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Pharmacological effects and therapeutic potential of natural compounds in neuropsychiatric disorders: An update

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Neuropsychiatric diseases are a group of disorders that cause significant morbidity and disability. The symptoms of psychiatric disorders include anxiety, depression, eating disorders, autism spectrum disorders (ASD), attention-deficit/hyperactivity disorder, and conduct disorder. Various medicinal plants are frequently used as therapeutics in traditional medicine in different parts of the world. Nowadays, using medicinal plants as an

Abbreviations: ABA, applied behavioural analysis; b.w., body weight; BDNF, brain-derived neurotrophic factor; COMT, catechol-O-methyltransferase; CNS, central nervous system; CBT, cognitive-behavioural therapy; cAMP, cyclic adenosine monophosphate; FA, ferulic acid; GABA, gamma-aminobutyric acid; HPA, hypothalamic-pituitary-adrenal; IL, interleukin; IL-1β, interleukin 1 beta; i.p., intraperitoneal administration; MDD, major depressive disorder; MAOIs, monoamine oxidase inhibitors; p.o., oral administration; PDE-4, phosphodiesterase-4; SNRIs, serotonin-norepinephrine reuptake inhibitors; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-alpha.

alternative medication has been considered due to their biological safety. Despite the wide range of medications, many patients are unable to tolerate the side effects and eventually lose their response. By considering the therapeutic advantages of medicinal plants in the case of side effects, patients may prefer to use them instead of chemical drugs. Today, the use of medicinal plants in traditional medicine is diverse and increasing, and these plants are a precious heritage for humanity. Investigation about traditional medicine continues, and several studies have indicated the basic pharmacology and clinical efficacy of herbal medicine. In this article, we discuss five of the most important and common psychiatric illnesses investigated in various studies along with conventional therapies and their pharmacological therapies. For this comprehensive review, data were obtained from electronic databases such as MedLine/PubMed, Science Direct, Web of Science, EMBASE, DynaMed Plus, ScienceDirect, and TRIP database. Preclinical pharmacology studies have confirmed that some bioactive compounds may have beneficial therapeutic effects in some common psychiatric disorders. The mechanisms of action of the analyzed biocompounds are presented in detail. The bioactive compounds analyzed in this review are promising phytochemicals for adjuvant and complementary drug candidates in the pharmacotherapy of neuropsychiatric diseases. Although comparative studies have been carefully reviewed in the preclinical pharmacology field, no clinical studies have been found to confirm the efficacy of herbal medicines compared to FDA-approved medicines for the treatment of mental disorders. Therefore, future clinical studies are needed to accelerate the potential use of natural compounds in the management of these diseases.

KEYWORDS

neuropsychiatric disorders, natural compounds, pharmacological mechanisms, bioactive compounds, preclinical pharmacology

1 Introduction

Neuropsychiatric disorders are a group of disorders that cause great morbidity and disability. Globally, the psychiatric disorder's prevalence is estimated at 6.7%. The symptoms of psychiatric disorders include anxiety, depression, eating disorders, autism spectrum, attention-deficit/hyperactivity, and conduct disorder. Different studies have been probed to clarify the basic molecular mechanism involved in such a disease's occurrence. Recently, it has been shown that early-life experiences can affect adulthood behaviour. Nurturance, genetics, and environment are important factors that influence behaviour in adulthood. Like other multifactorial disorders, non-genetic factors are important factors in the aetiology of this condition (Martens and van loo, 2007; Cannon and Greenamyre, 2011).

Neuropsychiatric disorders are dealing with mental and cerebral disorders often associated with brain dysfunction (Yudofsky and Hales, 2002; Nussbaum et al., 2017). Many researchers use beneficial therapies with the least side effects to treat these patients. Therefore, choosing the right type of treatment depends on the variety of diseases that the person is suffering from (Reddy et al., 2020). Patients with any brain injury are more sensitive to the side effects of chemical drugs than patients without injury. Therefore, the physician should be careful in choosing the appropriate type of medication, dose, and duration of treatment (Silver et al., 1990; Silver et al., 1991; Silver et al., 1994). Numerous studies on animal models have shown that some chemical drugs, such as haloperidol, benzodiazepines, and clonidines, may interfere with the recovery of neuronal damage and eventually disrupt the normal physiological processes in the brain (Kuhn et al., 2019). Current medications for neuropsychiatric diseases mainly target disease symptoms. Therefore, there is a critical necessity to develop therapeutics which can delay, stop or reverse the progression of the condition (Paul and Snyder, 2019).

Clinical studies use antioxidants to interfere in disease progression, but the results are not satisfactory. Most of the antioxidants non-specifically target neuroprotective pathways. Consequently, new studies are needed to discover new potential agents that restore redox balance along with reducing neuronal damage (Underwood et al., 2010). Nowadays, using medicinal plants as an alternative medication has been considered due to their biological safety (Quetglas-Llabrés et al., 2022). In this article, we discuss the most important and common psychiatric illnesses mentioned in various studies

along with conventional therapies and their pharmacological therapies.

2 Search methodology

For this comprehensive review, data were obtained from electronic databases such as MedLine/PubMed, Science Direct, Web of Science, EMBASE, DynaMed Plus, ScienceDirect, and TRIP database. The following MeSH terms were used for the search: "Plants, Medicinal", "Antidepressive Agents/isolation and purification," "Antidepressive Agents/pharmacology," "Action Potentials/drug effects," "Animals," "Disease Models," "Animal, Plant Bark/chemistry," "Plant Extracts/chemistry," "Serotonin/metabolism," "Synapsis agonists," "Brain/drug effects," "Brain/metabolism," "Seizures/prevention and control," "Attention Deficit Disorder with Hyperactivity/drug therapy," "Phytotherapy/methods," "Phytotherapy/adverse effects," "Evidence-Based Medicine," "Treatment Outcome," "Autism/natural products/treatment," "schizophrenia/natural products/treatment." Preclinical pharmacological studies were included to explain the effects and potential mechanisms of natural bioactive compounds in some common neuropsychiatric disorders. Only papers written in English that included the potential mechanisms of natural compounds in psychiatric disorders were selected. The plants' taxonomy has been validated according to PlantList (Heinrich et al., 2020; Plantlist, 2021). Duplicate papers, communications, and studies that included homeopathic preparations or other brain conditions such as tumors were excluded.

3 Treatment of neuropsychiatric disorders in conventional meaning, using approved drugs and bioactive compounds: Underlying potential mechanisms

3.1 Major depressive disorder

Major depressive disorder (MDD) is identified by two characteristics: depressive state in several conditions and apathy with somatic and cognitive disturbances (World Health Organization, 1992; Otte et al., 2016; Vlad et al., 2020). The most common time of onset is between the ages of 20 and 30, and women are twice as likely as men to be affected (American Psychiatric Association, 1980; Wulff et al., 2015). Its lifetime prevalence is 16.6% per person (Weissman and Olfson, 1995; Kessler et al., 2005). The physiopathology of the disease is not yet clear, but it is associated with abnormalities in the brain's monoamine receptors or neurotransmitters, metinflammation conditions and as well as the serotonergic, noradrenergic, and neuropeptide systems are abnormal (Manji et al., 2001; Charney and Manji, 2004). Numerous studies have shown that the hypothalamic-pituitary-adrenal (HPA) axis is involved in this process and contributes to neuronal atrophy (Nestler et al., 2002; Mann and Currier, 2006).

