Perimenopausal depression: Targeting inflammation and oxidative stress (Review)

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Abstract. Depressive disorder is a highly disabling condition that affects more than 300 million individuals worldwide, with women affected at a higher rate than men. With the aging of the population, the incidence of perimenopausal depression has risen markedly, seriously jeopardizing women's physical and mental health. Symptoms of perimenopausal depression include feelings of depression, stress, anxiety and endocrine dysfunctions, particularly hypogonadism and senescence. During perimenopause, estrogen and progesterone levels fluctuate erratically, adding to the risk of developing depression associated with perimenopause. As a result of these hormonal changes, proinflammatory mediators are produced and oxidative stress is induced, which finally leads to progressive neuronal damage. The present study mainly reviewed roles of neuroinflammation in perimenopausal depression and explained potential anti-inflammatory and anti-oxidative stress mechanisms for clinically effective therapeutic treatment.

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Contents

1. Introduction

Perimenopause is the stage through which women pass as they move from adulthood to old age. During this period, due to the decline in ovarian function and the decrease in estrogen levels, women develop a group of syndromes called perimenopausal syndromes, which are characterized by disorders of the vegetative nervous system accompanied by neuropsychological symptoms (1). Perimenopausal syndrome is commonly accompanied by significant mood disorder problems (2,3). Depression and anxiety are considered a harmful mood disorder characterized by persistent feelings of worry, despair, tension and distress, accompanied by physical symptoms such as tachycardia, nervousness and an inability to relax (4-6). Medication and psychotherapy are the conventional treatments for perimenopausal depression, with the former being considered the standard treatment and the latter being insufficient on its own in most cases (7). Tricyclic antidepressants, monoamine oxidase inhibitors and selective serotonin reuptake inhibitors are main conventional antidepressant medications used to treat perimenopausal depression (8-10). New pharmacotherapies, including serotonin and norepinephrine reuptake inhibitors, glutamatergic agents and selective estrogen receptor modulators, have also been developed in recent years (11,12).

The monoamine hypothesis, currently important in the field of depression, was proposed after the discovery of the

antidepressant effects of monoamine oxidase inhibitors (MAOIs) (13). According to it, depression is caused by low levels of serotonin, norepinephrine and dopamine in the central nervous system. By increasing these neurotransmitter concentrations, MAOIs and tricyclic antidepressants alleviate depression symptoms (14). Furthermore, patients with depression have lower plasma tryptophan levels and less serotonin in the cerebrospinal fluid. As a result, serotonin was also included in this hypothesis, leading to the development of selective serotonin reuptake inhibitors (15). It seems most individuals are in agreement that boosting monoamine levels would alleviate depressive symptoms. However, we still do not understand more about this hypothesis or know how to find new drugs that target the central monoamine system.

In recent years, an increasing number of studies have focused on the role of neuroinflammation in the perimenopausal depression (16-19). There are several processes associated with neurodegeneration that may contribute to neuroprogression, including apoptosis, decreased neurogenesis, reduced neuronal plasticity and an increase in autoimmune responses (20). Elevated oxidative stress markers and a neuroinflammatory signature are consistently observed in the blood of individuals with depression (21). The present study mainly introduced the roles of neuroinflammation and oxidative stress in perimenopausal depression and then analyzed potential anti-inflammatory and anti-oxidative stress mechanisms for estrogen, acupuncture and Chinese medicines.

2. Neuroinflammation in perimenopausal depression

Recently, the peripheral immune system has been found to play an important role in neuroinflammation. Activated endothelial cells cause disruption of the blood-brain barrier, allowing peripheral immune cells to infiltrate the CNS and transendothelial migration of immune cells tends to exacerbate neuroinflammation (22). Inflammatory differentiation of monocytes in the central nervous system by dendritic cells and macrophages drives neuroinflammation and transforms neuroglia into a deleterious phenotype, even leading directly to nerve damage (23). Over-activated microglia release TNF-α and IL-1β, while activating peripheral T cells into the CNS, creating a positive feedback loop. A significant increase in proinflammatory cytokines secreted by CD4 T cells is associated with perimenopause, including IL-8 and TNF-α (24). Among perimenopausal women, estradiol levels in peripheral serum correlate inversely with serum IL-8, TNF-α and microglial and astrocytic reactivity (25). Moreover, estrogen deficiency can activate immune cells, resulting in proinflammatory cytokine milieus, such as IL-1, IL-6 and TNF-α (26). The interleukins area very important family of cytokines. IL-1 is one of the most common and potent inflammatory factors of the family and IL-1β is the major secreted form of IL-1, which plays an important role in the inflammatory process (Fig. 1).

