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The emerging role of copper in depression

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Copper (Cu) is an essential trace element in the brain and serves as an important cofactor for numerous enzymes involved in a wide range of biochemical processes including neurobehavioral, mitochondrial respiration, and antioxidant effects. Recent studies have demonstrated that copper dyshomeostasis is tightly associated with the development of depression by inducing oxidative stress and inflammatory responses. However, these findings have remained controversial so far. Cumulative studies have shown a positive association, while some other studies showed no association and even a negative association between serum/plasma copper level and depression. Based on these conflicted results, the association was speculated to be due to the clinical features of the population, stages of the disease, severity of copper excess, and types of specimens detected in these studies. In addition, there was an inverse association between dietary copper intake and depression. Furthermore, increasing copper intake could influence dietary zinc and iron intake to prevent and treat depression. Thus, copper supplementation may be a good measure to manage depression. This review provided a deeper understanding of the potential applicability of copper in the prevention and treatment of depression.

KEYWORDS

copper, depression, homeostasis, oxidative stress, inflammatory response, dietary supplementation

1. Introduction

Depression is one of the leading mental disorders, and the number of people with depression has reached approximately 280 million worldwide from World Health Organization (WHO) statistics, making it a major contributor to the overall global burden of diseases (World Health Organization, 2023a,b). Given the deleterious effect of depression on human health, WHO's Mental Health Gap Action Programme (mhGAP) has listed it as a priority condition in its Mental health action plan 2013–2030 (Institute of Health Metrics and Evaluation, 2023). There are many etiologies involved in depression including social, psychological, and biological factors (Ferrari et al., 2016). It is characterized by several symptoms such as depressed mood, hopelessness about the future, and thoughts of dying or suicide (World Health Organization, 2023a,b). Depression can be categorized as mild, moderate, and severe on the basis of the number and severity of symptoms, as well as the impact on the individual's functioning. Depending on the severity and pattern of depressive episodes, different treatments are recommended, including psychological treatment and antidepressant medications (Shusharina et al., 2023), but a significant proportion of people who received treatment still fail to achieve remission (Mauskopf et al., 2009; Moriarty et al., 2020) and more than 75% of people in low and middle-income countries do not receive any treatment (Evans-Lacko et al., 2018). Hence, it is

imperative to look for new risk factors and effective treatments to prevent and treat depression.

Copper (Cu) is an essential trace element and the third most abundant trace metal after iron and zinc in the human body (Barceloux, 1999). It is almost entirely absorbed in the gastrointestinal tract, stored in the liver, and eliminated through biliary excretion (Halliwell and Gutteridge, 1984). It is a vital cofactor of numerous important enzymes, such as dopamine monooxygenase, cytochrome oxidase, and the free radical scavenger superoxide dismutase (Uauy et al., 1998; Turnlund, 2000), and is involved in a wide range of biochemical processes including neurobehavioral, mitochondrial respiration, and antioxidant effects (Uriu-Adams and Keen, 2005). The roles of copper in mental diseases have attracted the attention of researchers due to its high levels in the brain (Rihel, 2018). An imbalance in copper levels in the brain has been reported to be associated with many neuropathic diseases, such as depression, Alzheimer's disease, Menkes disease, and Wilson's disease (An et al., 2022). Several studies have explored the association between copper levels in the human body and depression, but their conclusions remain controversial. Cumulative studies have shown a positive association between serum/plasma copper levels and depression (Russo, 2011; Habibi et al., 2017; Islam et al., 2018; Ni et al., 2018; Ullas Kamath et al., 2019; Wu et al., 2022), while some other studies showed that there were no associations (Styczeń et al., 2016; Siwek et al., 2017) and even negative associations between serum/plasma copper level and depression (Styczeń et al., 2016; Li et al., 2018; Twayej et al., 2020; Ding and Zhang, 2022). Given these conflicting results, we focused on the role of copper in depression and its underlying mechanisms in this review, aiming to provide a better understanding of its potential applicability in preventing and treating depression.