3.1.1 Treatment of major depressive disorder using approved drugs

Conventional disease treatments include lifestyle changes such as exercise and smoking cessation (Goldberg et al., 2005; Taylor et al., 2014), somatic treatments such as electroconvulsive therapy (effective in resistant depression) (Paul et al., 1981; Prudic et al., 1996), focused psychotherapies (such as relaxation and mindfulness, behavioural therapy, and interpersonal therapy) (DeRubeis et al., 2005), and pharmacotherapy.

Pharmacotherapeutic therapies include selective serotonin reuptake inhibitors (SSRIs) such as citalopram, escitalopram, paroxetine, etc. (Papakostas, 2010); serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine (Stahl et al., 2005); tricyclic antidepressants such as ampitripitillin, clomipramine, doxepine, etc. (Moore and O'Keeffe, 1999); and monoamine oxidase inhibitors (MAOIs) such as phenelzine, vortioxetine and others (Table 1 (Quitkin et al., 1984; Quitkin et al., 1988).

3.1.2 Treatment of major depressive disorder and bioactive compounds

MDD is a significant prospect of global mental and economic burden. In most patients, the specific clinical features following symptoms such as sleep dysregulation, depressed mood, fatigue, suicidal thoughts, and loss of interest and appetite are observed (Yeni et al., 2022). The change in serotonin, norepinephrine and dopamine levels has been linked to clinical symptoms based on the monoamine hypothesis (Shyn and Hamilton, 2010; Willner et al., 2013).

Some plants are effective in modifying the mood by the effect on the monoamine neurotransmission, similar to *Hypericum perforatum*, as well as have an impact on GABA, opioid, and cannabinoid systems (Table 2) (Spinella, 2001; Heinrich et al., 2017).

For example, membrane-like alkaloids in plants like *Narcissus* (Amaryllidaceae) and *Sceletium* have potential antidepressant properties (Hanks, 2002; Berkov et al., 2020). *Narcissus* is a source of neuroactive substances like galantamine that has been used in the treatment of Alzheimer's disease (Smith et al., 1996). Mesembrine-like alkaloids demonstrated some SSRI activity in mood disorders (Gericke and Van Wyk, 2001a). In addition, mesembrine alkaloids have been shown to phosphodiesterase-4 (PDE-4) inhibition. They act by changing the levels of cyclic AMP (cAMP) as well as the induction of Brain-Derived Neurotrophic Factor (BDNF) mRNA, which has an antidepressant effect in patients who accompany MDD (Fujimaki et al., 2000).

TABLE 1 Approved drugs and their biological function in the treatment of important neuropsychiatric disorders.

Disease	Main group of drugs	Biological functional	References
MDD	Citalopram (Celexa)	Serotonin reuptake inhibitors (SSRIs)	(Fava et al., 2004; Papakostas, 2010; Ravindran and Stein, 2010)
	Escitalopram (Lexapro)		
	Paroxetine (Paxil, Paxil CR)		
	Sertraline (Zoloft)		
	Fluvoxamine (Luvox)		
	Fluoxetine (Prozac)		
	Venlafaxine (Effexor, Effexor XR)	Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Stahl et al. (2005)
	Desvenlafaxine (Pristiq)		
	Duloxetine (Cymbalta)		
	Amitriptyline (Elavil)	Blocking the activity of serotonin 5-HT2 receptors	(Snyder and Yamamura, 1977; Preskorn and Simpson, 1982; Lavoie et al., 1990; Atkinson et al., 1998; Moore and O'Keeffe, 1999; Menza et al., 2009)
	Clomipramine (Anafranil)		
	Doxepin (Adapin)		
	Imipramine (Tofranil)		
	Trimipramine (Surmontil) Desipramine (Norpramin) Nortriptyline (Pamelor) Protriptyline (Vivactil)		
	Amoxapine (Asendin)		
	Maprotiline (Ludiomil)		
	Phenelzine (Nardil) Tranylcypromine (Parnate) Isocarboxazid (Marplan)	Monoamine oxidase inhibitors (MAOIs)	(Quitkin et al., 1984; Quitkin et al., 1988; Lane and Baldwin, 1997; Association, 2006)
	Selegiline (Eldepryl)		
	Selegiline transdermal (Emsam)		
Schizophrenia	First-generation antipsychotics (Phenothiazines, Butyrophenones, Thioxanthenes, Dihydroindolones, Dibenzepines, Diphenylbutylpiperidines)	Dopamine antagonist (Blocking dopamine receptors)	Freedman, (2010)
	Second-generation antipsychotics (clozapine, olanzapine, quetiapine, risperidone, paliperidone, ziprasidone, and molindone	Serotonin-Dopamine Antagonists (D2, 5-HT1A, and 5-HT2A receptors)	(Gupta et al., 1994; Seeger et al., 1995; Möller, 2005; Schmid et al., 2014; Brenner and Stevens, 2017)
	Third-generation antipsychotics (aripiprazole, brexpiprazole and cariprazine)	D2 partial agonists	(Burris et al., 2002; Shapiro et al., 2003; De Deurwaerdère, 2016; Hope et al., 2018)
Autism	Risperidone	Serotonin-Dopamine Antagonists	(Leskovec et al., 2008; Rapin and Tuchman, 2008; Ji and Findling, 2015)
	Aripiprazole		
	Fluoxetine and fluvoxamine	Serotonin reuptake inhibitors (SSRIs)	Johnson and Myers, (2007)
	Methylphenidate	Norepinephrine—dopamine reuptake inhibitor (NDRI)	
Bipolar Disorder	mood stabilizers (Lithium, Divalproex, Carbamazepine)	↓ norepinephrine release and increasing serotonin synthesis	(Allen et al., 2006; Malhi et al., 2009; Miura et al., 2014)
	antipsychotic drugs (aripiprazole, Quetiapine, Risperidone, Olanzapine, Paliperidone)	Blocking dopamine D2 receptors	Jain, (2020)
ADHD	Methylphenidate	Norepinephrine—dopamine reuptake inhibitor (NDRI)	Storebø et al. (2015)
	Viloxazine	Norepinephrine reuptake inhibitor	Banaschewski et al. (2004)
	Atomoxetine	Norepinephrine reuptake inhibitor	
	Bupropion	Norepinephrine–dopamine reuptake inhibitor (NDRI) and antagonist of several nicotinic acetylcholine receptors	
	Guanfacine	Activating α_{2A} adrenoceptors	
	clonidine	Agonist of alpha-2A adrenergic receptor	

(Continued on following page)

TABLE 1 (*Continued*) Approved drugs and their biological function in the treatment of important neuropsychiatric disorders.

Disease	Main group of drugs	Biological functional	References
Epilepsy	Phenytoin Carbamazepine	Sodium channel blocker	(Nevitt et al., 2018; Nevitt et al., 2019) Uk, (2012)
	Valproate		
	Lamotrigine		
	Levetiracetam		
	Phenobarbital	↑chloride ions into post-synaptic neuron s	
		↓excitability of the neurons	Newton and Garcia, (2012)

Polyphenols like curcumin (*Curcuma longa*) are strongly recommended in the treatment procedures for MDD (Darvesh et al., 2012) (Table 2). Some authors reported that curcumin affects stressed mice by modulation of the various neurotransmitter systems in forced swim test (FST), similar to imipramine affection (Xu et al., 2005a; Xu et al., 2007). In another study, modulation of the serotoninergic system was approved via the cAMP pathway induced by curcumin (Li et al., 2009). Also, glutamate receptors are involved in curcumin's antidepressant effect by inhibiting the presynaptic voltage-gated calcium channels (Lin et al., 2011). In one study, the inhibitory effect of curcumin on glutamate release and the enhancement of the antidepressant activity of fluoxetine were reported (Kulkarni et al., 2008; Wang et al., 2008; Wang et al., 2010; Lin et al., 2011; Zhang et al., 2013). In the reports, apigenin, one of the bioflavonoids in behavioral test models, displayed significant anti-immobility action and neurotransmitters turnover induction in the mice model (Nakazawa et al., 2003). Moreover, haloperidol reversed the antidepressant action of apigenin (Han et al., 2007). The molecular mechanism behind its antidepressant activity was the inhibition of interleukin 1β and the activation of NLRP3 inflammasome in rat brains (20 mg/kg b. w., intragastrically) (Li et al., 2016). Amentoflavone is a bioflavonoid apigenin dimer (Hossain et al., 2021; Rajib et al., 2021), inhibited the flumazenil binding to rat brain at GABA receptors (Gutmann et al., 2002; Colovic et al., 2008; Ishola et al., 2012). Some authors reported that oral administration of amentoflavone in forced swim test (FST) was more potent than imipramine (Ishola et al., 2012).

