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REVIEW
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Mechanisms Underlying Curcumin-Induced Neuroprotection in Cerebral Ischemia

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Ischemic stroke is the leading cause of death and disability worldwide, and restoring the blood flow to ischemic brain tissues is currently the main therapeutic strategy. However, reperfusion after brain ischemia leads to excessive reactive oxygen species production, inflammatory cell recruitment, the release of inflammatory mediators, cell death, mitochondrial dysfunction, endoplasmic reticulum stress, and blood–brain barrier damage; these pathological mechanisms will further aggravate brain tissue injury, ultimately affecting the recovery of neurological functions. It has attracted the attention of researchers to develop drugs with multitarget intervention effects for individuals with cerebral ischemia. A large number of studies have established that curcumin plays a significant neuroprotective role in cerebral ischemia via various mechanisms, including antioxidation, anti-inflammation, anti-apoptosis, protection of the blood–brain barrier, and restoration of mitochondrial function and structure, restoring cerebral circulation, reducing infarct volume, improving brain edema, promoting blood–brain barrier repair, and improving the neurological functions. Therefore, summarizing the results from the latest literature and identifying the potential mechanisms of action of curcumin in cerebral ischemia will serve as a basis and guidance for the clinical applications of curcumin in the future.

Keywords: cerebral ischemia, curcumin, neuroprotection, oxidative stress, inflammation, blood–brain barrier, apoptosis, mitochondrial dysfunction

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INTRODUCTION

Ischemic stroke is the most common type of stroke and is associated with high mortality and morbidity. Early restoration of blood supply to ischemic tissues is currently an effective treatment strategy that improves the energy metabolism, oxygen supply, and neurological outcomes. At present, recombinant tissue plasminogen activator (r-TPA) is used for thrombolytic therapy; however, with the limitation of usage within 4.5 h after the onset of stroke, only 3–5% of stroke patients meet the criteria and use r-TPA in a timely fashion (Wardlaw et al., 2014; Marlier et al., 2015; Moretti et al., 2015; Campbell et al., 2019; Campbell and Khatri, 2020). Therefore, current research focuses on exploring pathological mechanisms and discovering the novel potential therapeutic targets for cerebral ischemia. Cerebral ischemia causes acute brain injury, while reperfusion results in chronic brain injury. In the acute stage of ischemia, cellular homeostasis and microcirculation are impaired, cell energy metabolism is disrupted, and the structure of the blood–brain barrier (BBB) is destroyed. During the reperfusion period, these structures and functions are not restored; many

substances and cells that would not otherwise reach the brain, such as inflammatory cells and macromolecules of inflammatory factors, enter the brain through the damaged BBB. This leads to further aggravation of injury following cerebral ischemia (Pan et al., 2007; Jung et al., 2010; Badruddin et al., 2011). In short, the damage caused by cerebral ischemia and reperfusion involves oxidative stress, apoptosis, the inflammatory response, BBB destruction, and energy metabolism disorder, among other pathological mechanisms. Therefore, it is critical to developing drugs that can intervene with multiple targets.

Curcumin is the most important polyphenol active component of turmeric and is slightly soluble in water but soluble in ethanol and acetone. The ratio of compounds in turmeric is about 5% dimethoxylcurcumin, 15% demethoxylcurcumin, and 80% curcumin. It is challenging to dissolve, extract, and absorb curcumin, resulting in low bioavailability and limited clinical applications (Esatbeyoglu et al., 2012; Kotha and Luthria, 2019). In recent years, numerous drug delivery systems using liposomes, nanoparticles, and microemulsion as carriers have been successfully developed, which significantly increased the solubility, stability, and safety of curcumin, and greatly improved its biological activity in treating or preventing diseases, showing great promise for clinical application (Aggarwal and Sung, 2009; Mahmood et al., 2015; Abd El-Hack et al., 2021; Jabczyk et al., 2021; Feltrin et al., 2022).

