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Phytochemicals That Act on Synaptic Plasticity as Potential Prophylaxis against Stress-Induced Depressive Disorder

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Abstract

Depression is a neuropsychiatric disorder associated with persistent stress and disruption of neuronal function. Persistent stress causes neuronal atrophy, including loss of synapses and reduced size of the hippocampus and prefrontal cortex. These alterations are associated with neural dysfunction, including mood disturbances, cognitive impairment, and behavioral changes. Synaptic plasticity is the fundamental function of neural networks in response to various stimuli and acts by reorganizing neuronal structure, function, and connections from the molecular to the behavioral level. In this review, we describe the alterations in synaptic plasticity as underlying pathological mechanisms for depression in animal models and humans. We further elaborate on the significance of phytochemicals as bioactive agents that can positively modulate stress-induced, aberrant synaptic activity. Bioactive agents, including flavonoids, terpenes, saponins, and lignans, have been reported to upregulate brain-derived neurotrophic factor expression and release, suppress neuronal loss, and activate the relevant signaling pathways, including TrkB, ERK, Akt, and mTOR pathways, resulting in increased spine maturation and synaptic numbers in the neuronal cells and in the brains of stressed animals. In clinical trials, phytochemical usage is regarded as safe and well-tolerated for suppressing stress-related parameters in patients with depression. Thus, intake of phytochemicals with safe and active effects on synaptic plasticity may be a strategy for preventing neuronal damage and alleviating depression in a stressful life.

Key Words: Stress, Depression, Synaptic plasticity, Phytochemicals, Preventive agents

INTRODUCTION

Depression is a disabling mental disorder characterized by persistent feelings of sadness and enormous personal suffering, which inflicts severe social and economic burdens (Duman *et al*., 2016; GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). According to the World Health Organization, more than 350 million people are affected by depression worldwide (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Furthermore, depression can be fatal because of an elevated risk of suicide and increased mortality in patients, particularly those with comorbidities, such as cardiovascular disorders (Rajan *et al*., 2020). Although the neurobiology underlying depression has not been fully investigated, dysfunction of the neuronal circuitry is known to play a pivotal role in the onset of depression. Synaptic plasticity is one of the fundamental functions of neural networks in the brain; it confers the ability to sense complex information and to make appropriate adaptations in response to internal or external stimuli by reorganizing its structure, function, and connections, at many levels, from the molecular to the cellular, systemic, and behavioral levels (Citri and Malenka, 2008; Cramer *et al*., 2011). Several studies have demonstrated that persistent stress induces structural and functional alterations in mood-related neuronal circuits, leading to depression. Post-mortem analysis of the brain of patients with depression showed reduced synaptic numbers and volume of the prefrontal cortex (PFC) and hippocampus (Radley *et al*., 2015). Several antidepressant medications, including typical antidepressants such as selective serotonin

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reuptake inhibitors (SSRIs) and the rapid-acting agent, ketamine, reportedly counteract these effects by regulating the signal transduction and gene expression pathways linked to synaptic plasticity (Duman and Aghajanian, 2012; Duman *et al*., 2016). However, current medications (e.g., citalopram, SSRIs) administered to patients who already have significant neuronal alterations and synaptic dysfunction seem to have limitations in complete reversal (Trivedi *et al*., 2006), along with limited efficacy and safety (Carvalho *et al*., 2016). Phytochemicals have a wide therapeutic index and may be of great significance in preventing stress-induced synaptic dysfunction in daily life. In this review, we describe the alterations in synaptic plasticity in stress-induced depressive disorder at the cellular and molecular levels and summarize the potential of phytochemicals in regulating synaptic plasticity in animals and as bioactive agents in human clinical trials.

ALTERATIONS IN SYNAPTIC PLASTICITY IN STRESS-INDUCED DEPRESSION

Basic mechanisms of synaptic plasticity

The molecular mechanisms of synaptic plasticity: Most studies on the mechanisms of synaptic plasticity have focused on glutamatergic synapses, which constitute the vast majority of excitatory synapses in the central nervous system. Glutamate is detected at postsynaptic terminals by both ionotropic glutamate receptors (GluRs) and G protein-coupled receptors (GPCRs). N-methyl-d-aspartate receptors (NMDARs) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs) are the most important known triggers for long-term synaptic plasticity and synaptogenesis, and are known to function in excitatory neurotransmission. NMDARs are tetrameric protein complexes that typically consist of two NR1 and two NR2 subunits. The simultaneous binding of glutamate to the two NR2 subunits and the co-agonist, glycine, on each of the NR1 subunits can activate the NMDAR functions (Kew and Kemp, 2005). AMPARs are also tetramers and are composed of GluR1–GluR4 subunits; their function is mainly regulated by GluR1 and GluR2 subunits. Metabotropic GluRs (mGluRs) are seven-transmembrane domain G protein-coupled receptors and are divided into groups I and III. Among these, mGluR1 and mGluR5 of group I are primarily involved in regulating synaptic plasticity to mediate many cellular processes through the cyclic AMP and phosphatidylinositol pathways.

Long-term potentiation (LTP) can occur at most excitatory synapses throughout the brain but is best studied at the glutamate synapse in the hippocampus. When the presynaptic neuron is stimulated by a weak signal, only a small amount of glutamate is released. Although both receptors (NDMARs and AMPARs) are bound to glutamate, only AMPARs are activated by this weak stimulation. Sodium influx through the AMPAR results in slight de-polarization of the postsynaptic membrane. NMDARs remain closed because their pores are blocked by magnesium ions. When the presynaptic neuron is stimulated by a strong or repeated signal, a large amount of glutamate is released; the AMPARs remain open for a longer time, admitting more sodium into the cell, thus resulting in greater de-polarization. The increased influx of positive ions removes magnesium from NMDARs, which are then activated, allowing sodium as well as calcium into the cell. In the early phase, calcium initiates signaling pathways that activate several protein kinases. They phosphorylate the existing AMPARs, thereby increasing the conductance of AMPARs to sodium and transporting more AMPARs from intracellular stores to the postsynaptic membrane. This phase is considered the basis of short-term memory, which lasts several hours. In the late phase, new proteins are formed, and gene expression is activated to further enhance the connection between neurons. These include newly synthesized AMPARs and the expression of other proteins involved in the growth of new dendritic spines and synaptic connections. The late phase may be correlated with the formation of long-term memory.

