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Phytochemicals as Antidepressants: The Involvement of Serotonin Receptor Function, Stress Resistance and Neurogenesis

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1. Introduction

Mood disorders are among the most prevalent forms of mental illness and a major cause of morbidity worldwide. Depression is one of the top ten causes of morbidity and mortality worldwide based on a survey by the World Health Organization (Berton and Nestler, 2006). Depression (major depressive disorder, major depression, unipolar depression, clinical depression) is a chronic, recurring and potentially life-threatening mood disorder that has been estimated to affect 21% of the world population (Schechter et al., 2005). It is estimated that 40% of the risk for depression is genetic, though the specific genes involved in the risk is still limited understanding. The other 60% non-genetic risk remains poorly defined, with suggestions as diverse as acute or chronic stress, childhood trauma, viral infections and even random processes during brain development might be involved (Akiskal, 2000; Berton and Nestler, 2006).

Stress occurs in every day life. Among psychiatric disorders, depression is probably the most common stress-related diseases. The theoretical premise is that depression is the outcome of an eventual inability to cope with a stream of dissimilar unpleasant stimuli imposed by the environment (Ferretti et al., 1995). The link between genetic predisposition and life stressors in the etiology of depression remains unclear because the mode of transmission of mood disorders is likely to be complex. However, interactions between a genetic predisposition and some environmental stressors are probably necessary to induce depression (Caspi and Moffitt, 2006). In addition, not only the hypothalamic-pituitary-adrenal (HPA) axis, but also brain neuronal systems, including the monoaminergic systems and in particular the serotonin (5-HT) containing neuronal one, play critical roles in stress-related disorders (Lanfumeey et al., 2008; Xu et al., 2006). The structural alterations of neurons in stress-induced depression, such as a progressive decrease in the volume of the frontal cortex and hippocampus, have also been found to be related to dysfunctions of HPA axis, abnormalities in 5-HT and its receptors (Drevets, 2000; Reines et al., 2008; Tsuji et al., 2001). But, so far, no clear consensus has evolved in pathological mechanism of inter-neuronal communication and post-receptor signal transduction of depression.

Early theories of depression focused on imbalance of neurotransmitter system, especially depletion of the serotonin (5-HT), norepinephrine (NE) and/or dopamine in depression and related mood disorders, since the efficacy of tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) in the treatment of these disorders. Current theoretical and experimental developments in serotonin and noradrenaline research extend the previous studies, the robust therapeutic effects of newer antidepressants are discovered, such as selective serotonin reuptake inhibitors (SSRIs), noradrenaline reuptake inhibitors (NRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). However, the current therapeutic options of depression are far from ideal: most of the pharmacological interventions are not effective in more than 50% cases, and are often associated with a range of serious side effects and drug-drug/drug-food interactions (Baker et al., 2003; Meijer et al., 2004).

Polyphenolic nutraceuticals (phytochemicals) present in vegetables and fruits are believed to reduce the risk of several major diseases including cardiovascular, autoimmune and neurodegenerative disorders. Six such polyphenols are curcumin, low molecular proanthocyanidin, resveratrol, fisetin, piceatannol and ferulic acid, which have been used throughout Asia as traditional herbal medicines. They show strong antioxidant and anti-inflammatory properties. The wide ranging activity of these compounds and the repeated demonstration that they can decrease the stress response, oxidative damage, inflammation, neuronal damage and act as neuroprotectants, strongly suggest these compounds might have a significant impact on stress-induced depression and other affective disorders.

In this review, we integrate our current knowledge to define the present state of depression and assessment of the position of serotonergic function in the pathophysiology of depression. We also summarize the status of a few novel approaches and compounds that are under investigation for the treatment of major depression. We attempt to provide a progress report on the pharmacological profile of multiple polyphenolic phytochemicals as promising herbal antidepressants.

