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 alternative treatment option in the treatment of neuropsychiatric disorders is gaining more attention.

**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; Wolif et al., 2015). Its lifetime prevalence is 16.6% per person (Weisman and Olifon, 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 serotoninergic, 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 amitriptilin, 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 (Gerici 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).
| 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)                                                               | Serotonin reuptake inhibitors (SSRIs)                                                   |                                                                            |
|                  | Paroxetine (Paxil, Paxil CR)                                                         | Serotonin reuptake inhibitors (SSRIs)                                                   |                                                                            |
|                  | Sertraline (Zoloft)                                                                  | Serotonin reuptake inhibitors (SSRIs)                                                   |                                                                            |
|                  | Fluvoxamine (Luvox)                                                                  | Serotonin reuptake inhibitors (SSRIs)                                                   |                                                                            |
|                  | Fluoxetine (Prozac)                                                                  | Serotonin reuptake inhibitors (SSRIs)                                                   |                                                                            |
|                  | Venlafaxine (Effexor, Effexor XR)                                                    | Serotonin-norepinephrine reuptake inhibitors (SNRIs)                                    | (Stahl et al., 2005)                                                      |
|                  | Desvenlafaxine (Pristiq)                                                             | Serotonin-norepinephrine reuptake inhibitors (SNRIs)                                    |                                                                            |
|                  | Duloxetine (Cymbalta)                                                                | Serotonin-norepinephrine reuptake inhibitors (SNRIs)                                    |                                                                            |
|                  | 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)                                                             | Blocking the activity of serotonin 5-HT2 receptors                                      |                                                                            |
|                  | Desipramine (Norpramin)                                                              | Blocking the activity of serotonin 5-HT2 receptors                                      |                                                                            |
|                  | Nortriptyline (Pamelor)                                                              | Blocking the activity of serotonin 5-HT2 receptors                                      |                                                                            |
|                  | Protriptyline (Vivactil)                                                              | Blocking the activity of serotonin 5-HT2 receptors                                      |                                                                            |
|                  | Amoxapine (Asendin)                                                                  | Blocking the activity of serotonin 5-HT2 receptors                                      |                                                                            |
|                  | Maprotiline (Ludiomil)                                                               | Blocking the activity of serotonin 5-HT2 receptors                                      |                                                                            |
|                  | Phenelzine (Nardil) Tranylcypromine (Parnate)                                        | Blocking the activity of serotonin 5-HT2 receptors                                      |                                                                            |
|                  | Isocarboxazid (Marplan)                                                              | Blocking the activity of serotonin 5-HT2 receptors                                      |                                                                            |
|                  | Selegiline (Eldepryl)                                                                | Blocking the activity of serotonin 5-HT2 receptors                                      |                                                                            |
|                  | Selegiline transdermal (Emsam)                                                       | Blocking the activity of serotonin 5-HT2 receptors                                      |                                                                            |
| Schizophrenia    | First-generation antipsychotics (Phenothiazines, Butyrophenones, Thioxanthenes,     | Dopamine antagonist (Blocking dopamine receptors)                                       | Freedman, (2010)                                                          |
|                  | Dibenzepines, Dihydroindolones, Diphenylbutylpiperidines)                           | Dopamine antagonist (Blocking dopamine receptors)                                       |                                                                            |
|                  | Second-generation antipsychotics (clozapine, olanzapine, quetiapine, risperidone,   | 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) |
|                  | paliperidone, ziprasidone, and molindone)                                           | Serotonin-Dopamine Antagonists (D2, 5-HT1A, and 5-HT2A receptors)                       |                                                                            |
|                  | Third-generation antipsychotics (aripiprazole, brexpiprazole and cariprazine)       | D2 partial agonists                                                                     | (Burris et al., 2002; Shapiro et al., 2003; De Deurwaerder, 2016; Hope et al., 2018) |
| Autism           | Risperidone                                                                         | Serotonin-Dopamine Antagonists                                                         | (Leskovec et al., 2008; Rapin and Tuchman, 2008; Ji and Findling, 2015)   |
|                  | Aripiprazole                                                                         | Serotonin-Dopamine Antagonists                                                         |                                                                            |
|                  | 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)                                       | Storebo 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  |                                                                            |
|                  | Guanfacine                                                                           | Norepinephrine—dopamine reuptake inhibitor (NDRI) and antagonist of several nicotinic  |                                                                            |
|                  | clonidine                                                                           | Activating a2A adrenoceptors                                                            |                                                                            |
|                  |                                                                                     | Agonist of alpha-2A adrenergic receptor                                                 |                                                                            |