In other studies, chlorogenic acid, a polyphenol (in coffee), could enhance mood in patients (Cropley et al., 2012). The mechanism of the antidepressant action of chlorogenic acid was hypothesized to act through the opioidergic pathway (Kwon et al., 2010; Park et al., 2010; Girish et al., 2012), but also reduce neuroinflammation and oxidative stress conditions (Chen et al., 2021). Ferulic acid (FA) induces an anti-immobility effect in behavioral despair models, including FST and TST (Zeni et al., 2012) and can be effectively supplemented in depressive disorders accompanying epilepsy (Singh and Goel, 2016). Some research showed the antidepressant activity of quercetin bioflavonoid by inhibiting MAO activity in the brain (Figure 1) (Butterweck et al., 2000; Haleagrahara et al., 2009; Clarke and Ramsay, 2011; Lam et al., 2012; Soofiyani et al., 2021) and by regulating the copine 6 and TREM1/2 imbalance related to the BDNF factor (Fang et al., 2020). In addition, quercetin showed antidepressant-like action in streptozotocin-induced diabetic mice compared to fluoxetine or imipramine (Kaur et al., 2007; Kawabata et al., 2010). Quercetin in some studies showed the inhibition of the breakdown of serotonin neurotransmitters in mouse brain mitochondria (Yoshino et al., 2011). The other molecule, hesperidin reduced the immobility period in the locomotor activity animal model (Souza et al., 2013).

Other acts of hesperidin are anti-inflammatory (reduction of TNF-α, Interleukin 1 beta (IL-1b) levels) and antioxidant activity in strokes (Figure 1) (Raza et al., 2011). *Hypericum perforatum* has a glycoside flavonol—rutin–that is used for the treatment of depression (Machado et al., 2008; Galeotti, 2017) and exhibits anti-inflammatory properties (Parashar et al., 2017) and immobility time-reducing action (30–120 mg/kg p.o. in mice) (Yusha'u et al., 2017). Rutin showed spatial memory enhancement and increased the levels of natural polyphenols in managing significant depression in the hippocampus of aged rat brains (Pyrzanowska et al., 2012). Resveratrol, another phenolic compound in grapes, significantly decreases the immobility period in animal models of locomotor activity and increases noradrenaline and serotonin levels (Yáñez et al., 2006; Xu et al., 2010b; Park et al., 2012; Zhang et al., 2012). The antidepressant action of resveratrol increased dopamine in the brain of female mice, similar to synthetic estrogen (Di Liberto et al., 2012). The antidepressant activity of the anthocyanidins in animal models was indicated by scientists and antidepressant activity in the animal model was due to the change in the locomotor activity (Xu et al., 2010a; Yi et al., 2011).

3.2 Schizophrenia

3.2.1 Treatment of schizophrenia using approved drugs

Another mental disorder characterized by periods of continuous or recurrent psychosis with symptoms such as delusions, hallucinations, disorganized speech or behaviour,

TABLE 2 Summarizes the effects and potential effects for the most important phytochemicals as a promising therapy for treating major depressive disorders.

Compounds	Main group of compounds	Verified effective concentrations/ model	Potential effects	References
Alkaloids	membrane-like alkaloids	Dose = 25 mg randomized double-blind placebo-controlled study	↑amygdala response to scary facial expressions ↑serotonin ↓cAMP	(Chiu et al., 2014) (Chiu et al., 2017) (Gericke and Van Wyk, 2001b) (Napoletano et al., 2001; Houslay et al., 2005)
	Curcumin	Dose = 5–10 mg/kg mice	↑NA	(Xu et al., 2005b; Darvesh et al., 2012)
			↑serotonin in the frontal cortex and hippocampal brain	Xu et al. (2007)
			↓MAO-A, ↓MAO-B	Wang et al. (2008)
Phenolic Phytochemicals		*in vivo*	↑hippocampal neurogenesis	Li et al. (2009)
			Modulation of the serotoninergic system	Lin et al. (2011)
			↓AC/cAMP, ↓cAMP	(Wang et al., 2008; Wang et al., 2010)
			↓glutamate	Kulkarni et al. (2008)
			↑neurotrophic factors	
			↑serotonin, ↑dopamine	
	Amentoflavone	Dose = 6.25–50 mg/kg mice *in vivo*	↓immobility inhibition flumazenil binding to GABA receptor	Ishola et al. (2012), Baureithel et al. (1997)
	Chlorogenic acid	Dose = 200–400 mg/kg mice *in vivo*	↓MAOB, ↓ ROS	(Wu et al., 2016; Lim et al., 2018) (Park et al., 2010) (Chen et al., 2021)
			↑ axon and dendrite growth	
			↑serotonin release through enhancing synapsin expression act through the opioidergic pathway	
			↑ neuroinflammation and oxidative stress	
	Ellagic acid	Dose = 25–100 mg/kg mice *in vivo*	↓immobility period in both FST and TST effect in monoaminergic neurotransmitter receptors	Girish et al. (2012)
	Ferulic acid	Dose = 0.01–10 mg/kg mice *in vivo*	↓ serotonin reuptake anti-inflammatory	(Zeni et al., 2012) (Sasaki et al., 2019)
			antioxidant	
			neuroprotective	
	Fisetin	Dose = 10–25 mg/kg mice *in vivo*	↓MAO	(Zheng et al., 2008; Zhen et al., 2012; Yao et al., 2020)
			↓5-HT, ↓NA, ↓DA reuptake	
			↓oxido-nitrosative stress, ↓ROS, anti-inflammatory effect	
	Quercetin	Dose = 50–100 mg/kg mice	depression-like effect through the participation of α2 adrenergic receptors in its mechanism of action	(Anjaneyulu et al., 2003; Clarke and Ramsay, 2011)
		in vivo	↓MAO isoenzymes	Yoshino et al. (2011)
			↑ BDNF	(Fang et al., 2020)
			Regulation of Copine 6 and TREM1/2 imbalance	
	Resveratrol	Dose = 20–80 mg/kg mice	↓immobility period in mouse models of behavioral despair without affecting locomotor activity.↑noradrenaline, ↑serotonin	(Yáñez et al., 2006; Xu et al., 2010a)
		in vivo	↓MAO isoenzymes	
			↓ serotonin uptake	
	Hesperidin	Dose = 0,1–1 mg/kg mice	↓immobility period and the antidepressant-like activity was independent of alterations in locomotor activity anti-inflammatory	(Raza et al., 2011; Carlos Filho et al., 2013)
		in vivo	antioxidant activity	
	Rutin	Dose = 0,1–3 mg/kg mice *in vivo*	↓inactivity in TST modulation of monoaminergic neurotransmitter systems	(Machado et al., 2008; Ramos-Hryb et al., 2018))
	Naringenin	Dose = 0,1–50 mg/kg mice *in vivo*	↓immobility in the TST	(Olsen et al., 2008) (Olsen et al., 2008) (Olsen et al., 2008) (Olsen
			↓pro-inflammatory mediators	

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TABLE 2 (*Continued*) Summarizes the effects and potential effects for the most important phytochemicals as a promising therapy for treating major depressive disorders.