2. Biological correlates of stress-induced depression and neurogenesis: Evidence for serotonergic function

2.1 Stress, corticosterone and depression

Glucocorticoid release is regulated by the HPA axis in physical conditions. Corticotropin-releasing hormone (CRH) released by the paraventricular nucleus of the hypothalamus stimulates the release of corticotropin (ACTH) from the anterior pituitary, which, in turn, stimulates glucocorticoid secretion from the adrenal cortex. HPA axis is an essential component of an individual's capacity to cope with stress (Berton and Nestler, 2006). Stress may be described as any environmental change, either internal or external, that disturbs the maintenance on homeostasis (Leonard, 2005). The stress response is to maintain homeostasis, which includes a series of physiological reactions such as endocrine activation (especially of the HPA axis) and cardiovascular changes (Sapolsky, 2003). The symptomatology, such as irritability, anxiety and a feeling of being unable to cope with, may ultimately result in depression when exposure to a prolonged and sustained stress (Lanfumeijer et al., 2008). Chronic stress often acts as a trigger to the onset of major depression and is associated with a decreased sensitivity to HPA axis feedback inhibition by cortisol in primates or corticosterone in rodents. Excessive stimulation of the axis further increases the secretion of glucocorticoids, which affects many aspects of peripheral and neuronal function, including immune, epithelial cell growth and energy metabolism, neuronal connections, and synaptic transmission (McEwen and Stellar, 1993).

It is a common finding that around 50% of depressed patients (80% if severely depressed) show hyperactivity of the HPA axis (Young et al., 1991). Interestingly, similar changes in the hyperactivity of the HPA axis have been reported in animals subjected to chronic stress (Leonard, 2005). Elevated corticosterone level is a hallmark of HPA axis feedback inhibition evidenced by animal studies (Centeno and Volosin, 1997). This feedback is mediated by two types of corticosteroid receptors in the brain, the mineralocorticoid receptor (MR) and the GR (McEwen, 2000). The MR is a high-affinity receptor which binds corticosterone at low concentration ($K_d \sim 0.5nM$). MR is almost completely occupied (90%) by basal corticosterone levels and this contributes to maintaining homeostasis. When normal secretion of glucocorticoids is altered during stress, leading to increased levels of corticosterone, GR becomes substantially occupied by the hormone ligand. GR has a widespread distribution in limbic regions such as the hippocampus, paraventricular nucleus (PVN), the locus coeruleus and the dorsal raphe nucleus (DRN) (Harfstrand et al., 1986; Reul and de Kloet, 1986). Glucocorticoids diffuse passively through cellular membranes and bind to intracellular glucocorticoid receptors (GR), causing their translocation into the nucleus (Gillespie and Nemeroff, 2005). In the nucleus, these ligand-activated transcription factors bind to specific DNA response elements and alter gene expression. In the brain, glucocorticoid-regulated gene changes mediate a variety of effects on neuronal excitability, neurochemistry and structural plasticity (McEwen, 2000).

2.2 Serotonin and its receptors in depression

5-HT was discovered in 1948 and is a phylogenetically conserved neurotransmitter (Rapport et al., 1948; Barnes and Sharp, 1999). It is synthesized from L-tryptophan both in the peripheral nervous system and the CNS, via tryptophan hydroxylase 1 and 2, respectively (Walther et al., 2003). In the CNS, 5-HT neurons are localized in the raphe nuclei and project, via ascending and descending pathways, to a wide range of brain regions (Dahlström and Fuxe, 1964). These receptors affect a wide range of physiological and psychopathological processes such as mood disturbances, sleep, temperature control appetite, sexual behavior, movement, pain perception, and gastrointestinal motility. It is well established that the 5-HT is a phylogenetically conserved monoaminergic neurotransmitter which is crucial for a number of physiological processes and is dysregulated in several disease states including depression, anxiety and schizophrenia. As an important neurotransmitter, serotonin exerts its functions through 14 5-HT subtypes receptors. Exposure of experimental animals to various stressors, such as restraint stress and electroshock, has been shown to increase the turnover of serotonin and its receptors in the frontal cortex, hippocampus, amygdala and other brain regions (Inoue et al., 1994).

Fourteen different 5-HT receptors have been cloned and pharmacologically characterized (Barnes and Sharp, 1999; Dahlstrom and Fuxe, 1964; Walther et al., 2003; Millan et al., 2008). The human 5-HT receptors are divided into 7 distinct families (5-HT₁₋₇) (Davis et al., 2002). With the exception of the 5-HT₃ receptor as a ligand-gated ion channel, all other serotonin receptors (5-HT_{1A-E}, 5-HT_{2A-C}, 5-HT₄, 5-HT₅, 5-HT₆, 5-HT₇) are G protein-coupled receptors that activate an intracellular second messenger cascade to produce an excitatory or inhibitory response. Activation of the specific G-protein can affect enzymes (5-HT₁- and 5-HT₅-class receptors decrease cAMP formation; 5-HT₂-class receptors increase inositol triphosphate and diacylglycerol formation; and 5-HT₄, 5-HT₆ and 5-HT₇ receptors increase cAMP formation) and the function of cation channels especially K⁺ and Ca²⁺ (Kushwaha and Albert, 2005).