As an important part of the limbic system, the hippocampus plays an important role in spatial and contextual memory. There is relatively high expression of IL-1, its receptor (IL-1R) and the natural IL-1R antagonist (IL-1RA) in the hippocampus, indicating their potential to modulate hippocampal memory functions (27). As a result, excessive or dysregulated IL-1 signaling may be associated with deficits in hippocampus-dependent memory processes (28). Glutamate, a neurotransmitter converted into gamma-aminobutyric acid (GABA) by glutamic acid decarboxylase (GAD), can be affected by pro-inflammatory cytokines (29). The influence of pro-inflammatory cytokines occurs through complex interactions with N-methyl-D-aspartate (NMDA) and amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors (30). It has been shown that chronic elevations in IL-1 induced by intraventricular infusions of lipopolysaccharide (LPS) reduce both NMDAR-dependent and NMDAR-independent forms of long-term potentiation in the hippocampal region (31). Hippocampal-dependent memory is mediated by long-term potentiation, which is triggered by high-frequency stimulation and theta bursts. In an autoimmune encephalomyelitis mouse model, activated microglia secreted IL-1β that suppressed GABAergic inhibitory transmission, which may lead to neuroplastic damage (32). IL-6 plays an important role in regulating the age-related loss of critical GABAergic interneurons that express parvalbumin by increasing the superoxide production of neuronal NADPH-oxidase and cognitive performance in aging mice is preserved by this effect (33). A key role for cytokines is their ability to mediate interactions between immune cells and the neuroendocrine system, especially through the hypothalamus-pituitary-adrenal (HPA) axis and the effects it has on immunosuppressive mechanisms (34,35). The increase in dialysate noradrenaline induced by IL-1β corresponds partly to the increase in plasma adrenocorticotropic hormone (ACTH) and corticosterone, supporting an association between noradrenaline, IL-1β and HPA axis activation (26). It has also been demonstrated that IL-1 can stimulate the hypothalamic corticotropin-releasing factor, thereby increasing ACTH and glucocorticoids secretion and, finally, can cause glucocorticoid resistance and disrupt HPA axis function (36).

The aforementioned inflammatory cytokines may not be the only cytokines related to perimenopausal depression. TGF-β may play an important role as well. In multicellular organisms, TGF-signaling promotes embryonic development, tissue homeostasis and damage repair through coordinated effects on cell proliferation, phenotypic plasticity, migration and metabolic adaptation (37-40). Defective TGF-β signaling specifically affects epithelial cells, tissue fibroblasts and immune cells, disrupting immune tolerance, promoting inflammation and making disease treatment more difficult. When adult mice are deficient in TGF-β, they are more susceptible to excitotoxic damage and develop an increased number of degenerating neurons. Synaptophysin and laminin are also reduced (41).

3. Oxidative stress in perimenopausal depression

Oxidative stress is an important pathological factor in depression and aging and is a common feature of various chronic diseases (42). Depressive disorders are associated with oxidative stress, an imbalance between oxidative and antioxidant reactions in the body. Excess reactive oxygen species (ROS) play a significant role in this process (43,44). Perimenopause in women is the process of aging, which is accompanied by a weakening of antioxidant activity, allowing the accumulation of ROS, which can trigger processes such as inflammation,

