, T.T. Lee, L. Innala, V. Viau, Sex differences in the HPA axis, Compr. Physiol. (2014).
[232] G. Aguilera, Regulation of pituitary ACTH secretion during chronic stress, Front. Neuroendocrinol. (1994).
[233] G.E. Hodes, V. Kana, C. Menard, M. Merad, S.J. Russo, Neuroimmune mechanisms of depression, Nat. Neurosci. (2015).
[234] I. Heuser, The hypothalamic-pituitary-adrenal system in depression, Pharmacopsychiatry (1998).
[235] J. Keller, B. Flores, R.G. Gomez, et al., Cortisol circadian rhythm alterations in psychotic major depression, Biol. Psychiatr. (2006).
[236] A. Lembke, R. Gomez, L. Tenakoon, et al., The mineralocorticoid receptor agonist, fludrocortisone, differentially inhibits pituitary-adrenal activity in humans with psychotic major depression, Psychoneuroendocrinology (2013).
[237] A.F. Schatzberg, J. Keller, L. Tennakoon, et al., HPA axis genetic variation, cortisol and psychosis in major depression, Mol. Psychiatr. (2014).
[238] P. Willner, Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation, Psychopharmacology (1997).
[239] J.L. Moreau, F. Jenck, J.R. Martin, P. Mortas, W.E. Haefely, Antidepressant treatment prevents chronic unpredictable mild stress-induced anhedonia as assessed by ventral tegmentum self-stimulation behavior in rats, Eur. Neuropsychopharmacol (1992).
[240] Y. Zhang, Y. Wu, T. Chen, et al., Assessing the metabolic effects of aromatherapy in human volunteers, Evid. base Compl. Alternative Med. (2013).
[241] T. Satou, H. Kasuya, K. Maeda, K. Koike, Daily Inhalation of α-Pinene in Mice: Effects on Behavior and Organ Accumulation, Wiley, 2013.
[242] A. Falk, E. Gullstrand, A. Lof, E. Wigaeus-Hjelm, Liquid/air partition coefficients of four terpenes, Occup. Environ. Med. (1990).
[243] A.A. Falk, M.T. Hagberg, A.E. Lof, E.M. Wigaeus-Hjelm, W. Zhiping, Uptake, distribution and elimination of α-pinene in man after exposure by inhalation, Scand. J. Work. Environ. Health (1990).
[244] S. Martin, E. Padilla, M.A. Ocete, et al., Anti-inflammatory activity of the essential oil of *Bupleurum fruticescens*, Planta Med. (1993).
[245] P. Consroe, A. Martin, V. Singh, Antiepileptic potential of cannabidiol analogs, J. Clin. Pharmacol. (1981).
[246] H.P. Singh, D.R. Batish, S. Kaur, K. Arora, R.K. Kohli, α-Pinene inhibits growth and induces oxidative stress in roots, Ann. Bot. (2006).
[247] A. Him, H. Ozbek, I. Turel, A.C. Oner, Antinociceptive activity of alpha-pinene and fenchone, Pharmacologyonline (2008).
[248] B. Ndjakou Lenta, C. Vonthron-Sénécheau, R. Fongang Soh, et al., In vitro antiprotozoal activities and cytotoxicity of some selected Cameroonian medicinal plants, J. Ethnopharmacol. (2007).
[249] V.W.A. Kumbol, W.K.M. Abotsi, E. Ekuadzi, E. Woode, Albizia zygia root extract exhibits antipsychotic-like properties in murine models of schizophrenia, Biomed. Pharmacother. (2018).
[250] W.K.M. Abotsi, S.B. Lamptey, E. Boakye-Gyasi, E. Woode, *Albizia zygia* (DC.) J.F. Macbr. (Leguminosae-Mimosoideae) root extract exhibits anti-nociceptive and antipyretic activities in murine models, J. Ethnopharmacol. (2017).
[251] S.B. Lamptey, W.K.M. Abotsi, *Albizia zygia* (DC.) Macbr. hydroethanol root extract exerts anti-oedemic and in vivo antioxidant activities in animal models, J. Appl. Pharmaceut. Sci. (2017).