5-HT, as an important neurotransmitter, has long been reported to exert an important mitogenic action in the central neural system (CNS) during development (Lauder et al., 1981; Whitaker-Azmitia, 1991). In the adult CNS, serotonin is involved in neuronal and synaptic plasticity, and its action on the serotonin 5-HT_{1A} receptor is particularly significant in this regard (Azmitia and Whitaker-Azmitia, 1997). It was also found that the powerful mitogenic effect of fenfluramine (a releaser of serotonin throughout the CNS) on the granule cell layer of the adult rat dentate gyrus (DG) could be completely blocked by pretreatment with a specific 5-HT_{1A} antagonist (Jacobs, 2002).

The 5-HT_{1A} and 5-HT_{2A} receptors are the most studied receptors in relation to affective disorders. It has been shown, in both human and animal studies, that 5-HT_{1A} (Blier et al., 1993; Nishi et al., 2009), 5-HT_{1B} (Benjamin et al., 1990; Clark et al., 2002; Kaiyala et al., 2003; O'Connor et al., 1994; Saudou et al., 1994; Sari, 2004), 5-HT_{2A} (Bhagwagar et al., 2006), and a 5-HT transporter (5-HTT) (Bhagwagar et al., 2007) play important roles in affective disorders as well as the action of antidepressants. Evidence is accumulating that dysfunction in the brain serotonergic system relates to mood and behavior disorders (Soares and Mann, 1997). The 5-HT_{1A} receptor is not only a presynaptic autoreceptor (as described earlier) but also a postsynaptic receptor, which is similar to the 5-HT_{2A} receptor and highly distributed in limbic areas and hypothalamus. In rodents, 60% of the neurons in the prefrontal cortex are expressing 5-HT_{1A} and/or 5-HT_{2A} receptors (Amargós-Bosch et al., 2004). Both of these receptors are expressed in different cell types including pyramidal cells and GABAergic interneurons in both frontal cortex and hippocampus. The 5-HT neurons in the dorsal raphe are regulated by somatodendritic presynaptic 5-HT_{1A} receptors and distal feedback via postsynaptic 5-HT receptors which regulate the glutamatergic neurons in the prefrontal cortex (Celada et al., 2001; Martín-Ruiz et al., 2001; Puig et al., 2003).

The potential role of 5-HT_{1A} receptors in the function and structure (e.g. DG neurogenesis) of hippocampus-related depressive disorders has been reported earlier (Gould, 1999; Radley and Jacobs, 2002), and the 5-HT_{1A} receptor is present at a particularly high concentration in the hippocampus, especially in the DG. The consistent neuroendocrine evidence in depression has already demonstrated a reduction in 5-HT_{1A} receptor function and number (Porter et al., 2004; Riedel et al., 2002; Drevets et al., 1999). The clinical reports have pointed out that the low level of 5-HT_{1A} receptors represents a risk factor in mood disorders (O'Neill and Conway, 2001; Cryan et al., 2005). Animal studies also suggest that the increase in the neurotransmission at postsynaptic 5-HT_{1A} receptors may mediate the therapeutic effects of some antidepressants (Welner et al., 1989). In addition, many studies suggest that increases in adult neurogenesis after the SSRI administration require the activation of 5-HT_{1A} receptors (Santarelli et al., 2003), which is consistent with the results that 5-HT_{1A} receptor antagonists or knockout mice decrease or lack cell proliferation in the dentate gyrus, respectively (Radley and Jacobs, 2002; Santarelli et al., 2003). Furthermore, it has been reported that the antidepressant effect of SSRIs are mediated by 5-HT_{1A} receptors (Tatarczynska et al., 2002; Hirano et al., 2002) by changing the receptor-mediated G-protein-coupled inwardly rectifying potassium (GIRK) currents (Cornelisse et al., 2007). Therefore, 5-HT_{1A} is definitely involved in depression as well as the action of antidepressants.