As a natural medicine, curcumin has a wide range of beneficial pharmacological activities, including antitumor, anti-inflammatory, antioxidation, anti-apoptosis, etc. (Zhou et al., 2011; Mandal et al., 2020; Fu et al., 2021). Numerous studies have revealed the beneficial role of curcumin in cancer, diabetes, metabolic diseases, autoimmune diseases, atherosclerosis, arthritis, pulmonary diseases, etc (Aggarwal and Harikumar, 2009; Jabczyk et al., 2021; Mahjoob and Stochaj, 2021). Recently, researchers discovered that curcumin also has neuroprotective effects on various neurological diseases, including neuropsychiatric disorders, neurodegenerative diseases, traumatic brain injury, spinal cord injury, and epilepsy (Dhir, 2018; Bhat et al., 2019; Yavarpour-Bali et al., 2019; Yuan et al., 2019; Farkhondeh et al., 2020; Nebrisi, 2021; Lamanna-Rama et al., 2022). The involved mechanisms may include the mediation of neurotransmitters and the hypothalamus-pituitary-adrenal cortex axis, the release of neurotrophic factors, and the promotion of nerve regeneration, thereby influencing a variety of signaling cascades, enhancing vitality and differentiation of neurons, and ultimately enhancing neurological functions (Xu et al., 2006; Srivastava et al., 2018; Ramaholimihaso et al., 2020; Yang et al., 2020; Yang et al., 2021). Multiple *in vitro* and *in vivo* experiments have been carried out to investigate the role and mechanism of curcumin in cerebral ischemia and revealed that curcumin participates in the recovery of ischemic injury by inhibiting the oxidation, apoptosis and inflammation, protecting the BBB, and restoring mitochondrial functions (Ovbiagele, 2008; Bavarsad et al., 2019). A summary of recent studies on curcumin treatment for cerebral ischemia will assist in identifying its shortcomings and benefits, thereby guiding future research studies, clinical translational applications, and the exploration of novel therapeutic strategies for ischemic stroke.

Mechanisms of Curcumin Against Cerebral Ischemia

Recently, numerous studies have demonstrated the neuroprotective effect of curcumin in cerebral ischemia (Bavarsad et al., 2019; Ułamek-Kozioł et al., 2020; Subedi and Gaire, 2021). Curcumin can attenuate neurological dysfunction, and reduce infarct volume and brain edema, thereby improving the outcome of an ischemic stroke. Various mechanisms are involved, including the inhibition of oxidative stress, inflammation, apoptosis, calcium overload, and endoplasmic reticulum stress, as well as the restoration of BBB, and mitochondrial structural functions (**Supplementary Table S1**). The details are described below.

Curcumin Reduces Oxidative Stress

Brain tissues have a higher metabolic rate, demand for oxygen and polyunsaturated fatty acids, and lower levels of antioxidant enzymes compared with other organs, making the central nervous system more vulnerable to oxidative damage (Cenini et al., 2019; Torres-Cuevas et al., 2019; Bhatt et al., 2020). Oxidative stress caused by the disruption of homeostasis between oxidative and antioxidant systems are a key mechanism of cerebral ischemic injury (Li et al., 2018; Torres-Cuevas et al., 2019; Yang, 2019). As a vital signaling molecule in the brain, reactive oxygen species (ROS) directly or indirectly mediates several pathological processes after cerebral ischemia (Fraser, 2011; Olmez and Ozyurt, 2012; Orellana-Urzú a et al., 2020). It has been demonstrated that the activity of nitric oxide synthase (NOS), cyclooxygenase (COX), xanthine dehydrogenase/xanthine oxidase, myeloperoxidase, myeloperoxidase (MPO), and other enzymes promoting ROS production increase following stroke, whereas the activity of enzymes that prevent ROS production, such as superoxide dismutase (SOD), catalase, peroxidase, glutathione peroxidase (GSH-Px) decrease, consequently destroying the dynamic balance of ROS, and leading to its accumulation. Excessive ROS can trigger lipid peroxidation, DNA damage, and protein oxidation damage (Sorce et al., 2012; Bazmandegan et al., 2017; Shao et al., 2020; Su et al., 2020; Duan et al., 2021). Therefore, the use of free radical scavengers or other antioxidants is one of the primary therapeutic options for cerebral ischemia (Ahmadinejad et al., 2017; Davis and Pennypacker, 2017; Zhou et al., 2021).