2. Regulation of copper homeostasis

Copper homeostasis, namely, the dynamic balance in copper levels, is a tightly regulated process by various key molecules, including copper chaperones, transmembrane transporters, and transcriptional regulators (Chen et al., 2022, 2023). These molecules cooperatively regulate the import, intracellular distribution, and export of copper to maintain homeostasis. As shown in Figure 1, copper is a redox-active metal ion that exists in two oxidation states: Cu^{+} and Cu^{2+} (Ge et al., 2022). Extracellular Cu^{2+} binding to ceruloplasmin is reduced by the metalloreductase six-transmembrane epithelial antigen of the prostate (SETAP) to Cu^{+}, and copper transporter 1 (CTR1) (also known as solute carrier family 31 member 1, SLC31A1) transports Cu^{+} into cells (Ohgami et al., 2006). Once it enters the cytoplasm, a part of Cu^{+} binds to glutathione (GSH) and is delivered to metallothionein 1/2 (MT1/2) to be restored, and other parts of Cu^{+} are either transferred to the nucleus or ATP7A/7B located in the trans-Golgi network (TGN) by the chaperone antioxidant-1(ATOX1) to facilitate the synthesis of cuproenzymes (Lutsenko et al., 2007) or delivered to superoxide dismutase 1 (SOD1) in the cytoplasm and mitochondrial intermembrane space by a copper chaperone for superoxide dismutase (CCS) to detoxify reactive oxygen species (ROS). In addition, Cu^{+} in the cytoplasm can be transported to the mitochondrial intermembrane space, in which Cu^{+} binds to chaperone cytochrome oxidase 17 (COX17) and is delivered to either the chaperone synthesis of cytochrome oxidase 1 (SCO1) or COX11, ultimately delivering to the cytochrome C oxidase (CCO) I (COX1) or II (COX2) subunits to involve them in the respiratory chain (Horng et al., 2004).

Because of the alteration of physiological or pathological conditions in the human body, the cellular copper content changes, resulting in the disturbance of copper homeostasis, namely, copper excess or copper deficiency. Based on the cellular copper status, the expression of some molecules involved in copper homeostasis is regulated. For example, CTR1 and CCS are down-regulated when intracellular copper overloads and up-regulated when intracellular copper is deficient (Bertinato and L'Abbé, 2003; Liang et al., 2012). Moreover, ATP7A and ATP7B, as the major transporters for exporting cellular copper, are commonly located in the TGN. However, when intracellular copper overloads, ATP7A and ATP7B translocate from the TGN to the plasma membrane to export copper. When intracellular copper recovers to the physiological condition, ATP7A and ATP7B return to the TGN (La Fontaine and Mercer, 2007). It is important to note that the expression of ATP7A and ATP7B is tissue-specific. ATP7A is expressed in various tissues and organs, whereas ATP7B is predominantly expressed in the liver, suggesting that ATP7A, but not ATP7B, is primarily involved in the exporting of copper into the brain cell (Lutsenko et al., 2007).

3. The role of copper in oxidative stress and inflammation

Some of the molecular mechanisms underlying copper-induced depression included oxidative stress, neurotransmitter imbalance, and impaired synaptic plasticity. Among these mechanisms, oxidative stress is regarded as a mainstay because of its effect on other depression-associated mechanisms (Bhatt et al., 2020; Correia et al., 2023). Oxidative stress is a biological process caused by a disturbance between production and accumulation of ROS in cells and tissues and is responsible for some diseases such as neuropathic diseases and cancer due to its deleterious effects (Pizzino et al., 2017). The redox activity of copper induces oxidative stress via redox and Fenton reactions (Pereira et al., 2016; Ruizs et al., 2021). A positive association was observed between copper level in the serum or brain and oxidative stress (Maes et al., 1997; Frey et al., 2007; Ozcelik and Uzun, 2009; Salustri et al., 2010; Lee et al., 2013; Bajpai et al., 2014; Liu et al., 2015; Kumar et al., 2019). Copper has been revealed as a key regulator in various cell signaling pathways such as membrane receptor-associated pathways and growth factor-associated pathways (Grubman and White, 2014). The signaling pathways associated with copper-induced oxidative stress have been explored mainly based on *in vitro* cell experiments and *in vivo* animal studies. These studies demonstrated that a large amount of copper intake can result in oxidative damage by activating the antioxidant protection signals mitogen-activated protein kinase 14 (MAPK14)/the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1)/NAD(P)H:quinone oxidoreductase 1 (NQO1) pathway, inhibiting cAMP-response element binding protein (CREB)/Brain-derived neurotrophic factor (BDNF) pathway or PI3K/AKT/mTOR pathway to induce apoptosis or autophagy (Figure 2; Filomeni et al., 2011; Boilan et al., 2013; Zhong et al., 2014; Wang Y. et al., 2018; Xie et al., 2020; Zou et al., 2021; Li et al., 2022; Lu et al., 2022; Zhong et al., 2022). Kim et al. also found that the autophagy kinase ULK1 can induce the autophagic