LTP and long-term depression (LTD) require Ca^{2+} influx through NMDARs and are associated with changes in the properties and trafficking of synaptic AMPARs in the hippocampal CA1 region. Initial Ca^{2+} influx through NMDARs and somatic voltage-dependent calcium channels (VDCCs) activates multiple pathways involved in LTP, including Ca^{2+}/calmodulin-dependent kinase (CaMK) isoforms (Bengtson and Bading, 2012), extracellular signal-regulated kinase (ERK), protein kinase B (PKB, also known as Akt) (Patterson and Yasuda, 2011), RAS–mitogen-activated protein kinase (RAS–MAPK) pathways, as well as cyclic AMP-responsive element-binding protein (CREB)-mediated induction of survival genes. For example, CREB promotes the expression of BDNF, which plays a key role in neurotrophic processes related to stress and mood disorders (Duman and Monteggia, 2006; Krishnan and Nestler, 2008). Crucially, these proteins cooperate with NMDARs to induce changes in neuroplasticity. Further, mammalian target of rapamycin complex 1 (mTORC1) is primarily responsible for regulating neuronal development, neurogenesis, and synaptic plasticity (Perluigi *et al*., 2015; Ignacio *et al*., 2016). NMDAR antagonists, such as ketamine, can increase the translation of synaptic proteins, including GluR1 and postsynaptic density 95 (PSD95), through the BDNF–tropomyosin-related kinase B (TrkB)–Akt–mTORC1 pathway, which depends on AMPAR activation (Li *et al*., 2010). The downstream components of mTORC1 include ribosomal protein S6 kinases (S6Ks) and eukaryotic initiation factor 4E (eIF4E)-binding proteins (4E-BP). The mTORC1 activation inhibits 4E-BP and activates S6Ks, both of which are involved in translation initiation in dendrites. The mTOR-dependent translation activation is essential for upregulating local protein synthesis in neuronal dendrites (Takei *et al*., 2004).

The role for neurotropic factors in the regulation of synaptic plasticity: Neurotrophic factors, notably BDNF, are key regulators of neural circuit development and function, including neuronal differentiation and growth, synapse formation, and plasticity, as well as higher cognitive functions (Park and Poo, 2013). BDNF is constitutively expressed and controlled via Ca^{2+} signaling and activation of Ca^{2+}/cAMP response elements (Bjorkholm and Monteggia, 2016). The initial transcript is translated to pre-proBDNF and then undergoes further processing and cleavage to proBDNF and finally to mature BDNF, which binds to the p75 neurotrophin receptor (p75NTR) and tyrosine kinase receptor, TrkB, respectively, to activate their signaling pathways (Castren and Kojima, 2017). Both are packaged into vesicles and undergo trafficking to dendrites as well as axon terminals, where mature BDNF undergoes activity-dependent release, whereas proBDNF shows low levels of constitutive release. *In vitro* studies have suggested that BDNF develops neurons and regulates the spinal density and

morphology of mature neurons in the hippocampus (Ji *et al*., 2010).

BDNF may also serve as a mediator of activity-induced LTP. In the hippocampus, BDNF stored in presynaptic sites is probably released by LTP-inducing high frequency stimulation, suggesting that BDNF may indeed mediate the downstream synaptic changes associated with LTP. It is also accompanied by persistent postsynaptic structural changes, including an increased number and volume of dendritic spines (Kasai *et al*., 2010). In mature glutamatergic synapses, BDNF exerts presynaptic and postsynaptic modulatory effects. On the presynaptic side, BDNF receptor–TrkB signaling activates the PLCγ pathway to increase intracellular Ca^{2+} levels and the Ras–MAPKs pathway to increase presynaptic neurotransmitter release. On the postsynaptic side, BDNF–TrkB downstream signaling causes tyrosine phosphorylation of NMDARs and voltage-gated channels, inducing Ca^{2+}/calmodulin-dependent kinase II (CaMKII) and protein kinase C (PKC), which phosphorylate AMPARs and increase their synaptic transmission. BDNF–TrkB signaling also stimulates actin polymerization in dendritic spines, which is required for LTP development. Increased microtubular stabilization promotes BDNF-induced changes in spine morphology and accumulation of the postsynaptic protein, PSD95 (Hu *et al*., 2011). Persistent enlargement of the dendritic spines by LTP-inducing synaptic activity depends on the secretion of endogenous BDNF (Tanaka *et al*., 2008). Thus, BDNF appears to act as an associative messenger for consolidating synaptic plasticity, and the protein synthesis process can regulate dendritic structures.

The role for microRNA in the regulation of synaptic plasticity: MicroRNAs (miRNAs) are small, non-coding RNAs that are key posttranslational regulators of gene expression. Regulation of the expression of specific miRNAs in the brain may be related to synaptic plasticity, such as activity-dependent translation and neuronal morphogenesis, synapse formation, cognition, and memory (Chandrasekar and Dreyer, 2009). Aberrant expression of various miRNAs contributes to synaptic plasticity and neural development. For example, the brain-specific miRNA, miRNA134, negatively regulates the size of dendritic spines and blocks Lim-domain-containing protein kinase 1 (LimK1), which is associated with dendritic spine formation and maturation (Schratt *et al*., 2006; Liu *et al*., 2017). Limk1 can regulate actin filament dynamics by inhibiting the activity of cofilin, a key actin depolymerizing factor located at postsynaptic sites, thereby preventing the cleavage of filamentous actin and stabilizing the actin cytoskeleton and spine size (Sarmiere and Bamburg, 2002). The expression of other brain-specific miR-132s is increased by CREB and BDNF, while miR-132 can amplify CREB activity through sensitization of adenylyl cyclases. Thus, CREB and miR-132 form a positive feedback loop that promotes dendritic spine development (Im and Kenny, 2012). Another miRNA, miR-137, can inhibit the incorporation of AMPAR into synaptic membranes, causing postsynaptic plasticity and maturation (Olde Loohuis *et al*., 2015).