Compounds	Main group of compounds	Verified effective concentrations/ model	Potential effects	References
				et al., 2008) (Olsen et al., 2008) (Olsen et al., 2008) (Olsen et al., 2008) (Olsen et al., 2008) (Olsen et al., 2008)
	Proanthocyanidins polyphenols	Dose = 25–50 mg/kg mice *in vivo*	↓alterations in the locomotor activity ↑serotonin ↑noradrenaline ↑synaptic plasticity	(Xu et al., 2010b; Wang et al., 2012)
	Nobiletin	Dose = 25–100 mg/kg mice *in vivo*	↓immobility period in both FST and TST serotoninergic, noradrenergic, dopaminergic effects	Yi et al. (2011)
Tannins	Tannic acid	Dose = 30 mg/kg rats *in vivo*	↑levels of monoaminergic neurotransmitters in the brain Non-selective inhibitor of monoamine oxidase	Luduvico et al. (2020)
Iridoids	Geniposide	Dose = 25, 50, 100 mg/kg rats *in vivo*	Upregulation the hypothalamic GR_{α} mRNA level Upregulation the GR_{α} protein expression	Cai et al. (2015)
Coumarins	Scopoletin	Dose = 1–100 mg/kg mice *in vivo*	Activation of postsynaptic α_1- and α_2-adrenoceptors	Capra et al. (2010)
	Umbelliferone	Dose = 15 mg/kg, 30 mg/kg rats *in vivo*	Downregulation of Rho-associated protein kinase (ROCK) signaling Upregulation of protein kinase B (Akt) signaling	Qin et al. (2017)
	Hypericum perforatum		Monoamine reuptake inhibitor Supportive towards the hypothalamic pituitary adrenal axis	Sarris et al. (2021)

Symbols: ↑, increase, ↓, decrease.

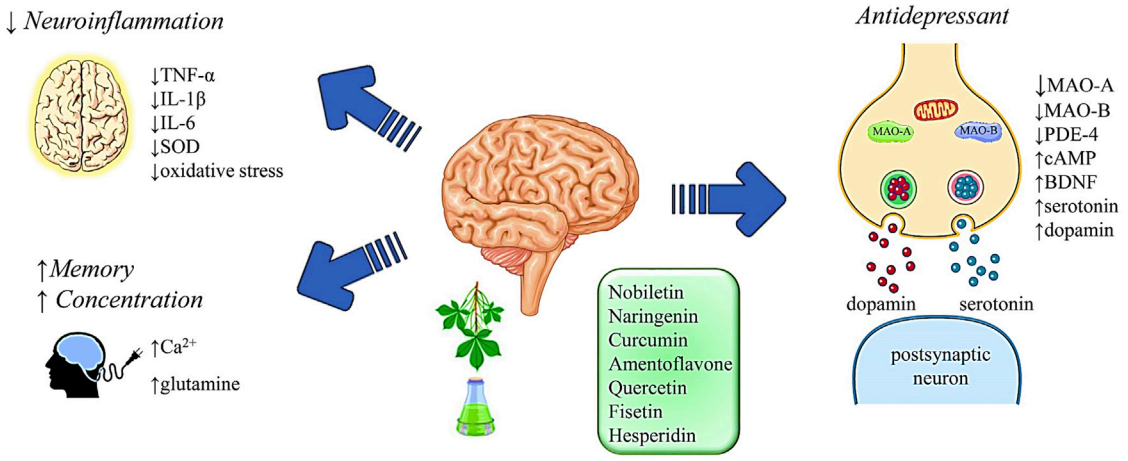

FIGURE 1
Schematic illustration of the possible mechanisms of natural compounds in neuropsychiatric disorders. Abbreviations and symbols: ↑, increase; ↓, decrease; TNF-α, Ca^{2+} tumour necrosis alpha; IL, interleukin; SOD, superoxide dismutase; MAO, monoaminoxidase; PDE-4, phosphodiesterase 4; cAMP, cyclic adenosine monophosphate; BDNF, brain-derived neurotrophic factor.

and impaired cognitive ability is called schizophrenia (World Health Organization, 1992; Lavretsky, 2008). The most important pathophysiological cause of the disease is abnormalities in neurotransmitters such as dopamine, serotonin, glutamate, aspartate, glycine, and gamma-aminobutyric acid (GABA) (Lavretsky, 2008). The prevalence of the disease in the United States is estimated to be between 0.6 and 1.9, and the prevalence is the same in men and women, but the onset of symptoms is seen faster in men than in women (Wu et al., 2006; Van Os and Kapur, 2009).

3.2.2 Treatment of schizophrenia and bioactive compounds

Schizophrenia treatment is divided into two categories: pharmacological and non-pharmacological: non-pharmacological treatments include targeting symptoms, preventing recurrence of the disease, and increasing adaptive function to eventually return the person to the community (Dipiro et al., 2014). The individual, group, and cognitive-behavioural psychotherapeutic therapies can also be used in non-pharmacological treatments (Dickerson and Lehman, 2011). Drug therapies include the use of first-generation antipsychotics, which are dopamine and serotonin antagonists such as lumateperone, risperidone (Marder and Meibach, 1994; Blair, 2020), clozapine (Leponex) (Stahl and Meyer, 2020), olanzapine (Zyprexa) (Bhana et al., 2001), quetiapine (Komossa et al., 2010), and ziprasidone (Lüllmann and Mohr, 2006). Also, fluoxetine was proved to bring positive outcomes when administered to patients, as it induced slight decrease in depressive symptoms (Spina et al., 1994). Some classifications of natural products are determined for their antipsychotic potentials, such as terpenoids, beta-caryophyllene, and limonene. Also, the antipsychotic saponin, polygalasaponin, was recognized for possessing antipsychotic properties by inhibiting cannabinoid receptors (Chung et al., 2002; Ajao et al., 2018). In the study of Abdul Rahim et al. 2022 *Polygonum minus* leaf extract (100 mg/L, 4 days) was found to decrease the level of cortisol in a zebrafish anxiety model, similarly to fluoxetine. In another study, a coumarin–scopoletin was described as an antidopaminergic agent with a U-shaped dose dependent activity towards the stereotyped behaviors in mice. The dose of 0.1 mg/kg b. w. (*per os*) was found effective in the alleviation of positive symptoms of schizophrenia psychosis. Another natural product, the derivative of anthracene–emodin was found to interfere with the schizophrenic responses induced in murine models (Mitra et al., 2018). The attenuation of pre-pulse inhibition and improvement of startle reponses were observed in neonatal rats treated with 15 and 50 mg/kg emodin in a subchronic model. Its possible mechanism of action may be related to the stimulation of the phosphorylation process of both ErbB1 and ErbB2. The efficacy of curcumin was determined in several *in vivo* clinical trials. This phenolic compound from turmeric tuber was administered to 36 schizophrenic patients (360 mg/day for 8 weeks) in a double-blind, placebo-controlled study to research its impact on the BDNF that is engaged in the neurodegeneration and cell survival processes (x). The compound was found to increase the level of BDNF. Furthermore, Hosseininasab and co-investigators (2021) described the influence of curcumin on both positive and negative symptoms in an 8-weeks- long clinical trial with 300 mg of curcumin added to the conventional medication. Curcumin was proved to alleviate memory processes and decrease the IL-6 levels and was well-tolerated by the patients. Table 3 presents natural products and their mechanism of action which were tested in the treatment of schizophrenia.