Recent studies have also pointed out an important role for 5-HT₂ receptors in the pathology of depression as well as the action of many antidepressants (Cryan and Leonard, 2000; Cryan and Lucki, 2000; Boothman et al., 2006). Treatment of some established antidepressants results in a reduction of 5-HT₂ receptor density in rat frontal cortex (Klimek

et al., 1994; Subhash et al., 1997). Indeed, most antidepressants can primarily down-regulate 5-HT_{2A} receptors, which indicates the therapeutic potential of this receptor (Toth and Shenk, 1994). In addition, some 5-HT_{2A/2C} receptor antagonists are found to enhance the antidepressant-like effects of SSRIs when given jointly (Redrobe and Bourin, 1997; Redrobe and Bourin, 1998), which suggests that the antagonism of these receptors may be implicated in the action of such antidepressants. Moreover, it has been reported that mRNA levels of 5-HT_{1A} and 5-HT₂ remained unchanged after the treatment of imipramine or citalopram, implying that the antidepressant outcome may involve the changes of the 5-HT receptor density as well as the functional effects of 5-HT receptors (Butler et al., 1993; Burnet et al., 1994; Spurlock et al., 1994).

2.3 Neurotrophic mechanisms in depression

Animal studies have already shown that acute or chronic stress can activate HPA axis and inhibit the cell proliferation in adult hippocampus (Warner-Schmidt and Duman, 2006; Paizanis et al., 2007). It has been shown that the psychosocial and physical stressors can inhibit the neurogenesis in various animal models and thus lead to decreased cell proliferation and survival (Joëls et al., 2007). In the chronic stressed model, both neurogenesis and proliferation were reduced in all rats (Joëls et al., 2007, Li et al., 2006). Moreover, treatment with diverse antidepressants, such as lithium, will reverse these changes (Knijff et al., 2007).

It is widely accepted that both stress and corticosteroid can decrease the levels of some neurotrophic factors in hippocampus while many classes of antidepressant as well as electroconvulsive shock treatment can reverse the decrease and prevent the action of stress, which is the base of the neurotrophic mechanism of depression (Duman and Monteggia, 2006). Neurotrophic factors, such as BDNF, NGF, neurotrophin-3 (NT-3), NT-4, NT-5 and NT-6, have been shown to enhance the cell proliferation and neurogenesis in the subgranular layer of the dentate gyrus (Banasr et al., 2004). These neurotrophic factors are critical to the viability and function of the neurons. Local infusion of BDNF into the midbrain or hippocampus regions has antidepressant-like effects in behavioral animal models of depression (Siuciak et al., 1994; Duman and Monteggia, 2006). For human studies, reduced levels of BDNF were detected in postmortem brain tissues of the depressed patients while antidepressant treatment can reverse it (Chen et al., 2001). All these data suggest that the action of antidepressants might be mediated via activating BDNF signaling in the hippocampus.

Increasing evidence has shown that the neuroprotective effects of the neurotrophic factors are mainly mediated by inhibiting the cell death/apoptosis pathways (Du et al., 2003). BDNF, as a major neurotrophic factor, can initiate various signaling pathways, such as MAPK/ERK and PI-3K/Akt pathways, through binding to its tyrosine kinase TrkB receptor and thus activate the downstream molecules which can promote neurogenesis and cell survival. The phosphor-ERK and PI-3K/Akt can further phosphorylate and activate cyclic adenosine monophosphate (cAMP) response element binding (CREB) (Banasr et al., 2004; Chen and Manji, 2006). For instance, BDNF and CREB levels are decreased in cerebral cortex of depressive patients, while the treatment of antidepressants can enhance the BDNF levels in patients (Karege et al., 2002). In the CREB knockout mice, BDNF up-regulation is abolished after the antidepressant treatment (Conti et al., 2002). Moreover, a variety of antidepressants, regardless of their mechanisms, up-regulate the BDNF expression in rodent hippocampus, while the non-antidepressant drugs are not effective (Duman and Monteggia,

2006). In addition, the phosphorylation of CREB will consequently activate the transcription of many survival-promoting genes, such as B-cell lymphoma 2 (bcl-2) and BDNF.

Bcl-2, a critical anti-apoptotic protein, has been shown to be upregulated by mood stabilizers in multiple animal studies (Chen et al., 1999; Manji et al., 2000; Chang et al., 2009). Reduced level of bcl-2 was also observed after stress: bcl-2 mRNA level was decreased by 70% when exposed to aggressive social stress after ischemia. Moreover, overexpression of bcl-2 will attenuate the infarcts caused by high level of corticosterone (DeVries et al., 2001). Actually, the survival-promoting effect of CREB might be attributed to its induction of bcl-2 transcription (Finkbeiner, 2000). There is accumulating evidence that CREB is a common target for different classes of antidepressants. Various kinds of antidepressants significantly increase the Phospho-CREB level as well as CREB binding activity in rat hippocampus (Nibuya et al., 1996; Koch et al., 2003). Moreover, the activation of CREB will in turn promote the transcription and synthesis of more BDNF (Riccio et al., 1999).