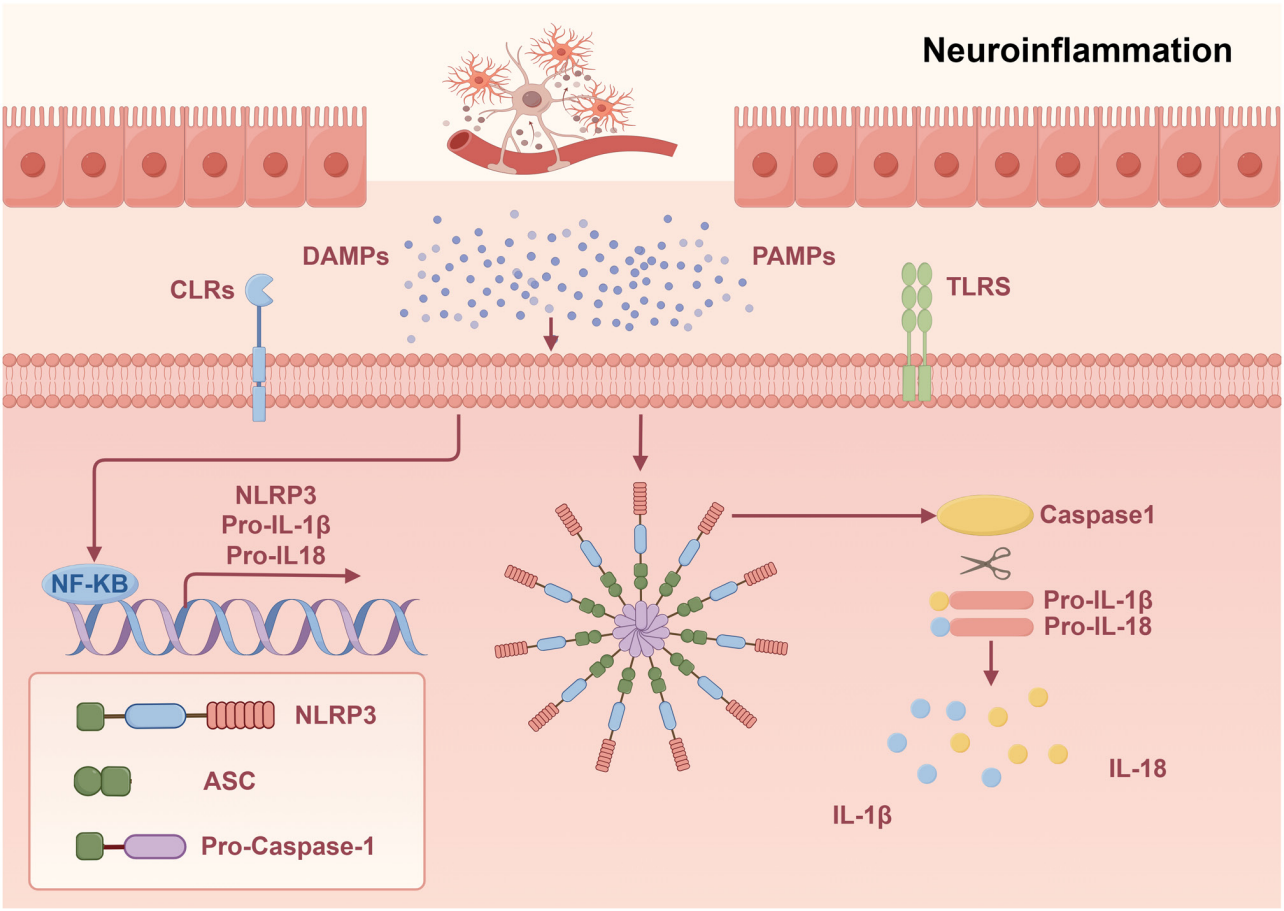

Figure 1. Neuroinflammation in perimenopausal depression. The NBD, LRR and NLRP3 activation promotes the synthesis of the inflammatory factors IL-1β and IL-18 to initiate inflammatory responses, which initiate the inflammatory response. Intracellular IL-1β normally exists as an inactive precursor and when an inflammatory response occurs, IL-1β requires shear activation by the IL-1β convertase caspase-1 and is then secreted outside the cell. Created using Figdraw (ID: IPPYU10334). NBD, nucleotide-binding domain LRR leucine-rich repeat; NLRP3 pyrin domain-containing protein 3; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; CLRs, C-type lectin receptors; TLRs, Toll-like receptors; ASC, apoptosis-associated speck-like protein.