3.3 Bipolar disorder

Bipolar disorder or chronic manic depression manifests as a recurrent illness with symptoms of depression or manic (Jann, 2014). The disease most often affects adolescents or adults, and sometimes the elderly (Tiihonen et al., 2017). The disease is classified into two categories: type I (episodes of depression and persistent mania) and type II (episodes of depression and hypomania) (Cooper, 2018). The prevalence of this disease worldwide is 1%–3% and its incidence is the same in men and women considering different ethnicities and races (Ferrari et al., 2011; Moreira et al., 2017). The exact pathophysiology of the disease has not yet been determined, but more than 85% of cases are due to heredity (McGuffin et al., 2003). It has been shown that there is a relative overlap of the catechol-o-methyltransferase (COMT) gene for schizophrenia and bipolar disorder, which controls dopamine metabolism (Berrettini, 2003; Murray et al., 2004).

3.3.1 Treatment of bipolar disorder using approved drugs

To treat Bipolar Disorder, two psychosocial methods (using physical methods to establish individual relationships to help change the behaviour of the individual in society) (Woodward, 2015) and pharmacological therapies are used. Medications include the use of mood stabilizers such as lamotrigine, lithium, clozapine, divalproex, carbamazepine, olanzapine, and atypical antipsychotics such as quetiapine, risperidone, aripiprazole, and ziprasidone; and antidepressants such as bupropion and SSRIs (Jain, 2020). Herbal products can be considered to treat symptoms of insomnia and anxiety in bipolar patients. Valerian, chamomile, ginkgo, hops, and passionflower might be beneficial. However, some of their constituents' effectiveness and safety have not been approved and need more studies (Baek et al., 2014).

3.3.2 Treatment of bipolar disorder and bioactive compounds

Oxidative stress is one of the major factors described in the etiology of mania. That is why several experimental studies focus on the development of drug candidates that could restore

TABLE 3 The most representative bioactive compounds and their major effects in treatment and prevention of schizophrenia.

Disease	Main group of compounds		Neuro-biological functions	References
Schizophrenia	Alkaloids	Huperzine A	reversible AChE inhibitor	(Zangara, 2003; Wang et al., 2006)
		L-SPD	agonist on D_1 receptors in the medial prefrontal cortex (mPFC)	Mo et al. (2007)
	Polygonum minus leaf extract		↓ cortisol level in zebrafish model	(Nurhidayaha et al., 2022)
	Coumarin	Scopoletin	↓positive symptoms and stereotyped behavior Antidopaminergic activity	Pandy and Vijeepallam (2017)
	Anthraquinone	Emodin	↑ phosphorylation process of both ErbB1 and ErbB2 ↓ pre-pulse inhibition and improvement of startle reponses in rats dose = 15–50 mg/kg b.w	Mitra et al. (2022)
	Phenolic compounds	Curcumin	improvement of positive and negative scales	Hossain et al. (2021)
			↓ IL-6, ↑BDNF	Wynn et al. (2018)
			24-weeks, double-blind, randomized, placebo-controlled study on thirty-eight patients with chronic schizophrenia. 3,000 mg/d curcumin or placebo combined with antipsychotics. significant response to curcumin in the treatment of negative symptoms	Miodownik et al. (2019)

TABLE 4 Bioactive compounds and their major effects in the treatment of bipolar disorders.

Disease	Main group of compounds	Neuro-biological functions	References
Bipolar Disorder	Ginkgo	↑cerebrovascular blood flow ↓hyperactivity	Nourbala and Akhoundzadeh, (2006)
	Monoterpenes	GABAergic activity	Nogoceke et al. (2016)
	Carvone	↓ locomotor activity sodium channels blockage	
	Phenolic compounds	↓ free radicals formation	Recart et al. (2021)
	Gallic acid	↓ hyperactivity prevented cholinergic dysfunctions	
	Quercetin	↓protein kinase C ↓ hyperlocomotion	(Kanazawa et al. (2016), Kanazawa et al. (2017)

oxidation-reduction balance. In the light of this information, natural products that are proved to exhibit antioxidant properties are important to drug candidates in the reduction of manic episodes (Recart et al., 2021). Herbal intervention in bipolar disorder is recommended and prescribed, accompanied by mood stabilizers (Currier and Trenton, 2002; Mohr et al., 2005). *Hypericum perforatum* might not be used in patients alone. A clinical trial using ashwagandha provided substantial benefits for cognitive performance compared with a placebo (Chengappa et al., 2013). Ethanolic extracts of saffron (*Crocus sativus*) have been used in preclinical animal models, and its constituents, safranal, and crocin have shown antidepressant effects (Hosseinzadeh and Noraei, 2009). *Curcuma longa* (turmeric) and *H. perforatum* (St John's wort) are other plants used in various nervous system disorders and have been used over the past decades in the treatment of MDD (Gopi et al., 2017; Kunnumakkara et al., 2017). Acute and chronic administration of carvone (50 and 100 mg/kg, i. p.)—a monoterpene present in volatile oils of several plant species, e.g., *Mentha* spp., *Carum carvi*, and others–in a methylphenidate mice mania model resulted in a decreased locomotor activity in the tested animals, possibly thanks to the GABAergic activity and sodium channels blockage (Nogoceke et al., 2016). Gallic acid (GA) a phenolic acid that is widely spread in the plant kingdom was used in the treatment of ketamine-induced mania in rats and compared to the action of lithium. Similarly to lithium (45 mg/g twice a day) GA (50 and 100 mg/kg) administered for 14 days decreased the hyperlocomotion of the animals, induced the antioxidant properties and prevented the cholinergic disfunctions in the brain (Recart et al., 2021). In the studies of Kanazawa and collaborators (2016, 2017) quercetine administered intraperitoneally (10–40 mg/kg b. w.) showed antioxidant properties and inhibition of protein kinase C. In turn the flavonoid regulated sleep deprivation and diminished the

induced hyperlocomotion in mice. Table 4 summarizes natural compounds which are used in the treatment of bipolar disorders.

3.4 Autism spectrum disorders

Autism is a disorder of the nervous system that is associated with poor communication, social interaction, and repetitive behaviours, and usually manifests itself in childhood or adolescence (Landa, 2008; Tuchman et al., 2010; Edition, 2013). Causes of autism include immaturity of brain parts (London, 2007), brain-intestinal axis abnormalities (Wasilewska and Klukowski, 2015; Israelyan and Margolis, 2019), synaptic dysfunction (Levy and Ds, 2009), and mutations in the genes of cellular adhesion proteins involved in the synaptic region (Walsh et al., 2008). The prevalence of this disease is 10–16 per 10,000 people, and boys are more likely to develop autism than girls (Fombonne, 2006; Fombonne, 2009). The rate of disease in the United States is increasing every year (Newschaffer et al., 2007).

3.4.1 Treatment of autism spectrum disorders using approved drugs

The treatment for autism includes two categories: pharmacological and non-pharmacological: non-pharmacological treatments include parent education (Kilpatrick et al., 2001), applied behavioural analysis (ABA) (Cooper et al., 2007), treatment and education of children with autism (Schopler et al., 2010), and cognitive-behavioural therapy (CBT) (Wood et al., 2009; Reaven et al., 2012). Atypical antipsychotic drugs called risperidone and aripiprazole can be used to treat aggressive and self-harming behaviours caused by autism (Leskovec et al., 2008; Rapin and Tuchman, 2008; Ji and Findling, 2015). Fluoxetine and fluvoxamine can be used to reduce ritualistic and repetitive behaviours. Methylphenidate is also used to treat hyperactivity in children with autism (Dubowitz et al., 2008).