As discussed above, the serotonergic system is intensely involved in the pathology and treatment of depression (Mattson et al., 2004). It is also widely accepted that 5-HT receptor activation is important for the pharmacotherapeutic effects of antidepressants (Ivy et al., 2003). Actually, there exist interactions between BDNF and serotonin systems (Martinowich and Lu, 2008). A critical pathway following 5-HT stimulation is cAMP/PKA signaling transduction which results in the phosphorylation of CREB (Nestler et al., 2002). Moreover, the CREB activation can induce BDNF transcription and then increase cell proliferation (Tao et al., 1997). Indeed, there is crosstalk between the two pathways: the activation of 5-HT receptors coupled to cAMP production and CREB activation can induce transcription of BDNF gene; on the other hand, increased BDNF synthesis will promote the growth and sprouting of 5-HT neuron axons which can increase the neuronal plasticity and survival (Mamourias et al., 1995). For example, BDNF can promote the neurogenesis of 5-HT neurons (Mamounas et al., 1995) and change the 5-HT receptor expression (Lyons et al., 1999). Moreover, the activation of 5-HT receptors will lead to the phosphorylation of the transcription factor cAMP responsive element binding protein (CREB), which will start the transcription of BDNF (Mattson et al., 2004). All these observations indicate the downregulation of neurotrophic factors might mediate, at least in part, the decreased neurogenesis and structural damage in the stressed brain. Under the "neurogenesis hypothesis", neurotrophic factors might also serve as promising targets for the treatment of depression.

3. Phytochemicals as antidepressants

3.1 Phytochemicals and serotonergic system

Health benefits associated with Mediterranean diets are due to the large intake of functional plant foods and beverages, i.e., fruits, vegetables, cereals, legumes, nuts, wine, beer, and olive oil, containing a great array of bioactive phytochemicals or nutraceutical compounds. Therefore, the low risk of chronic diseases, such as coronary heart disease and certain cancers, observed in some population groups, results from a diverse eating style, either in term of foods or food components. The paradigm of the relationship between the chemical diversity of a particular food and the array of its biological activities may be symbolized by grape. Despite the extensive knowledge about phenylpropanoids, principally polyphenols (stilbenes and anthocyanins) and condensed tannins (proanthocyanidins), in grape and wine, little it is known about the other compounds, such as tetrahydro-b-carbolines.

Recently, it has been attached importance to the dietary indoleamines, melatonin, and serotonin, in different plant foods, including grape, thus further supporting the hypothesis that health benefits, associated with Mediterranean dietary style, are due to plant food chemical diversity. Besides, because of plant sessile status, synthesis of phytochemicals represents a major strategy for counteracting unfavorable conditions, in terms of natural selection, biological evolution, and biodiversity.

Plant natural products can be roughly ascribed to three main classes of compounds, phenylpropanoids, isoprenoids, and alkaloids, widely distributed in plant foods and medicinal herbs (Facchini, 2001; Holstein and Hohl, 2004; Iriti and Faoro, 2004). Polyphenolic phytochemicals, which are active components found in many medicinal plants and regulate a variety of enzymes as well as cell receptors, are a group of plant secondary metabolites characterized by the presence of more than one phenolic unit which is linked directly to the aromatic rings (Bravo, 1998). These compounds are categorized by the number of phenol rings as well as the structural elements linked between the rings. The major classes include phenolic acids, flavonoids, stilbenes and lignans (Manach et al., 2004). A growing number of researchers have shown interests in polyphenolic phytochemicals. The major reasons include their antioxidative effects and potentials in preventing oxidative stress-induced diseases, such as neurodegenerative diseases and cancer (Scalbert et al., 2005).

Curcuma longa, one of the most extensively studied phytochemicals, is a major constituent of many traditional Chinese medicines, such as Xiaoyao-san, and has been used widely in Asian countries to manage mental disorders effectively. Curcumin is a major active component of *C. longa* and its antidepressant-like effect has been previously demonstrated in animal models of depression such as the forced swimming test (Xu et al., 2005) and chronic unpredictable mild stress model (Li et al., 2009). Moreover, the antidepressant effect of curcumin can be potentiated by various kinds of antidepressants when given jointly, such as fluoxetine, venlafaxine, and bupropion. Enhanced serotonin level has also been found in mice after curcumin administration (Kulkarni et al., 2008). The concomitant administration of curcumin and piperine, a bioavailability enhancer, showed a significantly enhanced level of serotonin (Bhutani et al., 2009). Wang et al., also demonstrated that the antidepressant effect of curcumin in the forced swimming test may involve 5-HT receptors, especially 5-HT_{1A/1B} and 5-HT_{2C} subtypes (Wang et al., 2008). The recent study also showed that curcumin attenuated the stress-induced decrease in 5-HT_{1A} mRNA level in rat hippocampus (Xu et al., 2007).