neurodegeneration, tissue impairment and cell death (45). Another study has shown that individuals with lower intake of antioxidants have a higher risk of depression (46). Other researchers have suggested that an imbalance between 5-hydroxytryptaminergic and noradrenergic neurotransmitters plays a key role in the pathogenesis of depression (47). Some researchers have found that chronically activated microglia in the central nervous system release large amounts of inflammatory cytokines (48). Activated microglia produce a variety of pro-inflammatory cytokines in response to inflammation and stress that contribute to depressive behaviors by evoking an imbalance of 5-hydroxytryptaminergic and noradrenergic neurotransmission via the HPA axis or by decreasing 5-hydroxytryptamine levels through increased indoleamine-2,3-deoxygenase activity (49).

In spite of the fact that oxygen is essential for neurons, some of its products can be neurotoxic in the brain (50). An excessive level of ROS disrupts neural cytoarchitecture and affects the function of multiple biomolecules, including lipids, proteins and nucleic acids. This results in some undergoing modifications and becoming anti-inflammatory, while others forming and becoming pro-inflammatory (20). ROS also damage nuclear and mitochondrial DNA by modifying bases, reducing purines, destroying ribose sugar and altering DNA-protein cross connections, as well as damaging DNA repair systems (51). As a result of all of these changes, genetic regulation can be altered and programmed cell death can occur. When DNA damage is not repaired, neurons may silence expression of the affected genomic region, which is important for cell survival (52). During a specific transformation of one of the DNA bases, 8-hydroxydeoxyguanosine is produced, which is widely used as a marker of DNA damage in clinical studies and elevated in those who are depressed (53,54).

A significant increase in oxidative stress is observed in postmenopausal women compared with premenopausal women by detecting derivatives of reactive oxygen metabolites and the biological antioxidant potential (55). In addition, higher levels of malonaldehyde, 4-hydroxynenal and oxidized lipoproteins and decreased levels of glutathione peroxidase are shown in postmenopausal women compared with fertile women, indicating that oxidative stress levels rise while antioxidant enzymes are synthesized less during postmenopause (56). Similarly, women who undergo total hysterectomy with bilateral salpingo-oophorectomy show increased oxidative stress and reduced mRNA expression of both superoxide