3.4.2 Treatment of autism spectrum disorders and bioactive compounds

Luteolin, a natural plant flavonoid, significantly counteracted IL-6 in astrocytes (Gullotta et al., 1985; Zuiki et al., 2017; Deb et al., 2020) and exhibited neuroprotective, anti-inflammatory activities (Bertolino et al., 2017). Luteolin formulation (NeuroProtek®) was prescribed accompanied to the drugs of children with ASD (Theoharides et al., 2012). Thus, luteolin was used for managing autistic behaviour and improvement of social behaviour (Chen et al., 2008; Tsilioni et al., 2015; Xu et al., 2015). Luteolin also inhibited the stimulation of activated T cells and reduced inflammatory molecules (Kritas et al., 2013). Daily intake of green tea extract (*Camellia sinensis*), a polyphenols source, is proved to exhibit health effects (Schimidt et al., 2017). This plant enhanced the locomotion activity in valproate-induced autistic mice (Banji et al., 2011; Takeda et al., 2011; Sundberg and Sahin, 2015; Kumaravel et al., 2017; Urdaneta et al., 2018). Major antioxidant enzymes such as superoxide dismutase were increased by catechin, in autistic children (Rossignol and Frye, 2014). The action of the piperine, a major alkaloid isolated from pepper species, displays considerable anti-oxidative effects and enhancement of memory with the regulation of Ca^{2+} ion entry into the neurons and the presynaptic release of glutamine (Wattanathorn et al., 2008; Fu et al., 2010; Pragnya et al., 2014). Piperine is progressing its future beneficial effects in autistic children (Wattanathorn et al., 2008).

Curcumin in *Curcuma longa* was found for its neuroprotective activities and cellular signalling role in regulating oxidative stress (Salehi et al., 2020). Moreover, curcumin could reduce inflammatory factors in diseases and exhibit antioxidant radical scavenging activities (Salehi et al., 2019a; Quispe et al., 2022). As a potential treatment for autism, Ginkgo Biloba extract was used accompanied by risperidone. The results showed that the treated group indicated fewer adverse effects as compared to the control group (Hasanzadeh et al., 2012). Several studies investigated the role of antioxidants and natural anti-inflammatory products such as curcumin, resveratrol, naringenin, and piperine to reduce the symptoms of autism spectrum disorder (*in vivo* and *in vitro*). In a study, curcumin increased the level of antioxidant enzymes and helped diminish dysfunctions. Curcumin in the dose of 200 mg/kg in autistic rats can attenuate oxidative stress and release tumor necrosis factor (TNF-α). However, exploring their potential clinical effects and drug delivery methods is essential (Fu et al., 2010; Al-Askar et al., 2017). Table 5 summarizes the effects of bioactive compounds as potential agents in the treatment of autism.

3.5 Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) is a mental-behavioural disorder associated with the development of the nervous system that presents with symptoms such as inattention, excessive energy, hyper-fixation, and impulsivity (American Psychiatric Association, 1980; Cotterill, 2019). These people have difficulty controlling their emotions and have difficulty in executive activities (Mandah and Osuagwu, 2020). The exact cause of the disease is not yet fully understood, but in more than 75% of cases, genetic causes are involved (Mandah and Osuagwu, 2020). Also, dysfunction of neurotransmitters such as dopamine and norepinephrine (Chandler et al., 2014; Stansfield, 2019) and signs of signal change in the Central Nervous System (CNS) such as paradoxical reaction is observed in this regard (Langguth et al., 2011). It affects 6%–7% of people in the age group of 18 years (Willcutt, 2012) and the incidence of the disease in men is three times higher than in women (Singh, 2008).

TABLE 5 Natural products used in the treatment of autism.

Disease	Main group of compounds		Neuro-biological functions	References
Autism	Polyphenols	Luteolin	neuroprotective	Bertolino et al. (2017)
			anti-inflammatory	Kritas et al. (2013)
			↓mast cell-dependent stimulation of activated T cells	
			↓histamine	
			↓leukotrienes	
		Camellia sinensis	↑dopamine	Takeda et al. (2011)
			↑serotonin	
		Curcumin	Attenuates oxidative stress	(Fu et al., 2010) (Al-Askar et al., 2017) (Salehi et al., 2020)
			↓ TNF- α	
			↑ neuroprotective properties	

TABLE 6 Bioactive compounds and their mechanism of action used as potential drugs in the treatment of ADHD.

Disease	Main group of compounds	Neuro-biological functions	Refs
ADHD	Ginkgo	↑cerebrovascular blood flow	Nourbala and Akhoundzadeh, (2006)
		↓hyperactivity due to boredom and lack of focus	
	Panax quinquefolium	Improvement of social problems measure	(Lyon et al., 2001) (Trebatická et al., 2006)
	Lobeline	↑ memory capacities	Martin et al. (2018)
	Bacopa monnieri	↓inattention	Kean et al. (2022)
		↓ error-making	
		↓ hyperactivity	
	Pine bark extract	↓inattention	Hsu et al. (2021)
		↓ hypersensitivity	
		↓ hyperactivity	

3.5.1 Treatment of attention deficit hyperactivity disorder using approved drugs

Treatments for this disease include behavioural therapies such as psychoeducational input, behaviour therapy, cognitive behavioural therapy, interpersonal psychotherapy, family therapy, school-based interventions, social skills training, behavioural peer intervention, organization training, and parent management training (Health, 2009; Evans et al., 2018; Lopez et al., 2018); Medical counselling; Medications such as stimulants, atomoxetine, alpha-2 adrenergic receptor agonists, and sometimes antidepressants (Wilens and Spencer, 2010; Bidwell et al., 2011); or as a combination therapy. Some studies have recommended the use of methylphenidate (Storebø et al., 2015).

3.5.2 Treatment of attention deficit hyperactivity disorder and bioactive compounds

Natural products, which may be potentially used in the treatment of ADHD were presented in Table 6. American ginseng (*Panax quinquefolium*) in children with ADHD improved significantly on a social problems measure (Lyon et al., 2001; Trebatická et al., 2006). Another plant, *Ginkgo biloba* enhanced cerebrovascular blood flow and reduced hyperactivity due to the lack of focus (Nourbala and Akhoundzadeh, 2006). It has been documented that *Passiflora* might be a novel therapeutic agent for treating ADHD (Salehi et al., 2010; Uebel-von Sandersleben et al., 2014). One study in adults with ADHD revealed that lobeline as an alkaloid improves working memory in patients with no significant impact on the attention noted (Martin et al., 2018). Whereas, a comprehensive study is needed to make more definitive statements regarding the effect of lobeline and the usage of methylphenidate. Lobeline could have different effects based on individual differences. Some pediatric patients with ADHD use natural products such as flavonoids. Although herbal remedies are generally considered safe when used appropriately with other treatment strategies (Martin et al., 2018).

A double-blind and placebo-controlled randomized trial (112 males aged 6–14 years) in a population of males supplemented with *Bacopa monnieri* extract showed the reduction of hyperactivity, inattention and decreased error-

TABLE 7 Phytochemicals and their potential effects in treatment and prevention of neuropsychiatric disorders in epilepsy.