Alterations in synaptic plasticity in depression

Altered synaptic plasticity in stress-induced, depressive animals: Many studies have demonstrated that depression is associated with reduced volume in brain regions that regulate mood and cognition, including the PFC and hippocampus, along with decreased neuronal function and synaptic density in these regions (Duman and Aghajanian, 2012). Animal studies typically use forms of stress, a well-accepted etiological factor in depression, to study the neurobiological correlates of depression-like behavior. In an animal model of chronic unpredictable restraint stress, MRI was used to indicate a reduced hippocampal volume, along with atrophy and loss of neurons (Duman and Aghajanian, 2012; Schoenfeld *et al*., 2017). Chronic exposure to corticosterone also decreases cortical levels of NR2B and GluR2/3, which may contribute to deficits in fear extinction (Gourley *et al*., 2009). Repeated stress suppresses the synaptic expression of AMPARs and NMDARs in the PFC, thus impairing object recognition memory (Popoli *et al*., 2011). Severe stress can impair LTP and enhance LTD in the hippocampus. Chronic mild stress (CMS) influences the expression of synaptic proteins, such as synapsin 1 and glutamate transporter 1, resulting in altered glutamate release and contributing to the disruption of synaptic transmission and impaired LTP (Fremeau *et al*., 2004). Decreased levels of synaptic vesicle proteins (i.e., synaptophysin and synaptotagmin) have also been reported in stress paradigms (Thome *et al*., 2001). The MAPK signaling pathway, which is required for sustained growth of dendritic spines (Patterson and Yasuda, 2011), is involved in the pathophysiology of depression and antidepressant responses (Duman *et al*., 2007). Furthermore, BDNF deletion increases depression-like behavior (Taliaz *et al*., 2010; Bjorkholm and Monteggia, 2016). Selective knockdown of BDNF in the hippocampus is reported to cause depressive behaviors (Taliaz *et al*., 2010). Consistently, BDNF levels are reduced in both the cortex and hippocampus of stressed animals (Duman and Monteggia, 2006). Mice with the genetic variant, BDNF (valine to methionine substitution at codon 66), show smaller hippocampal volumes, whereas those with the Met/Met gene show reduced dendritic complexity (Egan *et al*., 2003) and impaired working memory (Yu *et al*., 2012). Interestingly, these mice display reduced dendrite length and branching with a reduced spine–synapse number and function in the hippocampus and PFC (Chen *et al*., 2006; Liu *et al*., 2012). Further, TrkB knockdown produces anxiety-like behavior (Bergami *et al*., 2008).

Recent studies support the hypothesis that major depressive disorder (MDD) might be a consequence of disrupted mTOR-dependent translation regulation. Direct inhibition of mTORC1 through overexpression of 'regulated in development and DNA damage responses 1' (REDD1, a critical mediator of neuronal atrophy) in rodents can induce depressive-like symptoms without exposure to stress (Ota *et al*., 2014). Antidepressant such as ketamine have been shown to increase synaptogenesis via mTOR signaling (Zanos and Gould, 2018). Thus, abnormalities in mTOR signaling can cause deficits in synaptic proteins (Goswami *et al*., 2013), suggesting that mTOR signaling should be a major area of investigation in depression. Recently, dysregulation of miRNAs has been reported to be linked to MDD (Martins and Schratt, 2021; Gao *et al*., 2022). In rats with chronic unpredictable mild stress (CUMS), miR-134 is overexpressed in the ventromedial PFC (vmPFC) (Fan *et al*., 2018b), and dendritic spine size is reduced by the inhibition of Limk1 translation (Schratt *et al*., 2006). The cellular and molecular mechanisms of synaptic plasticity in the normal and stress-induced depressive states are shown in Fig. 1.

Altered synaptic plasticity in patients with depression: Post-mortem studies of patients with depression have dem-