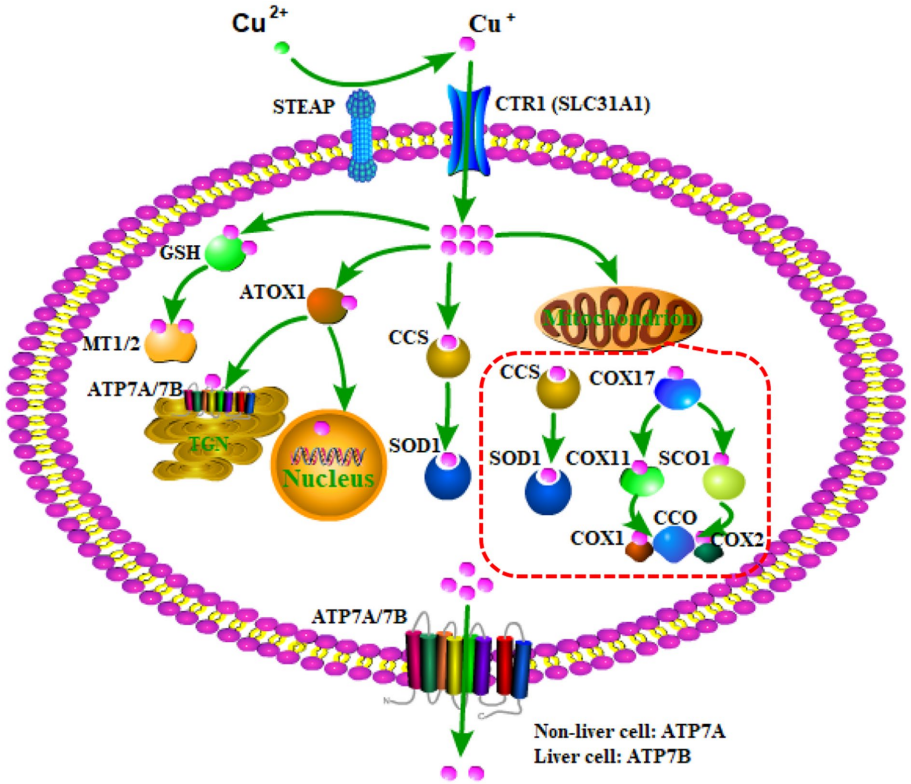

FIGURE 1
The regulation process of copper homeostasis. SETAP, metalloreductase six-transmembrane epithelial antigen of the prostate; CTR1, copper transporter 1; SLC31A1, solute carrier family 31 member 1; GSH, glutathione; MT1/2, metallothionein 1/2; ATOX1, the chaperone antioxidant-1; CCS, copper chaperone for superoxide dismutase; SOD1, superoxide dismutase 1; COX17, chaperone cytochrome oxidase 17; SCO1, chaperone synthesis of cytochrome oxidase 1; CCO, cytochrome C oxidase; COX1, cytochrome C oxidase (CCO) I; COX2, cytochrome C oxidase (CCO) II.

degradation of mitochondria by phosphorylating the ser-73 and ser-254 residues of Sestrin 2 under copper-induced oxidative stress conditions (Kim et al., 2020). In addition, copper can destroy the antioxidant defense system by decreasing antioxidant enzyme activities (SOD, CAT, and GSH-Px) to induce toxicity (Lai et al., 1996; West and Prohaska, 2004; Sun et al., 2018; Jian et al., 2020).