(Continued on following page)
Polyphenols like curcumin (*Curcuma longa*) are strongly recommended in the treatment procedures for MDD (Darvesh et al., 2013) (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 (Crockley 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; Soofiyan 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 fluzoxetine 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 flavonoid—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) (Yusoh’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; Haleagrahara et al., 2009; Clarke and Ramsay, 2011; Lam et al., 2012; Soofiyan 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 fluzoxetine 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).

### 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                                   | (Chiu et al., 2014) (Chiu et al., 2017) (Gercke and Van Wyk, 2001b) (Napoletano et al., 2001) (Houlay et al., 2005) |
| Curcumin        |                         | Dose = 5–10 mg/kg mice                 | ↑ serotonin in the frontal cortex and hippocampal brain                           | (Xu et al., 2005b; Darvesh et al., 2012)                                  |
| Phenolic Phytochemicals | in vivo              |                                        | ↑ serotonin                                                                  | (Chiu et al., 2014) (Chiu et al., 2017) (Gercke and Van Wyk, 2001b) (Napoletano et al., 2001) (Houlay et al., 2005) |
| Amentoflavone   |                         | Dose = 6.25–50 mg/kg mice              | ↑ immobility inhibition flumazenil binding to GABA receptor                       | Ishola et al. (2012), Baureithel et al. (1997)                             |
| Chlorogenic acid|                         | Dose = 200–400 mg/kg mice              | ↑ MAOB, ↑ ROS, ↑ axon and dendrite growth, ↑ serotonin release through enhancing synapsin expression act through the opioidergic pathway ↑ neuroinflammation and oxidative stress | (Wu et al., 2016; Lim et al., 2018) (Park et al., 2010) (Chen et al., 2021) |
| Ellagic acid    |                         | Dose = 25–100 mg/kg mice              | ↑ 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              | ↑ serotonin reuptake anti-inflammatory antioxidant                               | (Zeni et al., 2012) (Sasaki et al., 2019)                                   |
| Fisetin         |                         | Dose = 10–25 mg/kg mice                | ↑ MAO, ↑ 5-HT, ↑ NA, ↑ DA reuptake                                             | (Zheng et al., 2008; Zhen et al., 2012; Yao et al., 2020)                  |
| Quercetin       |                         | Dose = 50–100 mg/kg mice               | ↑ MAO isoenzymes, ↑ BDNF, ↓ MAO isoenzymes, ↓ serotonin uptake                  | (Anjaneyulu et al., 2003; Clarke and Ramsay, 2011) (Yoshino et al., 2011) (Fang et al., 2020) |
| Resveratrol     |                         | Dose = 20–80 mg/kg mice                | ↑ immobility period in mouse models of behavioral despair without affecting locomotor activity ↑ noradrenaline, ↑ serotonin uptake | (Yáñez et al., 2006; Xu et al., 2010a)                                     |
| Hesperidin      |                         | Dose = 0.1–1 mg/kg mice                | ↑ immobility period and the antidepressant-like activity was independent of alterations in locomotor activity anti-inflammatory ↑ antioxidant activity | (Raza et al., 2011; Carlos Filho et al., 2013)                             |
| Rutin           |                         | Dose = 0.1–3 mg/kg mice                | ↓ 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               | ↑ immobility in the TST                                                          | (Olisen et al., 2008) (Olisen et al., 2008) (Olisen et al., 2008) (Olisen et al., 2008) |