Curcumin, as an antioxidant, accelerates the removal of ROS by activating the antioxidant enzymes and inhibiting the brain tissue damage induced by oxidative stress (Vajragupta et al., 2003; Namgyal et al., 2021). The antioxidative effect of curcumin in cerebral ischemia has been widely explored, and it has been noted that curcumin could partially exert neuroprotection by alleviating oxidative stress-induced injury post-stroke (Rathore et al., 2008; Mukherjee et al., 2019; Zhang et al., 2021). It was previously reported that pretreatment and posttreatment administration of curcumin both improved the antioxidative ability of the injured neurons (Wu et al., 2015), while immediate and delayed (24 h

after ischemia) treatments with curcumin both prevented ischemia-induced neuronal damage and oxidative insult, indicating the wide range time window of curcumin treatment in cerebral ischemia (Al-Omar et al., 2006).

Moreover, curcumin can lower the production and accumulation of ROS and oxidation products (MDA, lipid peroxidation, etc.) (Hosseinzadehdehkordi et al., 2015; Seo et al., 2017; Khan et al., 2019). Other formulations of curcumin with polyethylene glycol (PEG)-ylated polylactide-co-glycolide (PLGA) nanoparticles or solid lipid nanoparticles (C-SLNs) are also capable of reducing ROS levels (Mukherjee et al., 2019). Interestingly, a comparative study investigating the antioxidative effect of three curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) using a polymeric N-isopropyl acrylamide nanoparticle formulation determined that curcumin had the most potent antioxidant activity (Ahmad et al., 2013). In addition, curcumin elevates the activity and expression level of antioxidases (NADPH oxidase 2, SOD, CAT, GSH-Px, glutathione reductase, etc.) (Dohare et al., 2008; Kakkar et al., 2013; Wu et al., 2020). Awad *et al.* demonstrated that curcumin synergistically enhanced the inhibitory action of candesartan on brain ischemia through the suppression of oxidative stress, implying the beneficial combined effects and potential therapeutic strategy of curcumin and other drugs on cerebral ischemia in the future (Awad, 2011). Various signaling pathways are involved in curcumin-induced antioxidation. For example, curcumin could alleviate the oxidative damage by regulating the miR-1287-5p/LONP2 axis and miR-7/RelA p65 axis in an OGD/R model (Xu H. et al., 2019; Zhang et al., 2021). Another study described that dienone monocarbonyl curcumin analogs protected the cellular growth by eliminating ROS generation by activating the Nrf2/HO-1 signaling pathway (He et al., 2021). Similarly, curcumin and hexahydrocurcumin enhanced antioxidant defense partially through the Nrf2/HO-1 pathway in a rat stroke model (Wicha et al., 2017). In addition, other signaling pathways such as SP1/Prdx6 (Jia et al., 2017), AMPK/UCP2 (Pu et al., 2013), Golgi reassembly, and stacking protein 65 (GRASP65) (Lin et al., 2016) are also involved in the antioxidant properties of curcumin.

Curcumin Inhibits Cellular Apoptosis

Apoptosis is an autonomous and programmed process of cell death that is the predominant form of cell death in cerebral ischemia and is closely related to the prognosis of stroke patients (Ferrer and Planas, 2003; Mitsios et al., 2007; Uzdensky, 2019; Gao et al., 2020). Previous research has described that cell necrosis and apoptosis co-exist in the acute stage of cerebral ischemia, while apoptosis is the primary type of delayed cell death post-stroke. Indeed, following the stroke onset, necrosis mainly occurs in the ischemic central region, whereas apoptosis chiefly occurs in the ischemic penumbra (Ueda and Fujita, 2004; Radak et al., 2017). The mechanism of apoptosis induced by cerebral ischemia is intricate and involves not only alterations in the expression of apoptosis-related genes but is also regulated by myriad internal and external factors. The mechanisms that mediate ischemic stroke-induced apoptosis mainly include the mitochondrial and endoplasmic reticulum stress and death receptor pathways (Cao et al., 2001; Zheng et al., 2003; Broughton et al., 2009; Iurlaro and Muñoz-Pinedo, 2016).