In addition to oxidative stress, accumulating evidence suggested that copper can exert toxicity, resulting in depression by triggering an inflammatory process. A number of studies revealed that high serum copper levels were associated with decreased levels of anti-inflammatory cytokines (IL4 and IL-10) and increased levels of pro-inflammatory cytokines (TNF-a, IL-6, IL-2, IL-8, and IL-1β) to trigger the pathogenesis of depression (Maes et al., 1995; Cattaneo et al., 2015; Habibi et al., 2017; Xu et al., 2021). Furthermore, there are various pathways that are involved in copper-regulated inflammation, including the nuclear factor kappa-B (NF-KB), MAPKs, JAK–STAT, and NLRP3 pathways (Deng et al., 2023). In addition, an alteration in the microbial richness and diversity of feces in Sprague–Dawley rats fed a high level of copper was associated with copper-regulated inflammatory responses (Zhang et al., 2017). Oxidative stress was deemed to be an important factor for the inflammatory response in the central nervous system (Ruiz et al., 2022). Consistent with it, increasing evidence suggested that copper-induced oxidative stress contributed to cellular inflammatory responses (Yang et al., 2020; Kouadri et al., 2021). Therefore, understanding copper-induced oxidative stress and inflammatory responses would be beneficial for the prevention and treatment of copper-related diseases.

4. Dysregulation of copper homeostasis and depression

Copper is abundant in the brain, especially in the cerebellum, hippocampus, basal ganglia, numerous synaptic membranes, cell bodies of cortical pyramidal, and cerebellar granular neurons (Desai and Kaler, 2008). It is regarded as an important cofactor for many enzymes that affect a variety of brain functions. Because the brain is a highly metabolizing organ, a small imbalance in copper levels may cause detrimental effects on the brain. Disturbance of copper homeostasis in the brain can cause copper excess or copper deficiency, leading to an array of diseases (Chakravarty and Chowdhury, 1984). This is because copper excess may result in injury, while copper deficiency may cause incomplete development (Sharma et al., 2014).

Copper excess has a higher incidence than copper deficiency in humans. It is toxic to many organs, especially the brain (Winge and Mehra, 1990). Multiple studies have suggested that copper levels in patients with depression were significantly higher than the control without depression (Narang et al., 1991; Butterworth, 2010; Russo, 2011; Habibi et al., 2017; Islam et al., 2018; Ullas Kamath et al., 2019;

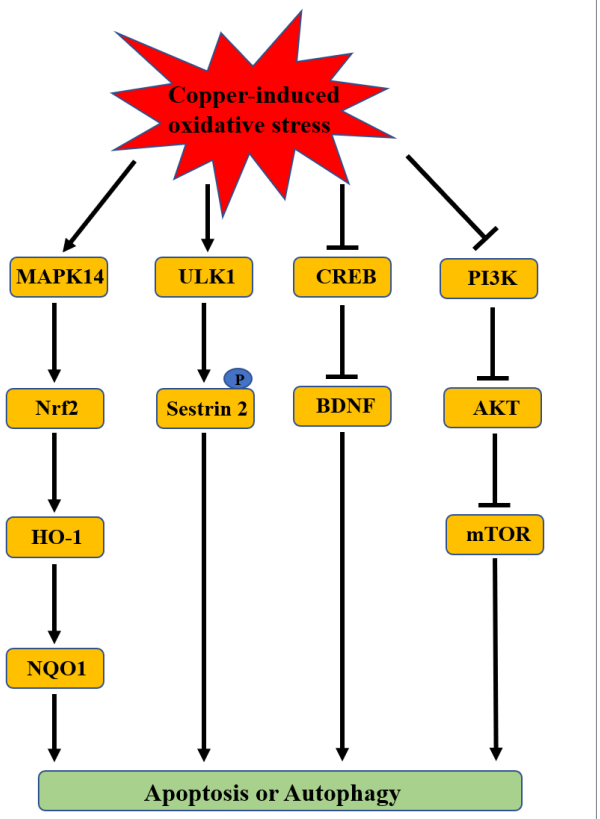

FIGURE 2
The associated signaling pathways of copper-induced oxidative stress.