Resveratrol is a key antioxidant that present in grapes and red wine. The trans-resveratrol, as the active component of *Polygonum cuspidatum* which is traditionally used to treat neuropsychiatric disorders in Asia countries, has been studied for anti-inflammation, amelioration of learning and memory impairment, and neuroprotection (Tredici et al., 1999; Chen et al., 2007; Kumar et al., 2007; Ranney and Petro, 2009). The recent studies have already shown the inhibitory effects of resveratrol on noradrenaline and 5-HT uptake activity in rats (Yáñez et al., 2006). Moreover, significantly decreased immobility time in mouse model of despair tests as well as the enhanced levels of serotonin and noradrenaline in brain regions have been demonstrated after trans-resveratrol application (Xu et al., 2010). The reduced activity of MAO, which catalyze the oxidative deamination of dietary amines and monoamine neurotransmitters, such as 5-HT, have been shown in both in vivo and in vitro experiments (Mazzio et al., 1998; Xu et al., 2010). All these data indicate the antidepressive effect of Resveratrol.

Proanthocyanidins, known as oligonols (catechin-type monomers, dimmers and trimmers) and oligomeric proanthocyanidins (oligomers), exists commonly in plants, such as grape seeds (DalBó et al., 2006). People have shown that proanthocyanidins have a wide range of pharmacological activities, including antioxidant effect, antinociceptive and cardioprotective properties (Preuss et al., 2000; Uchida et al., 2008; Sato et al., 2001). Recently, Xu et al. have shown that proanthocyanidin can reduce the duration of immobility in both tail suspension and forced swimming test. Moreover, significantly enhanced 5-HT concentrations were found in frontal cortex, hippocampus and hypothalamus of mice after the proanthocyanidin administration (Xu et al., 2010). However, the mechanisms underlying the antidepressant effect of proanthocyanidin is still not clear.

3.2 Phytochemicals and neurotrophic mechanisms

The emerging neurotrophic hypothesis of antidepressant actions suggests that the stress-induced BDNF reduction could, at least in part, induce the structural damage as well as the reduced neurogenesis, and most antidepressant treatment share the effect of increasing BDNF and neurogenesis, which might be via downstream mechanisms (Duman et al., 1997; Duman, 2004). Through cAMP-PKA and IP₃-Ca²⁺ dependent protein kinase secondary messenger systems, CREB can be regulated by 5-HT receptors (Duman, 1998; Rajkumar and Mahesh, 2008). The activation of CREB will start the BDNF transcription, which leads to the activation of downstream cascades including Ras-Raf-ERK and PI-3K/AKT via the TrkB receptor (Berton and Nestler, 2006). Accordingly, the chronic treatment of antidepressants increases cell proliferation and neurogenesis, accompanied with enhanced phosphorylated CREB (Sasaki et al. 2007; Li et al., 2009).

A number of researches have suggested that phytochemicals are neuroprotective. In the transient middle cerebral artery occlusion animal model, Cyanidin-3-O-beta-D-glucopyranoside extracted from mulberry extract showed a neuroprotective effect against the brain injury (Kang et al., 2006). Low concentration of (-)-epigallocatechin-3-gallate from green tea can reduce the neuronal cell death in serum-starved cells, and promote the neurite outgrowth (Reznichenko et al, 2005). Low dose of curcumin has been shown to activate the ERK signaling and enhance the neurogenesis in adult hippocampus, which indicates its capability to enhance neural plasticity and repair (Kim et al., 2008b). The oral administration of 10 and 20 mg/kg curcumin to mice can prevent the stress-induced decrease of BDNF level in hippocampus and enhance the hippocampal neurogenesis, which suggests that curcumin might protect hippocampal neurons from further damage in response to chronic stress via up-regulating BDNF in hippocampus (Xu et al., 2007). Curcumin application also prevents the cultured rodent cortex cells against glutamate excitotoxicity (Wang et al., 2008). Recently, it has been demonstrated in the chronic unpredictable mild stress (CUMS) rats, curcumin was also able to improve the CREB activity (Li et al., 2009). More importantly, studies have also shown that curcumin exerts the neuroprotective effects via BDNF/TrkB-mediated PI-3K/Akt and MAPK/Erk cascades, and thus stimulating the transcription factor CREB (Wang et al., 2008; Wang et al., 2010).