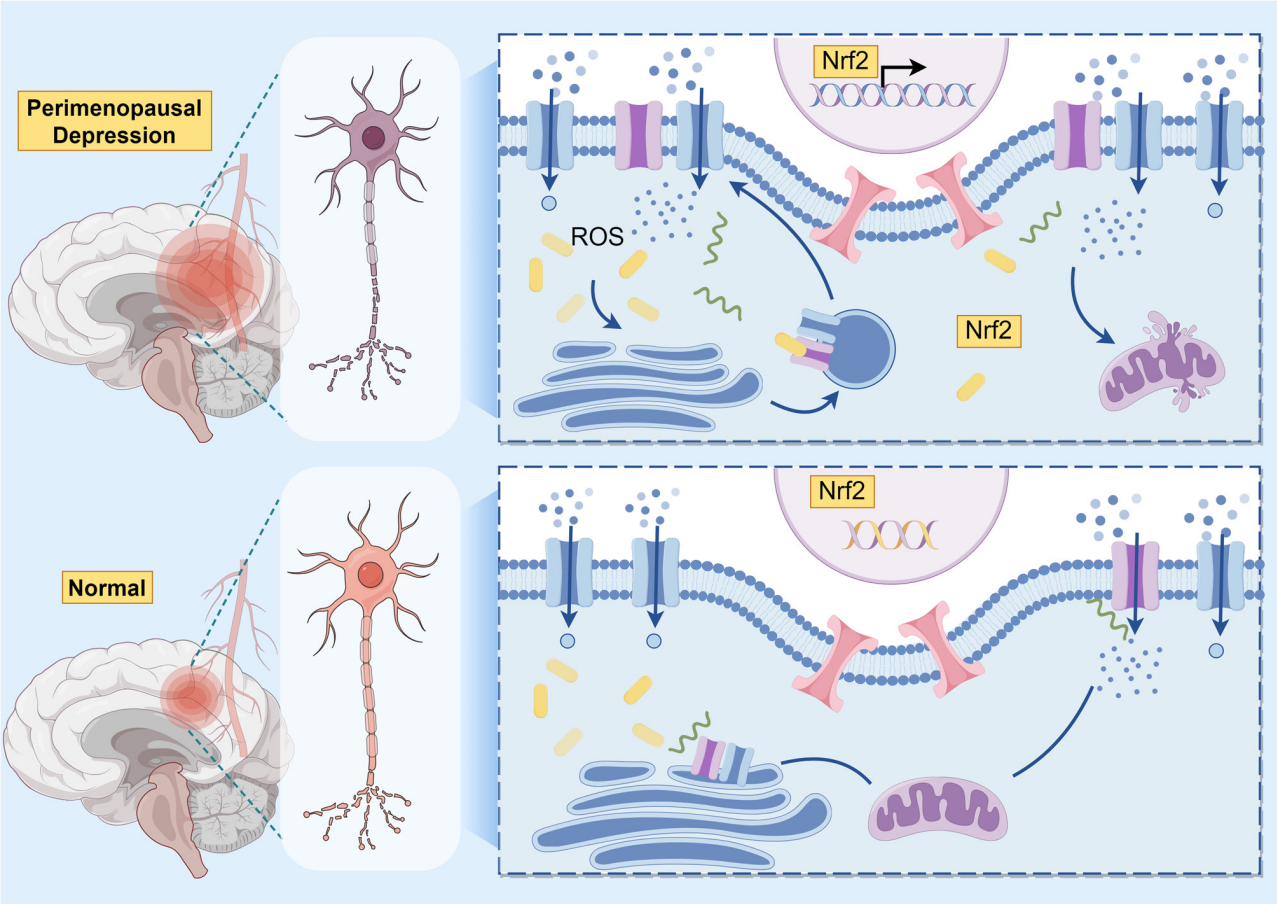

Figure 2. Nrf2 in perimenopausal depression. Created using Figdraw (ID: IAPYUfd933). Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species.

dismutase and glutathione peroxidases. By contrast, estrogen replacement therapy can prevent and counteract these modifications by regulating antioxidant gene expression (57). According to these results, estrogen regulates antioxidant enzyme synthesis in the body, reducing oxidative stress levels in women.

Nuclear factor erythroid 2-related factor 2 (Nrf2), the main cellular defense pathway that is activated in a wide range of cell types because of oxidative stress, induces the production of antioxidants and enzymes to fight apoptosis (58). The Kelch-like ECH-associated protein 1 binds to Nrf2 in the cytoplasm, degrading it through ubiquitination in unstressed conditions (20). When oxidative stress occurs, Nrf2 moves to nucleus where initiates genes transcription coding for proteins with cytoprotective effects (Fig. 2) (59). It also regulates key regulatory molecules, including protective proteins, such as brain-derived neurotrophic factor and IL-10 (60). It has been suggested that Nrf2 might be a potential target in the treatment of neurodegenerative diseases and depression because of its wide range of antioxidant effects (61-63). Using microarrays, researchers discovered that Nrf2 plays an important role in regulating immune and inflammation genes, along with growth factors, signaling proteins and neuron-specific genes (64). Inflammation caused by a deletion of Nrf2 can produce a depressive-like phenotype, while induction of Nrf2 may provide a new approach to developing antidepressants (65). Recent findings indicate that a menopause depression mouse model induced by activation of the Nrf2/HO-1 pathway shows significant amelioration of depression-like behaviors (66).

4. Clinical treatment evidence: Targeting inflammation and oxidative stress

Estrogen. A growing body of research suggests that estrogen has a protective effect on the central nervous system and that estrogen hormone therapy may play a role in the treatment of perimenopausal depression (9). Decreased estrogen levels can lead to the activation of immune cells resulting in the production of a pro-inflammatory cytokine milieu and these peripheral cytokines can negatively affect the central nervous system by entering the brain directly or indirectly through various pathways (67). A study by Maggioli *et al* (68) found that elevated levels of the anti-inflammatory protein Annexin A1 in the central nervous system of model mice treated with estradiol modulate the blood-brain barrier, reduce parietal endothelial cell permeability and inhibit the migration of lymphocytes to the brain.