Wu et al., 2022). Additionally, copper content in the human body gradually increased in pregnant women, which may be related to the elevated levels of circulatory progesterone and estrogens; thus, it can easily cause depression (Gernand et al., 2016). In a study of 574 women aged 30–60 years with various mental and behavioral disorders, the serum copper levels were significantly higher in women with a history of post-partum depression (PPD) than in non-depressed women and depressed women without a history of PPD (Crayton and Walsh, 2007). This is consistent with a study showing that the mean level of copper in the serum was higher in pregnant Iranian adolescents with depression than in those without depression (Bahramy et al., 2020). As aforementioned, this may be because an elevated concentration of cellular copper can cause neuronal injury, resulting in depression by inducing oxidative stress and inflammatory responses. However, an inverse relationship was observed between copper serum level and depression (Styczeń et al., 2016; Li et al., 2018; Twayej et al., 2020; Ding and Zhang, 2022) even though there were no associations between copper serum level and depression in several studies (Styczeń et al., 2016; Siwek et al., 2017). Based on these conflicted results, the association was speculated to be related to the clinical features of the population, stages of the disease, severity of copper excess, and types of detected specimens in these studies (Table 1). For example, the epidemiology data suggested that the incidence of depression is about twice as common in women than in men (Kessler, 2003; World Health Organization, 2023a,b). Obesity was also a risk factor for depressive symptoms in individuals with high serum copper levels (Wu et al., 2022). However, the role of age as a risk factor for depression remains controversial. A study by Clark et al. showed that there was no association between blood copper and age, but two other studies demonstrated that they were correlated (Clark et al., 2007; Ma et al., 2014; Ni et al., 2018). Siwek et al. found that serum copper concentrations in patients with stage 1 bipolar disorder (including depression) were significantly higher than those of patients in advanced stages (2 + 3 + 4) of bipolar disorder (including depression) (Siwek et al., 2017). Moreover, a systematic review and meta-analysis of observational studies demonstrated that blood levels of copper in patients with depression were higher than those of patients without depression, while there was no difference in copper content in the hair between the two groups, suggesting that copper levels in the blood may be more sensitive to pathological changes in patients compared to those in the hair (Harvey et al., 2009; Ni et al., 2018). Thus, the level of plasma copper is currently the most widely used criterion for detecting copper content. Further systematic studies are needed to better understand the association between copper excess and depression.

Although the incidence of copper deficiency is relatively lower than that of copper excess, it cannot be ignored because it results in some diseases. In humans, Menkes syndrome is a main manifestation of copper deficiency and causes serious neurological disorders (Danks et al., 1972; Mercer, 1998). The mechanism may be that copper deficiency affects brain functioning by impairing brain mitochondrial function to damage energy metabolism (Munakata et al., 2005). In addition, increasing evidence reveals that copper deficiency results in decreased levels of plasma iron, which may be due to a decrease in the absorption and inhibition of iron released from the liver (Reeves and Demars, 2006; Pyatskowit and Prohask, 2008). Iron deficiency can induce depression, and thus copper deficiency may result in depression by decreasing the iron levels in the human body. Iron deficiency in the brain can be reversed by iron injections (Pyaskowit and Prohaska, 2008).

5. Copper supplementation for the prevention and treatment of depression

Increasing evidence has indicated that nutrients played a vital role in preventing and managing depression (Lai et al., 2014; Marx et al., 2017; Salehi-Abargouei et al., 2019). For example, there was an inverse relationship between dietary patterns rich in fruits and vegetables and high depressive symptoms (Xia et al., 2017; Wang C. J. et al., 2018; Cheng et al., 2019). Thus, the identification of the dietary factors involved in depression has attracted researchers' attention in recent years. As aforementioned, copper is an essential dietary component in the human body. The adult human body contains approximately 75–100 mg of copper, and the recommended daily dosage is 0.9 mg/day in adults (Food and Nutrition Board, Institute of Medicine, 2001). Food is the primary source of daily copper intake (National Academy of Sciences, 2000). There is rich copper in various foods, such as shellfish, seeds, nuts, meats, and chocolate (Ma and Betts, 2000; Institute of Medicine (US) Panel on Micronutrients, 2001).

A number of studies have demonstrated that an imbalance in dietary copper intake contributed to the development of depression.

TABLE 1 The influencing factors for studies on the association between copper levels and depression.