It has been reported that resveratrol and its methylated derivatives exhibit neuroprotective effects in SH-SY5Y cells against parkinsonian mimetic 6-hydroxydopamine (6-OHDA)-induced neurotoxicity (Chao et al., 2010). Pretreatment of resveratrol has been shown to provide neuroprotection in animal models of cerebral ischemia (Della-Morte et al., 2009), which might be mediated through NMDA and estrogen receptor (Saleh et al., 2010). Moreover, Piceatannol (3,4,3',5'-tetrahydroxy-*trans*-stilbene) isolated from the seeds of

Euphorbia lagascae, is a metabolite of resveratrol existing in grapes and red wine (Ferrigni et al., 1984; Larrosa et al., 2004). Previous studies have shown that piceatannol exhibited protective effect against A β -induced neuronal cell death in cultured PC-12 cells (Kim et al., 2008). The following studies further demonstrated that the neuroprotective effect against oxidative stress is likely due to the inhibition on JNK (Kim et al., 2008) or c-Jun N-terminal kinase activity (Jang et al., 2009). Although the mechanisms of the neuroprotective effects of resveratrol and piceatannol are still unclear, their diverse pharmacological properties have already attracted wide attention.

Fisetin (3,3',4,7'-tetrahydroxyflavone) is a flavonoid which exists in many plants and foods, such as strawberries (Arai et al., 2000). Recently, people have demonstrated that fisetin can protect neuronal cells from oxidative stress induced cell death, and demonstrate neurotrophic effect of improving the differentiation of PC-12 cells (Ishige et al., 2001), which might depend on the activation of ERK signaling pathway (Sagara et al., 2004). Moreover, the recent studies found that fisetin can facilitate long-term memory in rats, which is mediated via ERK signaling and the CREB phosphorylation (Maher et al., 2006). All these data indicate that fisetin has neurotrophic effect and can promote cell proliferation, and therefore it may be useful in treating mental disorders, including depression.

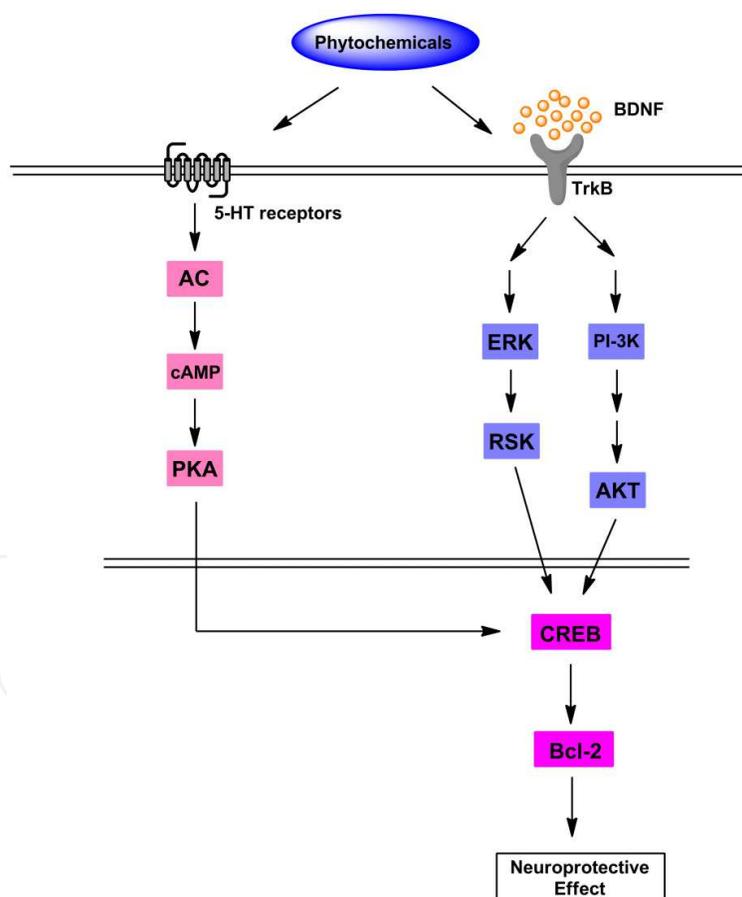


Fig. 1. Neuroprotective pathways targeted by phytochemicals. The activated BDNF receptor TrkB will initiate ERK and PI-3K signaling pathways. 5-HT receptors, which are usually coupled to G proteins, will activate the AC/PKA cascade. Phytochemicals can stimulate both 5-HT and BDNF signaling cascades which interweave and result in activation of CREB, and thus exert their neuroprotective effects.