Estrogen is derived from the adrenal glands in addition to the ovaries. When a woman enters perimenopause, the production of estrogen by the ovaries decreases and estrogen is mainly regulated by the adrenal glands, where the role of

the hypothalamus-pituitary-adrenal (HPA axis) is particularly important (69). Decreased estrogen levels exacerbate hyperactivity of the HPA axis, which is commonly seen in patients with depression (70). The inflammatory cytokines IL-1, IL-6 and TNF-α have been shown to activate the HPA axis (71). Decreased estrogen levels lead to decreased levels of serotonin and dopamine which further stimulate the HPA axis while also making the inflammatory response *in vivo* more persistent (72).

A therapeutic effect of estrogen on perimenopausal depression or clinical symptoms of perimenopausal depression has been demonstrated in several previous clinical trials (73,74). In addition, a clinical trial has shown that the combination of estrogen and antidepressants is more effective in alleviating perimenopausal depression than estrogen or antidepressants alone (75,76).

Acupuncture. Acupuncture is a uniquely Chinese means of treating disease (77). Acupuncture therapy is characterized by the fact that the cure does not rely on medication, but only on the patient's body with needles to stimulate the nerves and cause a local reaction, or warmth to stimulate specific areas of the human body, in order to achieve the purpose of curing the disease (78). It has been demonstrated that the use of traditional means such as acupuncture in the treatment of depression-related disorders is safer and more suitable for long-term treatment than medication (79-82). Acupuncture has a long tradition of use in the treatment of a variety of menopause-related conditions, including perimenopausal syndromes and menopausal syndromes, going back thousands of years (83,84) Neuroimaging reports show that acupuncture elicits a range of CNS responses involving the hippocampus, amygdala, cerebellum, hypothalamus and other limbic structures (85).

Xu *et al* (86) investigated the effects of electroacupuncture on a model of perimenopausal depression by means of a mouse model of perimenopausal depression. The mice treated with electroacupuncture showed a significant increase in the number of spontaneous activities, as well as a significant increase in the levels of T-lymphocyte and serum estrogen (E2) in serum and the levels of serotonin, dopamine and norepinephrine in brain tissues, a decrease in the levels of follicle-stimulating hormone (FSH) and luteinizing hormone in serum and an improvement in the hypothalamic lesions. Studies have shown that electroacupuncture therapy can regulate hormone level disorders and improve pathological changes in the hypothalamus in a mouse model of perimenopausal depression (87,88). In another study Jing *et al* (87) found that electroacupuncture therapy markedly improved depression-like behavior in rats in a depression model. Meanwhile, the changes of related biochemical indexes after treatment in rats were detected and it was found that electroacupuncture treatment could alleviate the decrease of E2, slow the weakening of antioxidant activity in the body and the progression of the disease. In addition, the results of the study also showed that electroacupuncture therapy can promote hippocampal neural proliferation in rats with perimenopausal depression by activating the Wnt/β-catenin signaling pathway and that acupuncture therapy may be an effective therapy for perimenopausal depression.

5. Chinese medicines and potential anti-inflammatory mechanisms

Previous research has shown that depression in women is associated with dramatic fluctuations in ovarian hormones in both clinical and preclinical studies (89-91). However, the controversy over hormone replacement therapy has never ceased in recent years because of the risk of cancer and other cardiovascular diseases (92-94). In China, individuals have been using Chinese medicines to alleviate illness for thousands of years. Modern medical research has shown that traditional compound Chinese medicines can effectively treat perimenopausal depression (95,96).

In a study by Cao *et al* (97), a Chinese herbal formula was used in conjunction with the treatment of perimenopausal depression. After 12 weeks of treatment, there was a significant reduction in depression scores in the experimental group. Additional biochemical indexes showed a significant decrease in FSH levels and triglyceride levels and an increase in high-density lipoprotein cholesterol levels in the experimental group. The results of the experiment indicated that herbal remedies hold promise for improving gonadal hormones and other related indicators. Improvements in the associated gonadal hormone profile can effectively reduce the level of oxidative stress or the level of inflammation in the body and have a positive effect on the treatment of perimenopausal depression.