[252] K. Lei, G.F. He, C.L. Zhang, et al., Investigation of the synergistic effects of haloperidol combined with *Calculus bovis sativus* in treating MK-801-induced schizophrenia in rats, Exp. Anim. (2018).
[253] H. Cai, Y. Guang, L. Liu, P. Yao, F. Qiu, The Protective Effects of in Vitro Cultivated *Calculus Bovis* on the Cerebral and Myocardial Cells in Hypoxic Mice, Journal of Huazhong University of Science and Technology, 2007.
[254] J.L. Ríos, M.C. Recio, R.M. Giner, S. Meñez, An update review of saffron and its active constituents, Phytother Res. (1996).
[255] M. Khazdair, M. Boskabady, M.H.-A. journal of, U, The effects of *Crocus sativus* (saffron) and its constituents on nervous system: a review, Avicenna Journal of Phytomedicine (2015), 2015.
[256] A. Talaei, M. Hassanpour Moghadam, S.A. Sajadi Tabassi, S.A. Mohajeri, Crocin, the main active saffron constituent, as an adjunctive treatment in major depressive disorder: a randomized, double-blind, placebo-controlled, pilot clinical trial, J. Affect. Disord. (2014).

[257] A. Ghajar, S.M. Neishabouri, N. Velayati, et al., *Crocus sativus* L versus citalopram in the treatment of major depressive disorder with anxious distress: a double-blind, controlled clinical trial, Pharmacopsychiatry (2017).
[258] M. Ahmadpanah, F. Ramezanshams, A. Ghaleiha, et al., *Crocus sativus* L. (saffron) versus sertraline on symptoms of depression among older people with major depressive disorders–a double-blind, randomized intervention study, Psychiatr. Res. (2019).
[259] L. Kashani, S. Esalatmanesh, F. Eftekhari, et al., Efficacy of *Crocus sativus* (saffron) in treatment of major depressive disorder associated with post-menopausal hot flashes: a double-blind, randomized, placebo-controlled trial, Arch. Gynecol. Obstet. (2018).
[260] B. Tadyon Najafabadi, K. Ghamari, T. Kermany Ranjabari, et al., Therapeutic effects of saffron (*Crocus sativus*) versus fluoxetine on Irritable Bowel Syndrome: a double-blind randomized clinical trial, Advances in Integrative Medicine (2019).
[261] M. Bangratz, S.A. Abdellah, A. Berlin, et al., A preliminary assessment of a combination of rhodiola and saffron in the management of mild–moderate depression, Neuropsychiatric Dis. Treat. (2018).
[262] J.D. Amsterdam, A.G. Panossian, *Rhodiola rosea* L. as a putative botanical antidepressant, Phytomedicine (2016).
[263] K.S. Yeung, M. Hernandez, J.J. Mao, I. Haviland, J. Gubili, Herbal medicine for depression and anxiety: a systematic review with assessment of potential psycho-oncologic relevance, Phytother Res. (2018).
[264] M. Perfumi, L. Mattioli, Adaptogenic and central nervous system effects of single doses of 3% rosavin and 1% salidroside *Rhodiola rosea* L. extract in mice, Phytother Res. (2007).
[265] V. Darbinyan, G. Aslanyan, E. Amroyan, et al., Clinical trial of *Rhodiola rosea* L. extract SHR-5 in the treatment of mild to moderate depression, Nord. J. Psychiatr. (2007).
[266] A. Coors, M. Brosch, E. Kahl, et al., *Rhodiola rosea* root extract has antipsychotic-like effects in rodent models of sensorimotor gating, J. Ethnopharmacol. (2019).
[267] A. Kiani, A. Firoozabadi, A. Salehi, et al., Effects of *Cuscuta chinensis* Lam. Versus fluoxetine for treatment of major depression: a double-blind, randomized controlled trial, Scientific African (2020).
[268] M. Parvizi, F. Fadai, M.R. Khodaei-Ardakani, et al., Effect of *Cuscuta epithymum* acquainted with risperidone on the improvement of clinical symptoms and cognitive impairment in patients with schizophrenia: a triple-blind randomized placebo-controlled trial, Galen Medical Journal (2019).