(Continued on following page)
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 |
|-------------------------|-------------------------|------------------------------------------|-----------------------------------------------------------------------------------|------------|
| 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 | Ludovico et al. (2020) |
| Iridoids                | Geniposide              | Dose = 25, 50, 100 mg/kg rats in vivo    | Upregulation the hypothalamic GRα mRNA level Upregulation the GRα protein expression | Cai et al. (2015) |
| Coumarins               | Scopoletin              | Dose = 1–100 mg/kg mice in vivo          | Activation of postsynaptic α1- and α2-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, tumour necrosis alpha; IL, interleukin; SOD, superoxide dismutase; MAO, monoaminooxidase; 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 zebra fish anxiety model, similarly to fluoxetine. In another study, a coumarin–scopolentin 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 responses 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, Hosseiniwasab 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 buproprion 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
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 (Hosseinzaehed 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 monoterpenes 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 b. w) administered for 14 days decreased the hyperlocomotion of the animals, induced the antioxidant properties and prevented the cholinergic dysfunctions 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

### 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) |
|               | Polygono musin leaf extract | L-SPD                 | agonist on D1 receptors in the medial prefrontal cortex (mPFC) | Mo et al. (2007) |
|               | Coumarin                | Scopoletin               | ↓ cortisol level in zebrafish model | (Nurhidayaha et al., 2022) |
|               | Anthraquinone           | Emodin                   | ↑ phosphorylation process of both ErbB1 and ErbB2 | Mitra et al. (2022) |
|               | Phenolic compounds      | Curcumin                 | ↓ pre-pulse inhibition and improvement of startle reponses in rats dose = 15–50 mg/kg b.w | (Hossain et al. 2021) |

### 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 | Nourbala and Akhoundzadeh, (2006) |
|               | Monoterpenes            | ↑ hyperactivity           | Nogoceke et al. (2016) |
|               | Carvone                 | ↑ locomotor activity sodium channels blockage | (Recart et al. 2021) |
|               | Phenolic compounds      | ↓ free radicals formation | (Kanazawa et al. (2016), Kanazawa et al. (2017) |
|               | Gallic acid             | ↓ hyperactivity prevented cholinergic dysfunctions | (Kanazawa et al. (2016), Kanazawa et al. (2017) |
|               | Quercetin               | ↓ protein kinase C         | (Kanazawa et al. (2016), Kanazawa et al. (2017) |
|               |                        | ↓ hyperlocomotion          | (Kanazawa et al. (2016), Kanazawa et al. (2017) |
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 Kłakowski, 2015; Isaeyan 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 compounds which are used in the treatment of bipolar disorders. 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 (Schimdt 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 Ca²⁺ 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).
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-
| Compounds            | Main group of compounds | Verified effective concentrations/model | Potential effects                                                                 | References                        |
|----------------------|-------------------------|-----------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------|
| **Alkaloids**        | Aconitum                | IC₅₀ = 0.1–1 µM rats hippocampal slices | ↓ GABA                                                                             | Ameri et al. (1996)               |
| **Isoquinoline**     | Montanine               | Dose = 64.7–67.6 mg/kg rats             | modulation of benzodiazepine GABA<sub>A</sub> receptors                           | Da Silva et al. (2006)            |
|                      | Berberine               | Dose = 10–20 mg/kg/i.p. mice            | modulation of neurotransmitter systems                                           | Bhutada et al. (2010)            |
|                      | Tetrahydropalmatine     | Dose = 10–50 mg/kg/i.p. mice            | ↓ dopamine output                                                                  | Lin et al. (2002)                 |
|                      | Palmatine               | Dose = 450 µM/7 days                    | ↓ locomotor activity                                                               | Gaswel et al. (2020)              |
|                      | Zebrafish               |                                         | ↓ BDNF and c-fos levels                                                            |                                   |
|                      | Amide alkaloid          | Pipilartine                             | ↓ epileptiform activity                                                            | Felipe et al. (2007)              |
| **Ergot alkaloids**  |                         | no data                                 | different doses                                                                    | Anlezark and Meldrum, (1978)      |
| **Piperidine**       | piperine                | Dose = 1–2.5 mg/kg/i.p. mice            | modulation of the GABAergic system                                                | Da cruz et al. (2013)             |
| **Flavonoids**       | Hesperidin              | Dose = 500 mg/kg mice                   | ↓ convulsant effects of PTZ                                                        | (Dimpfel, 2006; Kumar et al., 2014)|
|                      | Apigenin                | Dose = 25–50 mg/kg rats                 | ↓ GABA-activated chloride ion channel                                              | Avallone et al. (2000)            |
|                      | Fisetin                 | Dose = 10–25 mg/kg mice                 | antioxidant                                                                      | Raygude et al. (2012)             |
|                      | Wagonin                 | Dose = 5–10 mg/kg rats                  | ↑ Cl<sup>-</sup> influx                                                          | Park et al. (2007)                |
|                      | Baicalin                | Dose = 100 mg/kg rats and mice          | ↑ Cl<sup>-</sup> influx antioxidant                                             | (Yoon et al., 2011; Liu et al., 2012)|
|                      | Chrysin                 | Dose = 3 mg/kg rats and mice            | Acting on central RZD receptors                                                   | Medina et al. (1996)             |
|                      | 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)                |
|                      | Luteolin                | Dose = 10 mg/kg rats                    | ↓ frequency of seizures                                                           | Birman et al. (2012)             |
|                      | Hispidululin            | Dose = 10 mg/kg rats                    | positive modulator of GABA receptors                                              | (Kavvadas et al., 2004; Lin et al., 2012)|
|                      | Naringenin              | Dose = 20–40 mg/kg rats                 | modulation of the benzodiazepine site of the GABA receptors                        | (Golechha et al., 2014; Shakzad et al., 2017)|
|                      | Rutin                   | Dose = 90 mg/kg, i.p. rats              | Interacting with GABA Abenzodiazepine receptor                                    | Nassiri-ali et al. (2008)         |
|                      | Vitexin                 | Dose = 90 mg/kg, i.p. rats              | ↑ GABA                                                                            | Abbasi et al. (2012)              |