Compounds	Main group of compounds	Verified effective concentrations/model	Potential effects	References
Alkaloids	Aconitum	IC_{50} = 0,1–1 μM rats hippocampal slices	↓GABA	Ameri et al. (1996)
	in vitro		↓epileptiform activity	
Isoquinoline alkaloids	Montanine	Dose = 64.7–67.6 mg/kg rats	modulation of benzodiazepine $GABA_A$ receptors	Da Silva et al. (2006)
		in vivo		
	Berberine	Dose = 10–20 mg/kg/i.p. mice	modulation of neurotransmitter systems	Bhutada et al. (2010)
		in vivo		
	Tetrahydropalmatine	Dose = 10–30 mg/kg/i.p. mice	↓dopamine output	Lin et al. (2002)
		in vivo	↑ cholinergic receptor function	
	Palmatine	Dose = 450 μM/7 days	↓ locomotor activity	Gawel et al. (2020)
		Zebrafish	↓ BDNF and c-fos levels	
		in vivo	↓ number and mean duration of events	
Amide alkaloid	Piplartine	Dose = 50–100 mg/kg/ i.p. mice	↓epileptiform activity	Felipe et al. (2007)
		in vivo		
Ergot alkaloids	no data	different doses	effects at dopaminergic and serotoninergic synapses	Anlezark and Meldrum, (1978)
		in vivo and *in vitro*		
Piperidine alkaloids	piperine	Dose = 1–2.5 mg/kg/i.p. mice	modulation of the GABAergic system	Da cruz et al. (2013)
		in vivo		
Flavonoids	Hesperidin	Dose = 500 mg/kg mice	↓convulsant effects of PTZ	(Dimpfel, 2006; Kumar et al., 2014)
		in vivo	↓effects of enhanced calcium	
	Apigenin	Dose = 25–50 mg/kg rats	↓GABA-activated chloride ion channel	Avallone et al. (2000)
		in vivo	GABA antagonist	
			↑effect of diazepam of GABA receptors	
	Fisetin	Dose = 10–25 mg/kg mice	antioxidant	Raygude et al. (2012)
		in vivo	↓oxidative damage modulating GABAergic transmission	Liu et al. (2012)
	Wogonin	Dose = 5–10 mg/kg rats	↑ Cl^- influx	Park et al. (2007)
		in vivo	↓ GABA	
	Baicalein	Dose = 100 mg/kg rats and mice	↑Cl^- influx antioxidant	(Yoon et al., 2011; Liu et al., 2012)
		in vivo		
	Chrysin	Dose = 3 mg/kg rats and mice	Acting on central BZD receptors	Medina et al. (1990)
		in vivo		
	Oroxylin A	Dose = 3.67–60 mg/kg rats	antagonistic effects by adverse action on α-2,3,5 subunits of the GABA receptor	Huen et al. (2003)
		in vivo		
	Luteolin	Dose = 10 mg/kg rats	↓frequency of seizures	Birman et al. (2012)
		in vivo		
	Hispidulin	Dose = 10 mg/kg rats	positive modulator of GABA receptors	(Kavvadias et al., 2004; Lin et al., 2012)
		in vivo	↓voltage-dependent Ca^{2+} entry directly interfering with the exocytotic	
	Naringenin	Dose = 20–40 mg/kg rats	modulation of the benzodiazepine site of the GABA receptors	(Golechha et al., 2014; Shakeel et al., 2017)
		in vivo	↓lipid peroxidation	
			↓seizures	
	Rutin	Dose = 90 mg/kg, i.p. rats	Interacting with GABAAbenzodiazepine receptor	Nassiri-asl et al. (2008)
		in vivo		
	Vitexin	Dose = 90 mg /kg, i.p. rats	↑GABA	Abbasi et al. (2012)
		in vivo	↓oxidative injury	

(Continued on following page)

TABLE 7 (*Continued*) Phytochemicals and their potential effects in treatment and prevention of neuropsychiatric disorders in epilepsy.

Compounds	Main group of compounds	Verified effective concentrations/model	Potential effects	References
			Terpenoids	
	α-Terpineol	Dose = 100, 200,400 mg/kg rats	Protective effects against PTZ- and MES-induced convulsive seizures in mice	(De Sousa et al., 2007; Silva et al., 2009)
		in vivo		
	Carvacrol borneol	Dose = 50, 100, 200 mg/kg mice	↓GABA	Quintans-Júnior et al. (2010)
		in vivo		
	Isopulegol	Dose = 200 mg/kg rats	Positive modulation of benzodiazepine sensitive	Silva et al. (2009)
		in vivo	GABA receptors antioxidant	
	Eugenol	Dose = 100 mg/kg rats	↓neuronal excitability	Huang et al. (2012)
		in vivo	↑Ina inactivation	
			↓INa (NI)	
	Ursolic acid	Dose = 2.3 mg/kg rats and mice	↓GABA	(Taviano et al., 2007; Kazmi et al., 2012)
		in vivo		
Saponins	Saikosaponin	$IC_{50=}$1 μM *in vitro*	Voltage-gated sodium channel blocking	(Yu et al., 2012; Zhu et al., 2014)
	saponins fractions	Dose = 1, 2, 4 mg/kg mice	↓GABA	Singh and Goel, (2016)
		in vivo	↓calcium and sodium channel functions	
Phenolic compounds	6-gingerol	Dose=37.5 μM/6 days	↓GLU level	(Gawel et al., 2021)
		Zebrafish	↓GLU/GABA ratio	
		in vivo	↓ frequency of seizures	
			↓ length of seizures	
Coumarins	Esculetin	Dose = 1, 2, 5 mg/kg mice	↓seizures	Woo et al. (2011)
		in vivo	↓GABA	
	Osthole	Dose = 259–631 mg/kg mice	GABA modulation	(Luszczki et al., 2009; Łuszczki et al., 2010; Zhu et al., 2014)
		in vivo		
	Imperatorin	Dose = 300 mg/kg mice		
		in vivo		
	Oxypeucedanin	Dose = 300 mg/kg mice		
		in vivo		

making (Kean et al., 2022). Another clinical trial performed in a group of twenty males and females aged 10 ± 2.1 years described by Hsu and co-investigators (2021) denotes that the administration of 25 or 50 mg pine bark extract for 14 days resulted in a significant reduction of in inattention, hyperactivity, and impulsivity.

3.6 Psychiatric disorders associated with epilepsy

Epilepsy is a neurological diseases manifested by recurrent seizures is called epilepsy, which is classified as short and short periods to long and severe periods (Sharifi-Rad et al., 2021b; Kwon et al., 2022). The main mechanisms of epilepsy include abnormal activity in the cerebral cortex, brain damage, stroke, brain tumours, various brain infections, and genetic defects at birth (Begley et al., 2022; Kanner and Bicchi, 2022). The prevalence of this disease varies in different countries and is generally 7.6 people per 1,000 people (Kelvin et al., 2007; Fiest et al., 2017). The incidence of epilepsy is higher in men than in women and affects very young and very old people (Fiest et al., 2017).

3.6.1 Treatment of epilepsy using approved drugs

There are many treatments for epilepsy, including surgery (such as cutting the hippocampus, removing tumors, and removing part of the neocortex) (Ryvlin et al., 2014), specific

diet (for instance ketogenic diet) (Martin-McGill et al., 2020), avoidance therapy (reducing or eliminating certain triggers factors such as excessive light) (Verrotti et al., 2005), exercise (Arida et al., 2009), and medication such as midazolam, diazepam (Uk, 2012), lorazepam, phenytoin, lamotrigine, levetiracetam (Uk, 2012), carbamazepine, and valproate, etc. (Nevitt et al., 2018; Nevitt et al., 2019). In Table 2 are summarized data regarding used current pharmacological therapies.