Erxian decoction (EXD) is a well-known and empirical Chinese herbal formula of six herbs developed by Bernard Chang in the early 1950s. It is used for the treatment of perimenopausal syndrome in women, including perimenopausal depression (98). Zhang *et al* (99) investigated the antidepressant effects of EXD on perimenopausal mice. In behavioral tests, EXD improved spatial memory in mice with depressive symptoms. EXD reduced serum levels of FSH, luteinizing hormone and IL-6. This meant that EXD reduced oxidative stress as well as inflammation levels in mice. In addition, this study found that EXD markedly upregulated the expression of brain-derived neurotrophic factor and Bcl-2 in the hippocampus, as well as the expression of estrogen receptor in the uterus and adrenal glands, antagonizing the symptoms of estrogen deficiency in mice. In another study by Zhang *et al* (100) it was shown that EXD antagonized the damage of corticosterone on PC12 cells and improved depression-like behavior in mice. In this study, the EXD was neuroprotective against corticosterone-injured PC12 cells *in vitro*. EXD can effectively increase the levels of serotonin, dopamine and norepinephrine in the hypothalamus, reduce the inflammatory response to protect the neural tissues and effectively improve the depression-like behavior in mice. Furthermore, EXD markedly increased cell viability, inhibited corticosterone-induced apoptosis and modulated the expression of apoptosis-associated proteins Bcl-2, Bax, cystatinase-3 and cystatinase-8. Although some current studies have shown that EXD has good therapeutic effects on perimenopausal depression (101,102), its specific mechanism of action and active ingredients still need further research.

In addition, there are numerous researchers working on the drugs or chemically active ingredients in traditional Chinese medicine formulas that play a major role in treating or

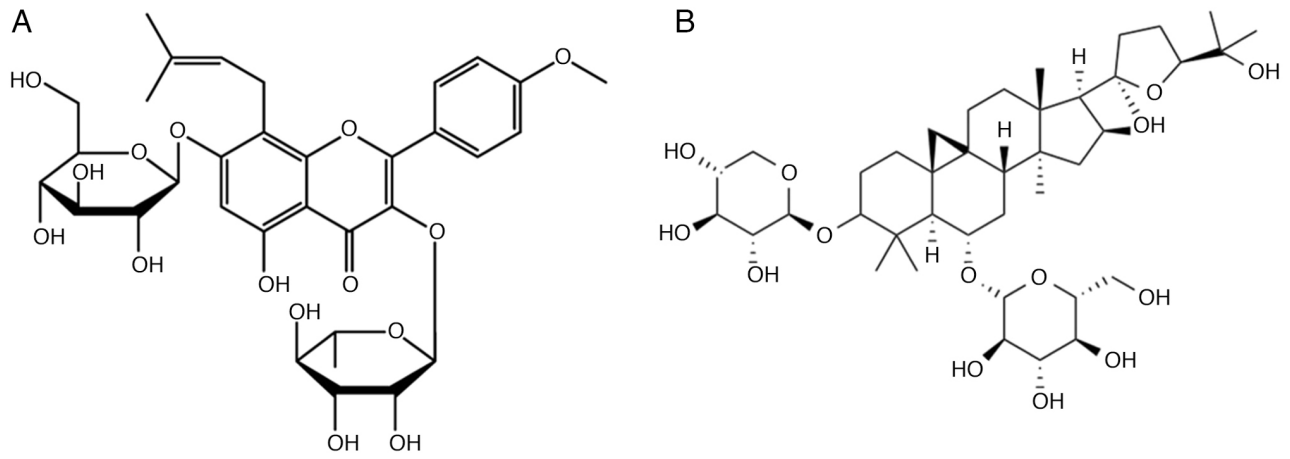

Figure 3. Chemical structure of active ingredients in traditional Chinese medicine. (A) Icariin and (B) astragaloside IV.