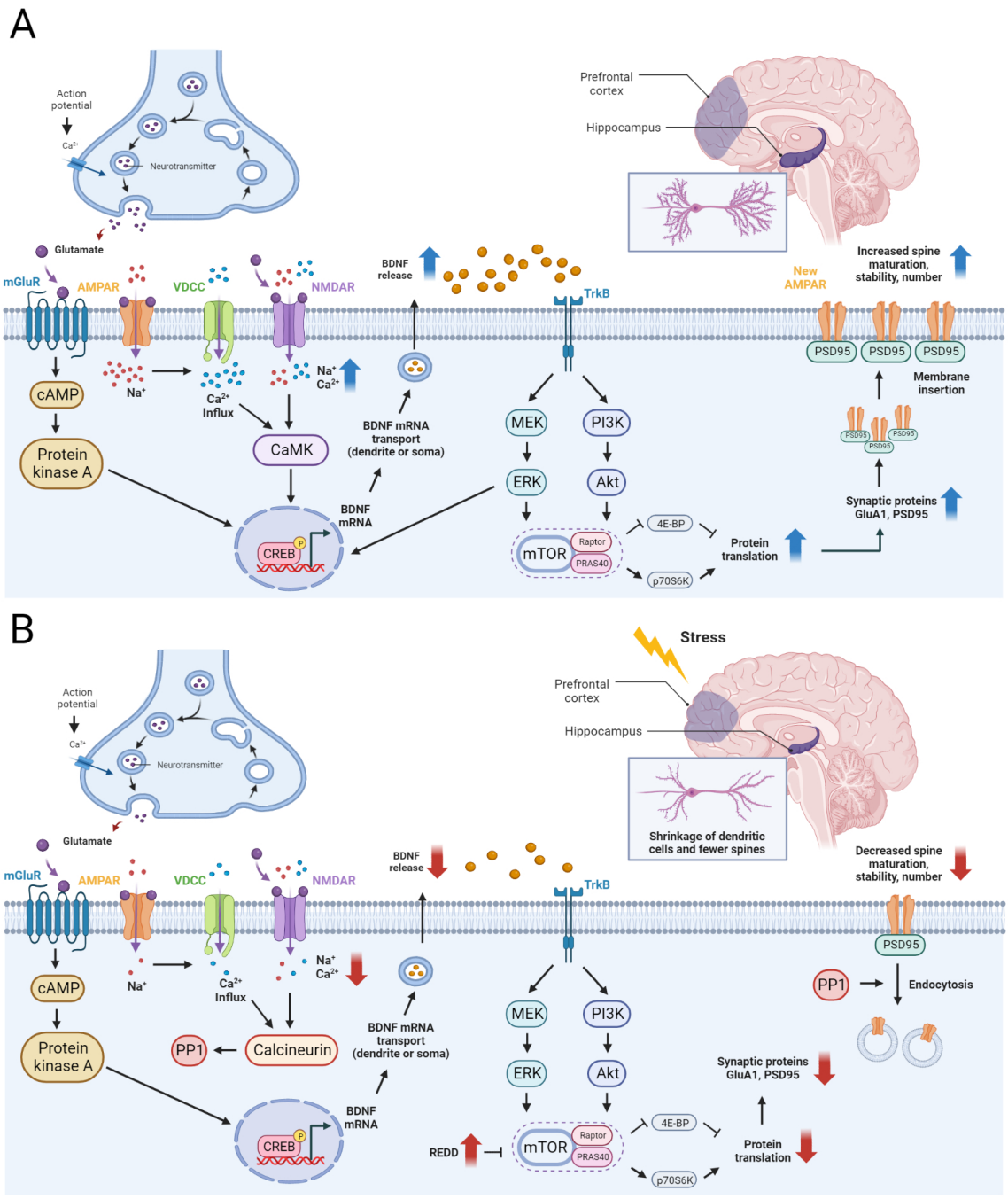

Fig. 1. The major signaling pathways involved in regulating spine remodeling and synaptic plasticity, including the NMDA and AMPA glutamate receptor subtypes, neurotrophic factors (i.e., BDNF), and related downstream signaling. (A) Repeated stimulations or strong signals induce the release of neurotransmitters such as glutamate at the presynaptic terminals of the neuron. Glutamate released from presynaptic terminals binds to its receptors (e.g., AMPA, NMDA, mGlu) leading to the release of ions (e.g., calcium, sodium) into the synaptic cleft and AMPAR phosphorylation, which results in the induction of LTP in postsynaptic neurons. Calcium influx through NMDARs and somatic voltage-dependent calcium channels (VDCCs) activate Ca^{2+}/calmodulin-dependent kinase (CaMK) isoforms, cyclic AMP, and phosphatidylinositol pathways, inducing the activation of cyclic AMP-responsive element-binding protein (CREB); this promotes BDNF expression. In dendrites, BDNF is packaged into secretory granules for the regulated secretion pathway and released into the synapse. When secreted BDNF binds its receptor, TrkB, phosphorylated TrkB activates the downstream protein, Akt, followed by the activation of mTOR by p-Akt. Then, mTOR activates two downstream signaling proteins, p70s6k and 4E-BP, and controls local translational activation and local proteins synthesis (GluA1, PSD95) enhancement. (B) Conversely, LTD can be induced by repeated low-frequency stimulation. Weak activity of presynaptic neurons leads to modest depolarization and calcium influx through the NMDA receptors. This preferentially activates phosphatases (protein phosphatase1, PP1), which dephosphorylate AMPA receptors, thus promoting receptor endocytosis and decreased efficacy of the synapse. Chronic stress decreases BDNF and mTORC1 signaling, in part via upregulation of the negative regulator 'regulated in DNA damage and repair' (REDD1), which decreases the synthesis of synaptic proteins and thereby contributes to a reduced number of spine synapses.

onstrated various alterations in synaptic plasticity in various regions of the brain (Kang *et al*., 2012; Duric *et al*., 2013). Reduced volume of the PFC, a significant nerve center for thinking and behavioral regulation, has been reported, and this decrease was correlated with the length of illness. Synaptic loss and reduced synaptic marker expression and synapse numbers were directly visualized in the PFC. Functional imaging studies indicated contrasting changes in activity in the two sectors. During the progression of depression, hyperactivity was observed in the vmPFC, whereas hypoactivity was observed in the dorsolateral PFC (dlPFC). In response to psychotherapy or medication for depression, hypoactivity was found in the vmPFC during the recovery phase, whereas hyperactivity was found in the dlPFC (Greicius *et al*., 2007). Furthermore, disruption of functional hippocampal connectivity within the prefrontal and parietal cortices has been revealed in patients with MDD using functional MRI (Milne *et al*., 2012). Many studies have revealed abnormal activation of the hippocampus in patients with MDD (MacQueen *et al*., 2008). The expression of BDNF and its receptor, TrkB, was found to be reduced in the brain samples of patients with depression (Guilloux *et al*., 2012; Tripp *et al*., 2012). Similarly, BDNF expression in the hippocampus of patients taking antidepressants was higher than that in patients without any antidepressant treatment (Chen *et al*., 2001). The level of TrkB was reduced, and the signaling pathways downstream of BDNF–TrkB were attenuated in individuals who committed suicide. Evidence suggests that the level of p75NTR, which contributes to neuronal atrophy, is increased in the PFC of suicide subjects (Castren and Kojima, 2017). Consistently, decreased BDNF–TrkB signaling contributes to a reduced volume of the PFC and hippocampus in patients with depression (MacQueen and Frodl, 2011). The mTORC1 signaling, which is responsible for regulating synaptic protein synthesis, is reduced in patients with MDD (Jernigan *et al*., 2011). The post-mortem evaluation of the PFC of patients with MDD also indicated a substantial reduction in the expression of the mTORC1-dependent translation initiation factors, mTOR, p70S6K, and eIF4B; these may be involved in regulating brain function and the pathophysiology of MDD (Jernigan *et al*., 2011). Post-mortem changes in brain tissue morphology co-occur with decreased levels of phosphorylated mTORC1-associated molecules such as mTOR, p70S6K, and ribosomal protein, S6 (Li *et al*., 2010). These findings indicate a strong connection between stress-related morphological changes in the brain, depression-like behavior, and the reduction in mTORC1 activity (Cholewinski *et al*., 2021). The miRNA-sequencing of post-mortem brain samples indicates that a large number of miRNAs are synaptically enriched and differentially regulated in patients with MDD, as the miRNA processing enzymes, DROSHA, DICER1, and TARBP2, are altered (Yoshino *et al*., 2021).