	Type of study	Countries	Results	References
Clinical features				
Sex	Epidemiology data	Worldwide	Incidence of depression was about twice as common in women than in men	World Health Organization (2023a,b)
Obesity	Cross-sectional study	America	Obesity (BMI ≥ 30 kg/m^2) was a risk factor for people with high serum copper levels to develop depression symptoms	Wu et al. (2022)
Age	Clinical study	Canada	No relationship in people aged 30–65 years old	Clark et al. (2007)
	Clinical study	China	A relationship in children aged 3–12 years old	Ma et al. (2014)
	A systematic review and meta-analysis of observational studies	–	A relationship between blood copper and depression in people under 50 years old, but not in people over 50 years old	Ni et al. (2018)
The severity of the disease	Clinical study	Poland	Serum copper concentrations in patients with stage 1 bipolar disorder (including depression) were obviously higher than that of patients in advanced stages (2 + 3 + 4) of bipolar disorder (including depression)	Siwek et al. (2017)
Types of detected specimen	A systematic review	–	Serum copper appears to be a useful biomarker of copper status at the population level	Harvey et al. (2009)
	A systematic review and meta-analysis of observational studies	–	Blood levels of copper in patients with depression were higher than that of patients without depression, while there was no difference in copper content in the hair between the two groups	Ni et al. (2018)

A cross-sectional study of 14,834 US adults (7,399 men and 7,435 women) aged 18 years or older suggested that total copper intake may be an inverse association with depression, and these enrolled people given the Recommended Dietary Allowance had an obviously lower incidence of depression compared to those given less than the Recommended Dietary Allowance (Li et al., 2018). Consistent with this result, a negative association was observed between dietary copper intake and depression in two cross-sectional Japanese studies and a meta-analysis (Nakamura et al., 2019; Thi Thu Nguyen et al., 2019; Ding and Zhang, 2022). Additionally, a case–control study of 849 Korean adolescent girls aged 12–18 years also indicated that there was a high risk of depression in participants who ate more instant and processed foods and that dietary copper intake was negatively related to depression, suggesting that a reasonable dietary pattern played an important role in preventing and managing depression (Kim et al., 2015). Furthermore, an inverse association between dietary copper intake and depression was observed to be more relevant in women than in men (Thi Thu Nguyen et al., 2019; Ding and Zhang, 2022). Therefore, adequate intake of copper and reasonable dietary pattern was very important in preventing depression.

In addition to a dietary pattern that results in the dysregulation of copper intake, an imbalance of other metal ions in the human body can also influence copper to be involved in the pathogenesis of depression. In a cross-sectional study of 139 men and women aged ≥60 years in Australia, copper concentrations and copper/zinc ratios were found to be negatively associated with depressive symptoms (Mravunac et al., 2019). This is because zinc can compete with copper for absorption in the small intestine (Mravunac et al., 2019). It has been suggested that a high-iron diet might result in copper deficiency; in turn, increasing copper intake would correct many of the notable high iron-related physiological perturbations (Klevay, 2001, 2016; Reeves and Demars, 2005; Ha et al., 2017; Wang T. et al., 2018). A negative association has been observed between depression and dietary zinc and iron intake (Li et al., 2017). Thus, copper supplementation may be an effective measure to prevent and treat depression by interfering with the metabolic processes of zinc and iron.

6. Conclusion

In summary, copper is an essential trace element in the brain, and serves as an important cofactor for numerous enzymes involved in a wide series of biochemical processes, including neurobehavioral, mitochondrial respiration, and antioxidant effects. Thus, a trace dyshomeostasis of copper may cause serious brain diseases such as depression. Recent research has demonstrated that copper dyshomeostasis was tightly associated with the development of depression by inducing oxidative stress and inflammatory responses. However, the conclusion had remained controversial so far. Cumulative studies tended to show a positive association between serum/plasma copper level and depression, whereas some other studies showed no association and even negative associations between serum/plasma copper level and depression. Based on these conflicted results, the association was speculated to be related to the clinical features of the population, stages of the disease, severity of copper excess, and types of detected specimens in these studies. Further systematic studies are needed to better understand the association between copper excess and depression.

Furthermore, there was an inverse association between dietary copper intake and depression. Food is the primary source of daily copper intake. Thus, adequate intake of copper and a reasonable dietary pattern is very important for preventing depression. Additionally, increasing copper intake can influence dietary zinc and iron intake and is involved in the pathogenesis of depression.

Therefore, copper supplementation may be a good strategy to prevent and treat depression.

Author contributions

JC reviewed these works of literature and drafted the manuscript. WS and WZ revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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