[269] A. Ahmad, S. Tandon, T.D. Xuan, Z. Nooreen, A review on phytoconstituents and biological activities of Cuscuta species, Biomed. Pharmacother. (2017).
[270] T.S. Firoozeei, M. Barekatain, M. Karimi, et al., Lavender and dodder combined herbal syrup versus citalopram in major depressive disorder with anxious distress: a double-blind randomized trial, Journal of Integrative Medicine (2020).
[271] V. Agyeman, D. Ofori, J. Cobbinah, M. Wagner, Influence of *Phytolyma lata* (Homoptera: psyllidae) on seedling growth of *Milicia excelsa*, Ghana J. For. (2010).
[272] W.M. Koné, A.G. Koffi, E.L. Bomisso, F.H. Tra Bi, Ethnomedical study and iron content of some medicinal herbs used in traditional medicine in Cote d'Ivoire for the treatment of anaemia, Afr. J. Tradit., Complementary Altern. Med. (2012).
[273] J. Betti, An Ethnobotanical and Floristical Study of Medicinal Plants Among the Baka Pygmies in the Periphery of the Ipassa- Biosphere Reserve, Gabon, European Journal of Medicinal Plants, 2013.
[274] J.A. Ibrahim, I. Muazzam, I.A. Jegede, O.F. Kunle, J.I. Okogun, Ethno-medicinal plants and methods used by Gwandara tribe of Sabo Wuse in Niger State, Nigeria, to treat mental illness, Afr. J. Tradit., Complementary Altern. Med. (2007).
[275] M.A. Sonibare, M.O. Soladoye, T.O. Subuloye, Ethnobotanical survey of anti-psychotic plants in lagos and ogun states of Nigeria, Eur. J. Sci. Res. (2008).
[276] L. Akinpelu, M. Akanmu, E. Obuotor, Antipsychotic effects of ethanol leaf extract and fractions of *Milicia excelsa* (moraceae) in mice, Journal of Pharmaceutical Research International (2018).
[277] J.R. Homberg, M. Van den Akker, H.S. Raasø, et al., Enhanced motivation to self-administer cocaine is predicted by self-grooming behaviour and relates to dopamine release in the rat medial prefrontal cortex and amygdala, Eur. J. Neurosci. (2002).
[278] C. Estanislau, A.C. Ramos, P.D. Ferraresi, et al., Individual differences in the elevated plus-maze and the forced swim test, Behav. Process. (2011).
[279] D. Gao, Z. Zheng, M. Han, X. Tang, X. Sun, Findings of P300-like and CNV-like potentials in rat model of depression following repeatedly forced swim stress, Int. J. Psychophysiol. (2009).
[280] C. Andrade, A. Aswath, S.K. Chaturvedi, M. Srinivasa, R. Raguram, A double-blind, placebo-controlled evaluation of the anxiolytic efficacy ff an ethanolic extract of *Withania somnifera*, Indian J. Psychiatr. (2000).
[281] K. Chandrasekhar, J. Kapoor, S. Anishetty, A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of Ashwagandha root in reducing stress and anxiety in adults, Indian J. Psychol. Med. (2012).
[282] K.N.R. Chengappa, J.S. Brar, J.M. Gannon, P.J. Schlicht, Adjunctive use of a standardized extract of *Withania somnifera* (ashwagandha) to treat symptom exacerbation in schizophrenia: a randomized, double-blind, placebo-controlled study, J. Clin. Psychiatr. (2018).
[283] J.M. Gannon, J. Brar, A. Rai, K.N.R. Chengappa, Effects of a standardized extract of *Withania somnifera* (ashwagandha) on depression and anxiety symptoms in persons with schizophrenia participating in a randomized, placebo-controlled clinical trial, Ann. Clin. Psychiatr. (2019).
[284] A. Smetanka, V. Stara, I. Farsky, I. Tonhajzerova, I. Ondrejka, Pycnogenol supplementation as an adjunct treatment for antidepressant-induced sexual dysfunction, Physiology International (2019).
[285] M. Anushiravani, A.A. Manteghi, A. Taghipur, M. Eslami, Comparing effectiveness of a combined herbal drug based on Echium amoenum with citalopram in the treatment of major depressive disorder, Curr. Drug Discov. Technol. (2018).