PHYTOCHEMICALS ACT ON SYNAPTIC PLASTICITY

The effect of phytochemicals in the regulation of synaptic plasticity: Evidence from animal models

Table 1 summarizes the phytochemicals that show antidepressive effects in animal models of stress-induced depression, together with their possible molecular mechanisms. Apigenin, found in *Carduus crispus* and *Elsholtzia rugulosa*, upregulates hippocampal BDNF levels in corticosterone-treated mice (Weng *et al*., 2016). Baicalein exerts antidepressant-like effects in experimental animal models, possibly through modulation of the ERK signaling pathway and BDNF levels in the hippocampus (Xiong *et al*., 2011). In a rodent model of depression, curcumin increased the hippocampal BDNF and ERK levels and had a positive effect on stress-induced learning and memory deficits (Xu *et al*., 2007; Hurley *et al*., 2013; Liu *et al*., 2014). Cytisine, a natural plant alkaloid, had antidepressant-like effects by modulating the BDNF and mTOR signaling in the hippocampus of a CUMS model (Han *et al*., 2016). *Godmania aesculifolia* contains a naturally occurring flavone, 7,8-dihydroxyflavone, which acts as a BDNF mimetic; it binds to the extracellular domain of TrkB, thereby promoting receptor dimerization, autophosphorylation, and activation of downstream signaling cascades (Liu *et al*., 2016a; Emili *et al*., 2022). The chemical standard, dihydromyricetin, activates the ERK1/2–CREB pathway and increases GSK-3β phosphorylation at ser-9 with upregulation of BDNF expression in the hippocampus (Ren *et al*., 2018). Various phytochemicals such as fisetin, gallic acid, (−)-gallocathechingallate, hesperidin, honokiol, nobiletin, paeoniflorin, quercetin, saikosaponin A, saikosaponin D, and silibinin have been found to regulate the BDNF/TrkB/CREB pathways in rodent models (Li *et al*., 2013, 2016; Song *et al*., 2016; Li *et al*., 2017; Wang *et al*., 2017; Chen *et al*., 2018; Wang *et al*., 2018a; Fang *et al*., 2019; Fu *et al*., 2019; Hu *et al*., 2019; Zhu *et al*., 2019; Ko *et al*., 2021). Dendritic spine density almost completely recovered as a result of increasing new functional connectivity in high-temperature-processed green tea extract-fed (gallocathechingallate is a major bioactive compound in green tea extract), ovariectomized rats experiment (Ko *et al*., 2021). Gallic acid, found in gallnuts, sumac, witch hazel, tea leaves, oak bark, and other plants, reversed the attenuation in the p-Akt, p-mTOR, p-p70s6k, and p-4E-BP-1 pathways (Zhu *et al*., 2019). Honokiol, the main active component of *Magnolia officinalis* was shown to increase the expression of BDNF mRNA and protein in the hippocampus in a CUMS rat model (Wang *et al*., 2018a). Nobiletin, a flavonoid isolated from citrus fruit, upregulated synaptic transmission and improved memory impairment in rodents and produced rapidly acting, antidepressant-like responses in CUMS, suggesting that the BDNF–TrkB pathway may play an important role in its antidepressant-like effect (Li *et al*., 2013). In perimenopausal animal models subjected to CUMS, saikosaponin A ameliorated depression through enhanced BDNF expression by promoting BDNF–TrkB signaling in the hippocampus (Chen *et al*., 2018). Saikosaponin D exhibits antidepressant activities by ameliorating dysfunction of the hypothalamic–pituitary–adrenal axis, consolidating hippocampal neurogenesis, and increasing the phosphorylation of CREB and BDNF in CUMS-induced depressive rats (Xu *et al*., 2019). Systemic injection of lipopolysaccharide can also lead to depression-like behavior in experimental animals, and is considered a classic model of depression. Treatment with S-equol, a major metabolite of dietary soy isoflavones, substantially upregulated the expression of the phosphosynapsin, PSD-95, in the hippocampus, providing insight into the potential for preventing depression via enhancement of synaptic plasticity (Lu *et al*., 2021). In a CUMS rat model, hyperforin treatment increased zinc concentration and BDNF level in the frontal cortex and hippocampus (Szewczyk *et al*., 2019). Additionally, isorhynchophylline regulated the PI3K/Akt/GSK-3β signaling pathway in a CUMS-induced depressive mouse

Table 1. Phytochemicals with anti-depressive effects in stress-induced depressive animals and their possible molecular mechanisms