ameliorating perimenopausal depression. Icariin ($C_{33}H_{40}O_{15}$; M_w=676.67; Fig. 3A) has been shown to be the main bioactive component of the traditional Chinese medicine Epimedium and its antidepressant mechanism of action has been increasingly evaluated and confirmed (103,104). Icariin is a type of prenylated flavonoid, showing extensive bioactivities such as antioxidant (105). Cao *et al* (106) explored the effects of epimedium glycosides on the expression of PI3K/AKT pathway-related proteins in a rat model of perimenopausal depression. It was found that epimedium glycosides markedly ameliorated apparent symptoms, increased organ indices of the uterus, spleen and thymus and ameliorated pathological changes in the ovaries in model rats. The results of the study showed that administration of epimedium glycosides could re-regulate the disordered sex hormones, regulate the secretion of neurotransmitters in the brain, enhance the immune function and ameliorate the perimenopausal syndrome in perimenopausal depressed rats.

Astragalus contains a variety of active ingredients, such as astragaloside, astragaloside polysaccharides and flavonoids. Among them, astragaloside IV ($C_{41}H_{68}O_{14}$; M_W=784.97; Fig. 3B) a tetracyclic triterpenoid saponin in the form of lanolin ester alcohol, is the most biologically active component (107). Studies have shown that astragaloside can exert antidepressant effects through the regulation of neurotransmitters and improvement of nerve cell damage (108,109). Yao *et al* (110) noted that Astragalus can be used for the recovery and treatment of perimenopausal depression from the perspective of M2 microglia polarization to alleviate neuroinflammation and thus promote the recovery of perimenopausal depression. The report investigated the effects of Astragalus on mice with simulated perimenopausal depression by modulating microglia polarization and examined markers of microglia polarization and their regulatory signals.

Curculiginis is a common Chinese herb that is known to strengthen bones and muscles. Previous studies have shown that curculiginis has a wide range of pharmacological effects and can be used for neuroprotective, anti-inflammatory, antioxidant and estrogenic effects (111,112).

Chaihu, a Chinese herb, is present in some of the herbal formulas for depression, such as Chaihu Jia Longgu Muli decoction (113-115), Chaihu-Shugan-San (116,117) and Chaihu Anxin Capsule (118). Chaihu saponin A, an active component of Chaihu, inhibits IL-6 and TNF-α in the intestinal tract of septic rats (119). Chen *et al* (120) demonstrated the antidepressant-like effect of Chaihu saponin A on perimenopausal rats by behavioral tests, serum corticotropin-releasing hormone, ACTH and corticosterone levels, as well as hypothalamic adrenocorticotropic hormone and hippocampal glucocorticoid receptors. Studies on the nervous system of rats have shown that Chai Hu Saponin A produces antidepressant effects in perimenopausal rats, possibly resulting from the restoration of neuroendocrine, neuroinflammatory and neurotrophic systems in their hippocampus (121,122).

6. Conclusions

Depressive patients during perimenopause have been demonstrated to possess high levels of ROS and inflammatory biomarkers and activation of stress kinases, promoting further oxidative stress and neuroinflammation and cell death, which may all contribute to depression. Therefore, the exploration of these pathways can provide potential therapeutic strategies for perimenopausal depression. It would be possible to develop potential therapeutic strategies aimed at treating perimenopausal depression by identifying ROS and inflammatory levels in patients. However, measuring ROS remains highly challenging, particularly *in vivo*, due to their short half-life. Given the cell type-specific and context-dependent nature of ROS functions and harmful effects, further research is needed in brain regions affected by perimenopausal depression to delineate specific mechanisms. As well, an understanding of the interactions between redox status and the immune-inflammatory system could help identify the correct targets for neuroprogression in perimenopausal depression.

Chinese medicines have been passed down in China for thousands of years and with the rise of modern medicine, the active/effective components in Chinese medicines as well as their mechanisms of action still need to be further investigated. The components in Chinese medicines are very complex and accurate extraction and purification of their active ingredients is a great challenge. The modernization of Chinese traditional medicine still has a long way to go and, although it is difficult, it has a bright future.

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Availability of data and materials

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Authors' contributions

YY, TYu, KL, YLi, HC and XW contributed to writing and editing of this review. YLu, TYa and WL revised the article. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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