(Continued on following page)
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 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; Fies et al., 2017). The incidence of epilepsy is higher in men than in women and affects very young and very old people (Fies 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

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**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 |
|-----------|--------------------------|----------------------------------------|-------------------|------------|
| α-Terpineol| Dose = 100, 200,400 mg/kg rats | Terpenoids | Protective effects against PTZ- and MES-induced convulsive seizures in mice | (De Sousa et al., 2007; Silva et al., 2009) |
| Carvacrol borneol| Dose = 50, 100, 200 mg/kg mice | GABA | | (Quintans-Júniorm e et al., 2010) |
| Isopulegol| Dose = 200 mg/kg rats | Positive modulation of benzodiazepine sensitive GABA receptors antioxidant | Silva et al. (2009) |
| Eugenol| Dose = 100 mg/kg rats | ↑ neuronal excitability, ▼ INa inactivation | Huang et al. (2012) |
| Ursolic acid| Dose = 2.3 mg/kg rats and mice | GABA | | (Taviano et al., 2007; Kazmi et al., 2012) |
| Saponins| Saikosaponin IC50=1µM in vitro | Voltage-gated sodium channel blocking | (Yu et al., 2012; Zhu et al., 2014) |
| Phenolic compounds| 6-gingerol Dose=37.5 µM/6 days | ▼ GLU level | (Gawel et al., 2021) |
| Coumarins| Esculetin Dose = 1, 2, 5 mg/kg mice | ▼ frequency of seizures, ▼ length of seizures | | (Wo et al., 2011) |
| | Osthole Dose = 259–631 mg/kg mice | GABA modulation | | (Łuszczki et al., 2009; Łuszczki et al., 2010; Zhu et al., 2014) |
| | Imperatorin Dose = 300 mg/kg mice | | | |
| | Oxypeucedanin Dose = 300 mg/kg mice | | | |

...
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 (Luszczi 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 methyl ester (L-NAME) on kindling induced by methionine sulfoximine (MSO) in PTZ-induced seizures of epilepsy (Avallone et al., 2000). In addition, naringin is 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 (ferropotosis) 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 Gavel 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 (Gavel 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 (Gavel 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 (Bunariu 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 (agonists of acetylcholine) known as atropine, scopolamine, and hyoscynamine isolated from *Datura* sp. have some anticholinergic activities (Tätwe 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; Guerne et al., 2016).

The therapeutic limitations of these compounds are represented by cytotoxic and cardiotoxic effects and must be used with caution (Al-snaifi, 2015). For example, securinact 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 compounds 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-analyses 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-analyses 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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