Name	Experimental model	Effects	References
Apigenin (*Carduus crispus; Elsholtzia rugulosa*)	Corticosterone induced depression	↑BDNF	Weng *et al*., 2016
Baicalein (The root of *Scutellaria baicalensis*)	Chronic unpredictable mild stress (CUMS)	↑BDNF, ↑pERK	Xiong *et al*., 2011
Curcumin (*Curcuma longa*)	Chronic mild stress (CMS)/ CUMS	↑BDNF, ↑p-ERK	Xu *et al*., 2007; Hurley *et al*., 2013; Liu *et al*., 2014; Choi *et al*., 2017
Cytisine (Natural plant alkaloid)	CUMS	↑pCREB, ↑BDNF, ↑pAkt, ↑pmTOR(p70s6k)	Han *et al*., 2016
7,8-dihydroxyflavone (Godmania aesculifolia)	CMS	↑BDNF	Chang *et al*., 2016
Dihydromyricetin (*Ampelopsis grossedentata*)	CUMS	↑ERK1/2-CREB pathway, ↑pGSK-3β(ser9), ↑BDNF	Ren *et al*., 2018
S-equol (Soy isoflavone metabolite)	LPS challenge	↑pSYN, ↑SYN, ↑PSD95	Lu *et al*., 2021
Fisetin (Strawberry extract)	Chronic restraint stress	↑TrkB signaling, ↑pTrkB	Wang *et al*., 2017
(-)-Gallocatechin gallate (high-temperature-processed green tea extract)	Ovariectomized rats	↑TrkB pathway, ameliorates the synaptic impairments	Ko *et al*., 2021
Gallic acid (Gallnuts, sumac, witch hazel, tea leaves, oak bark, and other plants)	CMS	↑BDNF, ↑pTrkB, ↑mTOR (p70s6k and 4E-BP-1)	Zhu *et al*., 2019
Hesperidin (*Hemerocallis citrina*)	CUMS	↑pERK1/2, ↑BDNF/TrkB pathways	Li *et al*., 2016; Fu *et al*., 2019
Honokiol (*Magnolia officinalis*)	CUMS	↑BDNF	Wang *et al*., 2018a
Hyperforin (*Hypericum perforatum* L.)	CUMS	↑BDNF	Szewczyk *et al*., 2019
Isorhynchophylline (The stem of *Uncaria rhynchophylla*)	CUMS	Modulating the PI3K/AKT/GSK-3β	Xian *et al*., 2019
Malvidin3′-O-glucoside (*Vaccinium arboreum*)	Repeated social defeat stress model	↑*Rac1* gene, ↑synaptic plasticity mediator that is involved in modulating dendritic spine formation	Wang *et al*., 2018b
Naringenin (Abundantly present in the peel of citrus fruits)	CUMS	↑BDNF	Yi *et al*., 2014b; Tayyab *et al*., 2019
Nobiletin (Citrus fruits)	CUMS	↑BDNF/TrkB pathways	Li *et al*., 2013
Oleanolic acid (Olive oil)	CUMS	BDNF/ERK/CREB signalling miR-132	Yi *et al*., 2014a
Paeoniflorin (*Radix paeoniae*)	CUMS	↑BDNF, ↑p-CREB	Hu *et al*., 2019
Psilocybin (*Psilocybe*, such as *P. azurescens*, *P. semilanceata*, and *P. cyanescens*)	Chronic multimodal stress paradigm	Promote synaptic strengthens hippocampal TA-CA1 synapses	Hesselgrave *et al*., 2021
Puerarin (*Bupleurum chinense* DC.)	Spared nerve injury-induced mice	Activating ERK/CREB/BDNF pathways	Zhao *et al*., 2017
Quercetin (*Rosa Chinensis Jacq. Hypericum perforatum*)	LPS challenge	↑BDNF, ↑pTrkB	Fang *et al*., 2019
Resveratrol (*Polygonum cuspidatum*)	CUMS	↑pmTOR, ↑pAkt, ↑ERK, ↑pCREB, ↑BDNF, ↑Synaptophysin	liu *et al*., 2016b; Shen *et al*., 2018
Ginsenoside Rg1 (*Panax ginseng*)	CUMS	↑BDNF, ↑p-CREB, ↑p-PKA, ↑PSD95, ↑Synaptic plasticity fators (miR-134↓, Limk1↑, p-cofilin↑), ↑Spine density, ↑Synapse number	Liu *et al*., 2016c; Zhu *et al*., 2016; Fan *et al*., 2018a; Yu *et al*., 2018

Table 1. Continued

Name	Experimental model	Effects	References
Ginsenoside Rg2, Rg3, Rg5 (*Panax ginseng*)	CUMS/chronic social defeat stress	↑BDNF, ↑pTrkB, ↑pCREB	Ren *et al*., 2017; Xu *et al*., 2017; You *et al*., 2017; Zhang *et al*., 2017
Ginsenoside Rh (*Panax ginseng*)	LPS challenge	↑BDNF↑, ↑TrkB	Chen *et al*., 2019
Rutin (*Hypericum perforatum* L.)	Maternal Separation Stress-induced mice	↓NR2B, ↓NR2A, ↑CA3 diameter	Anjomshoa *et al*., 2020
Saikosaponin A (*Bupleurum chinense* DC.)	CUMS	↑BDNF/TrkB pathways	Chen *et al*., 2018
Saikosaponin D (*Bupleurum chinense* DC.)	CUMS	↑pCREB, ↑BDNF	Li *et al*., 2017
Schisantherin B (*Schisandra chinensis* (Turcz.))	Forced swimming test-induced mice	↑GLT-1by promoting PI3K/AKT/mTOR pathway	Xu *et al*., 2019
Silibinin (*Silybum marianum*)	LPS challenge	↓Neuronal loss, ↑BDNF/TrkB pathways	Song *et al*., 2016
Sulforaphane (Cruciferous vegetables)	LPS challenge	Alteration of BDNF, PSD95, GluA1, dendritic spine density	Zhang *et al*., 2017
Tetramethylpyrazine (*Ligusticum wallichii*)	Chronic social defeat stress model	↑pCREB, ↑BDNF, ↑pERK, ↑pAKT	Jiang *et al*., 2015