Ferulic acid (4-hydroxy-3-methoxycinnamic acid; FA) is an ample phenolic phytochemical found in plant components (Srinivasan et al., 2007). Ferulic acid has been reported to have a number of pharmacological activities including antioxidative, anti-inflammatory, anti-cancer, anti-diabetic, anti-atherogenic and neuroprotective effects (Mukhopadhyay et al., 1982; Kawabata et al., 2000; Balasubashini et al., 2004; Kim and Kim, 2000; Yogeta et al., 2006). Ferulic acid can prevent neurons from A β -induced cell death, which is associated with its antioxidative activity (Sultana et al., 2005; Picone et al., 2007). The recent studies found that oral administration of ferulic acid can attenuate the stress-induced behavior in the depression-like model mice. Moreover, treatment of ferulic acid can increase the CREB phosphorylation. Accordingly, BDNF mRNA level in the hippocampus is also enhanced (Yabe et al., 2010). Although the molecular mechanisms of the antidepressant effect of ferulic acid still needs to be clarified, the current result indicated its therapeutic potential in the treatment of depressive disorder.

4. Future directions

It is widely accepted that phytochemicals are neuroprotective. The actions of the antidepressant effects of phytochemicals appear to involve many mechanisms, including monoamine neurotransmitters-based mechanism, HPA axis-based mechanism, and neurotrophic factors, or neurogenesis, based mechanisms. All these effects seem to be associated with the activation of the signaling cascades in brain, which can trigger a number of responses, such as promoting the neuronal survival and differentiation and inhibiting neuronal apoptosis. Despite the great advances in our understanding of depression, little is known about the antidepressant mechanisms of many phytochemicals because their antidepressant effects always involve multiple complex mechanisms. Therefore, it is very important to identify the bio-molecules and signaling network that can be specifically regulated by individual phytochemical.

There are many advantages of phytochemicals in regard to application to development of antidepressants. For instance, phytochemicals are natural products, or even isolated from some herbal medicines, so they can be readily moved to the clinical trials on humans. Moreover, chemical analogues of the druggable phytochemicals can be developed for better bioavailability and lower toxicity. However, although the consensus is developing that phytochemicals are potential antidepressant candidates, our understanding and knowledge of the active phytochemicals as well as their mechanisms of actions are limited. It is therefore of critical need to develop high-throughput assays to identify antidepressant phytochemicals. Further *in vivo* and *in vitro* studies are required to reveal in more details about the antidepressant mechanisms of phytochemicals.

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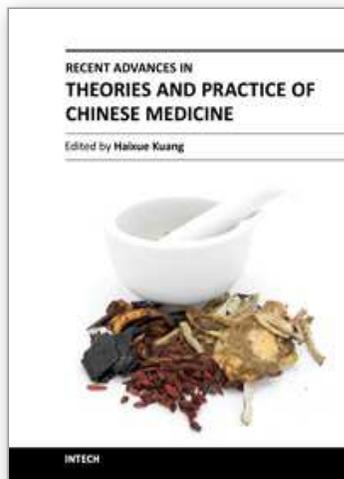
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During the recent years, traditional Chinese medicine (TCM) has attracted the attention of researchers all over the world. It is looked upon not only as a bright pearl, but also a treasure house of ancient Chinese culture. Nowadays, TCM has become a subject area with high potential and the possibility for original innovation. This book titled *Recent Advances in Theories and Practice of Chinese Medicine* provides an authoritative and cutting-edge insight into TCM research, including its basic theories, diagnostic approach, current clinical applications, latest advances, and more. It discusses many often neglected important issues, such as the theory of TCM property, and how to carry out TCM research in the direction of TCM property theory using modern scientific technology. The authors of this book comprise an international group of recognized researchers who possess abundant clinical knowledge and research background due to their years of practicing TCM. Hopefully, this book will help our readers gain a deeper understanding of the unique characteristics of Chinese medicine.

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