[286] K. Nishioka, T. Hidaka, S. Nakamura, et al., Pycnogenol®, French maritime pine bark extract, augments endothelium-dependent vasodilation in humans, Hypertens. Res. (2007).
[287] Z. Ďuračková, B. Trebatický, V. Novotný, I. Žitňanová, J. Breza, Lipid metabolism and erectile function improvement by Pycnogenol®, extract from the bark of *Pinus pinaster* in patients suffering from erectile dysfunction - a pilot study, Nutr. Res. (2003).
[288] H. Wang, Y. Chen, L. Wang, Q. Liu, S. Yang, C. Wang, Advancing herbal medicine: enhancing product quality and safety through robust quality control practices, Front. Pharmacol. (2023).
[289] R. Ding, Y. Lianhui, W. Chenghui, Z. Shihong, G. Rui, Quality assessment of traditional Chinese medicine based on data fusion combined with machine learning: a review, Crit. Rev. Anal. Chem. (2023).
[290] Y. Pan, Z. Hongxu, C. Yuan, G. Xingchu, Y. Jizhong, Z. Hui, Applications of hyperspectral imaging technology combined with machine learning in quality control of traditional Chinese medicine from the perspective of artificial intelligence: a review, Crit. Rev. Anal. Chem. (2023).
[291] J. Yang, L. Yuting, P. Yingfeng, S. Yingting, X. Xinyuan, P. Jianyang, Q. Haibin, Pharmaceutical process-omics for quality control of traditional Chinese medicine preparations: a 1H-qNMR assisted case study of Guanxinning injection, J. Pharmaceut. Biomed. Anal. (2024).
[292] K.X. Zhu, W. Min, B. Zhi-Lin, H. Shi-Liang, F. Li-Ming, G. Feng-Feng, W. Xue-Zhou, X. Sheng-Fang, Growing attention on the toxicity of Chinese herbal medicine: a bibliometric analysis from 2013 to 2022, Front. Pharmacol. (2024).
[293] P. Kulkarni, Prediction of drug-induced kidney injury in drug dKulkarni, Priyanka, Prediction of drug-induced kidney injury in drug discovery (2021). Drug Metabolism Reviews.
[294] L. Qiuju, X. Yan, Y. Zhang, J. Zhou, L. Yang, S. Wu, C. Peng, X. Pan, Risk compounds, potential mechanisms and biomarkers of traditional Chinese medicine-induced reproductive toxicity, J. Appl. Toxicol. (2022).
[295] S. Gavanji, Cardiotoxicity effects of herbal medicine, A review article, Biology, Medicine, & Natural Product Chemistry (2023).
[296] J. Kanungo, C.S. Barbara, J. Krzykwa, C.A. Mitchell, M. Embry, P. Spencer, G. Jean Harry, et al., Screening tools to evaluate the neurotoxic potential of botanicals: building a strategy to assess safety, Expet Opin. Drug Metabol. Toxicol. (2024).
[297] M. Zhi-Tao, S. Zhuo, X. Xiao-He, W. Jia-Bo, New insights into herb-induced liver injury, Antioxidants Redox Signal. (2023).
[298] C.-T. Che, V. George, T.P. Ijinu, P. Pushpangadan, K. Andrae-Marobela, Traditional medicine, in: Pharmacognosy, Academic Press, 2024.
[299] J. Stein, S. Shoptaw, D. Vigo, C. Lund, P. Cuijpers, J. Bantjes, N. Sartorius, M. Maj, Psychiatric diagnosis and treatment in the 21st century: paradigm shifts versus incremental integration, World Psychiatr. (2022).

[300] L. Kirmayer, H. Minas, The future of cultural psychiatry: an international perspective, Med. Anthropol. (2023).
[301] Y.M. Al-Worafi, Handbook of Complementary, Alternative, and Integrative Medicine: Education, Practice, and Research Volume 3: Research Evidence Based Clinical Practice, CRC Press, 2024.
[302] N.P. Ngubane, B.Z.D. Gama, A quantitative evaluation of traditional health practitioners' perspectives on mental disorders in KwaZulu-Natal: knowledge, diagnosis, and treatment practices, J. Spirituality Ment. Health (2024).