model (Xian *et al*., 2019). Malvidin-3′-O-glucoside (Mal-gluc) is effective in promoting resilience against stress by modulating brain synaptic plasticity, substantially increases RAS-related C3 botulinum toxin substrate 1 (Rac1) expression, and plays an important role in regulating dendritic spines and excitatory synapses (Luo *et al*., 1996; Wang *et al*., 2018b). Naringenin improved depression-like behavior and promoted BDNF expression in the hippocampus but not in the frontal cortex in a CUMS rodent model (Yi *et al*., 2014b). Oleanolic acid enhanced BDNF-related miR-132 expression and regulated postsynaptic (PSD95) and presynaptic (synapsin I) protein via miR-132-dependent and independent mechanisms, respectively, in a mouse CUMS model (Yi *et al*., 2014a). Psilocybin, a naturally-occurring plant psychedelic alkaloid administration induced excitatory synaptic strengthening in a depression-relevant brain region (hippocampal TA-CA1) using a chronic multimodal stress paradigm mouse model (Hesselgrave *et al*., 2021). In spared nerve injury-induced depression models, puerarin, a glycosyl isoflavone with multiple biological activities, induced BDNF expression and markedly promoted activation of the CREB pathway via the ERK pathway (Zhao *et al*., 2017). Similarly, resveratrol enriched with *Polygonum cuspidatum* demonstrated antidepressant-like action by phosphorylation of the Akt/mTOR pathway in the hippocampus and PFC (liu *et al*., 2016b) or by decreasing miR-134 and increasing CREB/BDNF levels in primary cultured hippocampal neurons in a CUMS rat model (Shen *et al*., 2018). Ginsenoside, an active compound of *Panax ginseng*, upregulates BDNF levels and the phosphorylation of TrkB and CREB in the hippocampus (Liu *et al*., 2016c; Zhu *et al*., 2016; Ren *et al*., 2017; Xu *et al*., 2017; Fan *et al*., 2018a; Yu *et al*., 2018; Chen *et al*., 2019). Fan *et al*. (2018a) reported that ginsenoside-Rg1, the major active ingredient of ginseng, attenuates dendritic spine and synaptic deficits through the upregulation of synaptic-related proteins in the PFC in a rat model of CUMS, and in particular, altered synaptic structure and spine density (Liu *et al*., 2016c; Fan *et al*., 2018a; Yu *et al*., 2018). Synaptic-related protein expression (including miR-134, Limk1, p-cofilin, PSD-95, and synaptophysin) was also found to change (Fan *et al*., 2018b; Yu *et al*., 2018). Similarly, in a mouse model of maternal separation stress, rutin exerted an antidepressant effect via a neuroprotective effect on the hippocampus, which included the inhibition of the NR2B- and NR2A-subunits of NMDAR, as well as modulation of the CA3 diameter and percentage of dark neurons in the hippocampus (Anjomshoa *et al*., 2020). Schisantherin B, a bioactive lignan isolated from *Schisandra chinensis* (Turcz.) Baill., acts as an antidepressant that increases GLT-1 (glial glutamate transporter-1, also known as EAAT2) levels by promoting the PI3K/Akt/mTOR pathway (Xu *et al*., 2019). Sulforaphane, an isothiocyanate compound found in broccoli, was found to substantially attenuate the reduced density of dendritic spines and reduction in BDNF, PSD95, and GluA1 expression in the hippocampus and PFC after lipopolysaccharide administration (Zhang *et al*., 2017). Tetramethylpyrazine, an identified component of *Ligusticum wallichii*, has neuroprotective effects and completely restored hippocampal neurogenesis and the chronic social defeat stress-induced decrease in the BDNF signaling pathway (Jiang *et al*., 2015). Taken together, many phytochemicals affect the level of hippocampal BDNF, TrkB receptors, and its downstream factors (ERK, Akt, and mTOR), and CREB/BDNF/TrkB signaling for enhancing synaptic plasticity in stress-induced

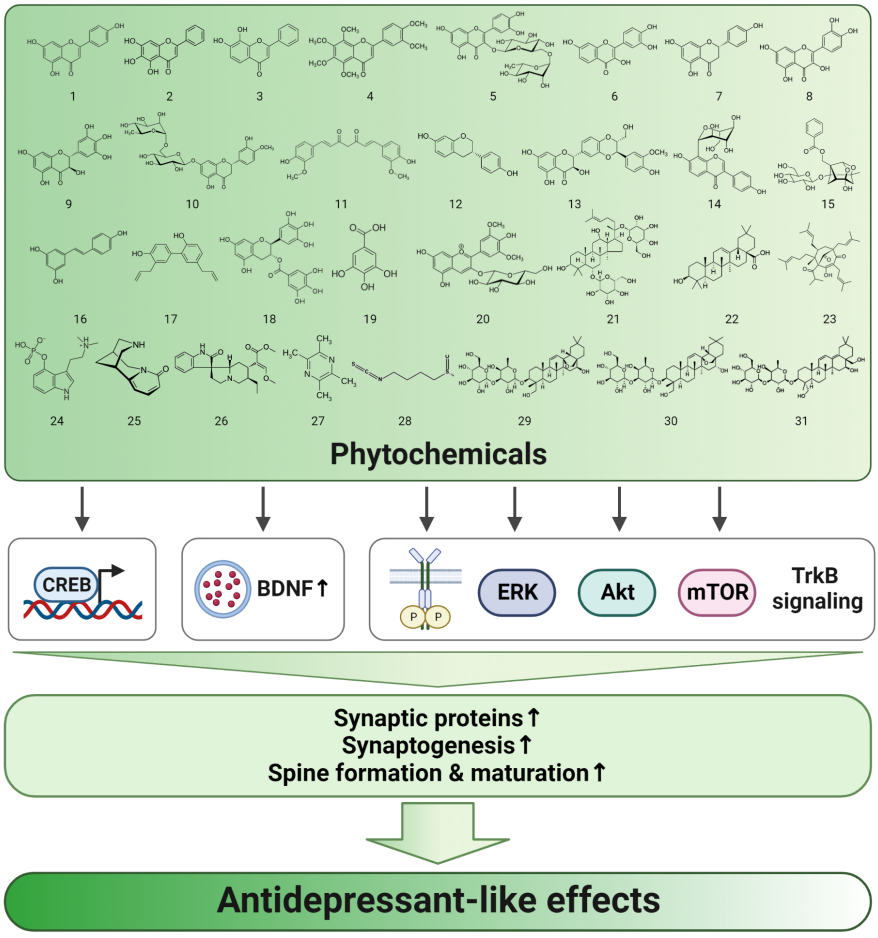

Fig. 2. Phytochemicals that target synaptic plasticity signaling in stress-induced, depressive animals. Many phytochemicals can increase hippocampal BDNF levels and stimulate TrkB receptor and its downstream factors, ERK, Akt, and mTOR; CREB/BDNF/TrkB signalings are associated with synaptic plasticity and antidepressive effects. (1) Apigenin, (2) baicalein, (3) 7,8-dihydroxyflavone, (4) nobiletin, (5) rutin, (6) fisetin, (7) naringenin, (8) quercetin, (9) dihydromyricetin, (10) hesperidin, (11) curcumin, (12) S-equol, (13) silibinin, (14) puerarin, (15) paeoniflorin, (16) resveratrol, (17) honokiol, (18) (-)-gallocatechin gallate, (19) gallic acid, (20) malvidin3'-O-glucoside, (21) ginsenoside, (22) oleanolic acid, (23) hyperforin, (24) psilocybin, (25) cytisine, (26) isorhynchophylline.

depressive animals (Fig. 2).