The use of anti-apoptotic agents or therapeutic strategies can protect against cell injury after cerebral ischemia (Rami et al., 2008; Luo et al., 2019; Youssef et al., 2021). A large number of studies have reported that various traditional Chinese medicines, including curcumin, can effectively alleviate cellular apoptosis after cerebral ischemia and improve neurologic dysfunction (Dong et al., 2016; Yu et al., 2020; Zhu et al., 2021). Curcumin can upregulate the expression of anti-apoptotic proteins such as Bcl-2 and downregulate the expression of apoptosis-related proteins such as Bax and caspase-3, thus effectively inhibiting cellular apoptosis and attenuating cerebral ischemia-induced injury (Xie et al., 2018; Xu L. et al., 2019). The specific mechanism of curcumin alleviating apoptosis after cerebral ischemia is well-documented. Curcumin-laden exosomes target ischemic brain tissues and alleviate ROS-mediated mitochondrial apoptosis (He et al., 2020). Additionally, curcumin can alleviate ischemia-induced brain injury and cell apoptosis via repressing CCL3, elevating glucose transporter (GLUT)1 and GLUT3, inactivating the TLR4/MyD88/MAPK/NF-κB and Wnt/JNK1 pathways, and promoting MEK/ERK/CREB, and PI3K/Akt pathway activation (Xia et al., 2018; Xu L. et al., 2019; Wang C. et al., 2020; Wu et al., 2020; Zhou et al., 2020). Xu et al. (2018) showed that a combination of curcumin and vagus nerve stimulation restored behavioral deficits by inhibiting apoptosis after cerebral ischemia, with the involvement of the Akt/ERK2 pathway. Notably, curcumin inhibits cellular damage and apoptosis by diminishing the endoplasmic reticulum stress (ERS) (Cheng et al., 2020; Keshk et al., 2020; Zhou et al., 2022). Chhunchha et al. (2013) reported that curcumin abated hypoxia-induced ERS-mediated cell death in mouse hippocampal cells by enhancing peroxiredoxin 6 (Prdx6) expressions and inhibiting NF-κB activation. Another *in vitro* research using the neuroblastoma cells exposed that curcumin relieved neurotoxicity via regulating the PERK-eIF2α pathway (Yan et al., 2022). Last, curcumin mitigated axonal injury and neuronal cellular apoptosis through the PERK/Nrf2 signaling pathway in a rat diffuse axonal injury model (Huang T. et al., 2018).

However, it is worthwhile noting that curcumin could play an antitumor role by promoting the apoptosis of tumor cells (Notarbartolo et al., 2005; Giordano and Tommonaro, 2019; Walker and Mittal, 2020). Furthermore, exploration of the mechanism of curcumin in diverse diseases and its effect on apoptosis under contrasting conditions will assist in evaluating the safety and effectiveness of curcumin treatment in cerebral ischemia in the future.

Curcumin Diminishes the Inflammatory Cascade

Neuroinflammation plays a key role in the progression of cerebral ischemia. Following cerebral ischemia, microglia, astrocytes, and neutrophils, as the main effector cells, release a large number of inflammatory cytokines, such as interleukins, chemokines, and tumor necrosis factor (TNF), induce neuronal apoptosis, and

contribute to microvascular dysfunction, secondary cerebral hemorrhage, and cerebral edema (Wang et al., 2019b; Shi et al., 2019; Jurcau and Simion, 2021). The activation and infiltration of inflammatory cells, as well as the synthesis and secretion of adhesive molecules and inflammatory mediators, promote the inflammatory cascade (Barrington et al., 2017; Hendriksen et al., 2017; Živančević et al., 2021).