3.6.2 Treatment of epilepsy and bioactive compounds

Lycopene, a carotenoid antioxidant, has neuroprotective properties against oxidative stress and mitochondrial dysfunction in PTZ-induced seizures of epilepsy (Sakurada et al., 2009; Bhardwaj and Kumar, 2016) (Table 7. Some authors reported that the extract of *Nardostachys jatamansi* (Valerianaceae) and the synergistic use with phenytoin reduced mental weakness as well as enhanced the seizure threshold in the animal model of generalized tonic-clonic seizures (Luszczki et al., 2009; Jiang et al., 2015). Aconitum alkaloids induce their anticonvulsant activities via interaction with voltage-dependent Na^+ channels in various experimental models, including PTZ (Charveron et al., 1984; Chen et al., 1996; Lin et al., 2002; Da Silva et al., 2006; Felipe et al., 2007; Da cruz et al., 2013) (Table 7).

Many flavonoids like hesperidin that prevent tonic-clonic seizures increased the protective effect of N-nitro-L-arginine methyl ester (L-NAME) on kindling induced by pentylenetetrazole (PTZ) as well as enhanced diazepam's effect. Phytochemicals and their biological function in the treatment of mentioned neuropsychiatric diseases except psychiatric disorders associated with epilepsy are summarized in Table 7 (Fernández et al., 2005; Kumar et al., 2013; Kumar et al., 2014). Apigenin acts as a GABA antagonist at flumazenil-insensitive $\alpha_1\beta_2$ GABA receptors (Avallone et al., 2000). In addition, naringin has an anticonvulsant effect in kainic acid and PTZ models (Golechha et al., 2011; Golechha et al., 2014; Jeong et al., 2015). An alkaloid, piperine, has been recognized as an adjunct therapy with antiepileptic drugs, carbamazepine, and phenytoin. Administration of piperine could increase the bioavailability of synthetic anti-epilepsy drugs and decrease the adverse effects of synthetic drugs by diminishing the dose. On the other hand, apigenin, a flavonoid, can decrease the myeloperoxidase-mediated oxidative stress and inhibit cell death dependent on iron. It is characterized by the accumulation of lipid peroxides (ferroptosis) for rapidly discovering additional antiepileptic agents to prevent and treat epilepsy. Moreover, apigenin and other flavonoids have potentially antiepileptic and neuroprotective activity by inhibiting the glutamate receptors in mice (Aseervatham et al., 2016; Shao et al., 2020).

Zebrafish model was found to be an efficient screening method for the development of new drug candidates with antiseizure properties. In the studies of Gawel and co-investigators, palmatine from *Beberis sibirica* and 6-gingerol isolated from *Zingiber officinale* were effectively reducing the length of seizures and their number. The effect of 6-gingerol administration might have been achieved by the reduced glutamate and glutamate-to-GABA ratio levels in the fish brains analyzed by HPLC-MS instrumentation (Gawel et al., 2021). The administration of palmatine (450 μM, 7 days) decreased *c-fos* and BDNF levels, whereas, in the behavioral assay, palmatine decreased locomotor activity of animals. The described activity was higher in the combination with berberine (Gawel et al., 2020).

4 Limitations, challenges and clinical gaps

Psychiatric disorders are mental health problems characterized by different symptoms. The classification of mood disorders is still ambiguous. Some categories are defined as subgroups due to the symptoms (Enatescu et al., 2020; Trofor et al., 2020). The cause of these disorders is social, environmental, genetic issues, or psychotropic drugs. Neurological and psychiatric disorders account for 13% of the world's total complications (Mondiale de la Santé, 2013). Many natural remedies are alternative procedures to increase the effectiveness of prescription drugs (Akhondzadeh, 2007; Salehi et al., 2019b; Sharifi-rad et al., 2021a). Herbal medicines contain a wide range of medicinal compounds with therapeutic effects (Butnariu et al., 2022; Taheri et al., 2022). Nowadays, many synthetic drugs originated from herbal medicines (Sharifi-rad et al., 2021d; Alshehri et al., 2022). Herbal medicines are still used in many diseases, primarily mental and neurological disorders (Sharifi-Rad et al., 2021c; Tsoukalas et al., 2021). According to the group of authors, plants used in traditional medicine contain main groups of components (Hossain et al., 2022; Painuli et al., 2022; Sharifi-Rad et al., 2022). Tropane alkaloids (antagonists of acetylcholine) known as atropine, scopolamine, and hyoscyamine isolated from *Datura* sp. have some anticholinergic activities (Taïwe and Kuete, 2014). For instance, scopolamine is an anti-muscarinic used as a sedative and analgesic (Steenkamp et al., 2004). The anti-muscarinic and anticholinergic effects of these compounds may explain the use of *Datura* in treating mental illness (Maiga et al., 2005). Anxiety effects and neuroprotective activity have been reported in flavonoids. They can bind to GABA receptors with significant affinity (Zhang, 2004). Quercetin significantly reduces ischemic brain damage (Lake, 2000; Dajas et al., 2003; Guenne et al., 2016).

The therapeutic limitations of these compounds are represented by cytotoxic and cardiotoxic effects and must be used with caution (Al-snafi, 2015). For example, securinin acts like strychnine in the range of 5–30 g/kg and causes spasms and death due to respiratory arrest (Maiga et al., 2005). Therefore, controlled use of these herbs should be promoted.

Integrative medicine concerning mental health is a concept that has developed a lot lately, in the conditions in which psychiatry no longer communicates notable advances in psychopharmacology in recent years. In this conjuncture of relative pharmacological stagnation, the complementary natural therapies capture the psychiatric patient, to the detriment of the indications from the treatment guidelines accepted by the psychiatric specialists. But extensive research to explore the combination of bioactive natural componds with synthetic psychotropic drugs in the treatment of mental disorders is needed in the future.

The limitations of the current review are the inclusion in the study of evidence from preclinical pharmacological models, and meta-analyzes focused on the therapeutic impact of bioactive compounds in psychiatric diseases and not from individual clinical trials. On the other hand, the inclusion and analysis of these meta-analyzes is a strong point of this review, as they focused on potential pharmacological mechanisms of action, thus opening new therapeutic windows beneficial to natural bioactive compounds in the therapy of neuropsychiatric diseases.

Although comparative studies have been scrutinized in the pre-clinical area, no clinical trial has been found where herbal medicines are compared to drugs approved by the FDA for the treatment of psychiatric disorders. This is very important to highlight because it must be clear that evidence for the clinical efficacy of these products is not confirmed by head-to-head comparative studies and the conclusions concerning their efficacy derive only from preclinical experimental studies.

5 Overall conclusion

There are many factors behind the growing popularity of herbal remedies for a variety of chronic diseases. Many people who use herbal remedies know that health care alternatives are more in line with their values, beliefs, and philosophical orientations towards health and life. Although many chemical drugs are available to treat mental disorders, clinicians have found that many patients are unable to tolerate the side effects of chemical drugs or do not respond well enough. Many herbal remedies have far fewer side effects. Therefore, they can be used as an alternative treatment and could increase the effectiveness of prescription drugs. While the demand for herbal medicines is increasing, herbal extracts and active ingredients isolated from them need to be scientifically approved before being widely accepted and used. Therefore, "phytochemicals" may guarantee a new source of beneficial neuroleptics.

Author contributions

All authors contributed and made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. That is, revising or critically reviewing the article; giving final approval of the version to be published; agreeing on the journal to which the article has been submitted; and, confirming to be accountable for all aspects of the work.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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