Evaluating the potential of phytochemicals as an antidepressant: Evidence from clinical trials

The bioactive phytochemicals examined in clinical trials of patients with depression are listed in Table 2. The effect of oral curcumin administration on depression has been evaluated in several clinical trials. Curcumin, when administered orally at doses ranging from 500 to 1000 mg daily, alone (Lopresti *et al*., 2015; Yu *et al*., 2015) or in combination with medicinal herbs (Lopresti and Drummond, 2017) or standard antidepressive agents (Bergman *et al*., 2013; Sanmukhani *et al*., 2014), produced a marked improvement in depression-related symptoms that were assessed using the relevant scales (Kanchanatawan *et al*., 2018). Further, curcumin appears to be safe and well-tolerated, with no adverse events reported in any of the trials. In a meta-analysis, Fusar-Poli *et al*. found a significant overall effect of curcumin on symptoms of depression and anxiety with a large effect size (Ng *et al*., 2017; Fusar-Poli *et al*., 2020). The first clinical trial of icariin, a flavonoid found in the medicinal plant, *Epimedium* L., demonstrated that icariin (up to 300 mg/day for 8 weeks) improved depressive symptoms and reduced alcohol consumption in individuals with bipolar disorder (a mental health condition that causes extreme mood swings, including emotional highs (mania) and lows (depression)) (Xiao *et al*., 2016). In a clinical study of patients with treatment-resistant depression, psilocybin markedly reduced depressive symptoms one week post-treatment. Maximal effects were observed at five weeks (Carhart-Harris *et al*., 2018). Similarly, another randomized, waiting list-controlled clinical trial showed substantial rapid and enduring antidepressant effects of psilocybin in patients with MDD. The effect of ketamine (a rapid-acting antidepressant drug) typically lasts for a few days to two weeks, whereas that of psilocybin continued for at least four weeks in 71% of the participants. Psilocybin has a low potential for addiction and a minimal adverse event profile (Davis *et al*., 2021). A randomized, double-blind, placebo-controlled study demonstrated that a 12-week intake of 10 mg of equol and 25 mg of resveratrol improved the quality of life of postmenopausal women with depressive

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Table 2. Bioactive phytochemicals studied in clinical trials of patients with depression

Drug	NCT (Country)	Pathological state	Patients (year) (age)	Dosage
Curcumin	NCT04744545 (United States)	Depression	60 (2021) (>18)	1,500 mg/day curcumin plus black pepper to aid absorption
	NCT01750359 (Israel)	Major depression	40 (2011) (20–65)	500 mg/day, 6 weeks
	NCT01022632 (India)	Major depressive disorder	60 (2010) (18-65)	500 mg twice/day, 6 weeks
	NCT02099890 (Canada)	Neuropathic Pain, Depression, Cognitive Impairment, Somatic Neuropathy.	20 (2015) (>18)	InflanNox capsule (400 mg curcumin) taken 3 times daily
	TCTR20170803002 (Thai) (Kanchanatawan *et al*., 2018)	Major depressive episode	65 (2017) (18-63)	500-1,500 mg/day, curcumin capsules, 12-16 weeks
	ACTRN12615000791538 (Australia) (Lopresti and Drummond, 2017)	Major depressive disorder	123 (2016) (18-65)	250 mg b.i.d. and 500 mg b.i.d., or combined 250 mg+saffron (15 mg b.i.d.) for 12 weeks
Icariin	NCT01979133 (United States) (Xiao *et al*., 2016)	Bipolar I or bipolar II disorders	11 (2015) (18-70)	300 mg/day, 8 weeks
Psilocybin	NCT03181529 (United States) (Davis *et al*., 2021)	Major depressive disorder	27 (2017) (21-75)	20 mg/70 kg in session 1, 30 mg/70 kg in session 2
	ISRCTN14426797 (United Kingdom) (Carhart-Harris *et al*., 2018)	Treatment-resistant major depression	20 (2015) (All)	10 and 25 mg, 7days apart
Equol+Resveratrol	ISRCTN10128742 (Italy) (Davinelli *et al*., 2017)	Depressive symptoms in postmenoausal women	60 (2011) (50-55)	200 mg of fermented soy (containing equol 10 mg+resveratrol 25 mg)
Soy isoflavone	NCT00042380 (United States)	Depression	120 (2005) (All)	Novasoy for 8 weeks
Sulforaphane	IRCT20090117001556N128 (Iran) (Ghazizadeh-Hashemi *et al*., 2021)	Depression with history of cardiac interventions	66 (2020) (40-65)	30 mg/day

symptoms (Davinelli *et al*., 2017). Sulforaphane is currently considered a potential bioactive compound for depression. A randomized, double-blind, placebo-controlled clinical trial was recently carried out in patients with depression with history of cardiac intervention. The sulforaphane group exhibited greater improvement in the Hamilton Rating Scale for Depression scores than the placebo group (Ghazizadeh-Hashemi *et al*., 2021). The effect of soy isoflavones on depression (NCT00042380) is currently under investigation in clinical trials.

CONCLUSIONS AND FUTURE PROSPECTS

Intake of several phytochemicals has been shown to have beneficial effects on depressive-like symptoms and behavior in animals and humans. Although phytochemicals possess a wide therapeutic index, additional safety investigations are required for their long-term use alone and in combination with other medications, including antidepressants, in human patients. Moreover, the efficacy of phytochemicals needs to be evaluated in large-scale clinical studies if daily intake in stressed humans is to be considered. Molecular mechanisms of each bioactive agent will need to be elucidated. Phytochemicals with sufficient safety and positive regulatory effects on synaptic plasticity may be considered as prophylactic medication for patients with depressive disorders.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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