Curcumin has been shown to possess anti-inflammatory properties in various neurological disorders, including acute brain injuries (spinal cord injury (Zhang N. et al., 2017), traumatic brain injury (Sun et al., 2020), stroke (Miao et al., 2016), and subarachnoid hemorrhage (Wakade et al., 2009)), and neurodegenerative diseases (Alzheimer's disease (Hamaguchi et al., 2010), Parkinson's disease (Ojha et al., 2012), Huntington's disease (Ullah et al., 2017), and multiple sclerosis (Mohajeri et al., 2015)). It attenuates the inflammatory response after cerebral ischemia through multiple mechanisms. For instance, curcumin can reduce the induction and release inflammatory cytokines such as IL-6, IL-1β, TNF-α, and COX-2 (Zhang Y. et al., 2017; Wicha et al., 2017). In addition, curcuminoids decrease neutrophil rolling and adhesion to the cerebrovascular endothelium, lower neutrophil numbers, and inhibit neutrophil activation, thereby ameliorating ischemic brain injury (Funk et al., 2013). NF-κB is a regulatory factor with diverse transcriptional effects, which are activated after cerebral ischemia and participates in the transcription of relevant target genes contributing to the inflammatory response. Numerous researchers have demonstrated that the anti-inflammatory effect of curcumin in cerebral ischemia is tightly associated with the modulation of NF-κB (Li et al., 2016, 2017; Li et al., 2021). Ran et al. (2021) observed that curcumin ameliorated white matter injury after ischemic stroke via NF-κB suppression and NLRP3 inflammasome inhibition in a rat stroke model. Triblock copolymer nanomicelles loaded with curcumin also exert an anti-inflammatory effect by inhibiting the NF-κB pathway after cerebral ischemia (Li et al., 2021). Other studies assessing the link between NF-κB and curcumin established that the anti-inflammatory impact of curcumin in cerebral ischemia is mediated by the inhibition of the TLR4/MyD88/MAPK/NF-κB, TLR2/NF-κB, and PPAR γ/NF-κB pathways (Liu et al., 2013; Tu et al., 2014; Wang C. et al., 2020). Likewise, the modulation of the TLR4/p38/MAPK, SIRT1 and JAK2/STAT3 pathways (Li L. et al., 2015; Miao et al., 2016; Huang L. et al., 2018) are involved in curcumin-induced inhibition of inflammation in cerebral ischemia. As a recent hotspot area in stroke, ERS also contributes to inflammation and apoptosis in cerebral ischemia. Zhu et al. (2017) described the inhibitory effect of curcumin on ERS by downregulating the expression of GADD153 and caspase-12 in a rat stroke model. Meanwhile, an *in vitro* study exposed that curcumin attenuated neurotoxicity in the hippocampus by suppressing the ERS-associated TXNIP/NLRP3 inflammasome activation in an AMPK-dependent manner (Li Y. et al., 2015).

Microglia are in a resting state under physiological conditions and play the role of "immune monitoring and defense" in the microenvironment of brain cells. Conversely, they are rapidly activated and polarized in the pathological state (Hu et al., 2015; Ma et al., 2017). After the onset of cerebral ischemia, microglia play a contrasting role in brain injury or neuroprotection through M1 or M2 polarization (Xiong et al., 2016; Zhao et al., 2017; Xue et al., 2021). M1 microglia have cytotoxic effects and cause inflammatory tissue damage, whereas M2 microglia have a neuroprotective effect and promote tissue repair and regeneration. The latter congregate in the ischemic area during cerebral ischemia and release inflammatory factors to enhance the inflammatory response. Interestingly, curcumin has a profound regulatory influence on microglial responses, shifting the microglial phenotype from the pro-inflammatory M1 state toward the anti-inflammatory and tissue-reparative M2 phenotype, and inhibiting microglia-mediated pro-inflammatory responses (Hu et al., 2012). The results from both *in vivo* MCAO and *in vitro* OGD models have corroborated that curcumin reduces inflammation through the inhibition of M1 microglial activation and by weakening the increase in TNF-α and IL-1β (Liu et al., 2017; Wang et al., 2019a).

Curcumin Has a Protective Effect on the Integrity of the BBB

The BBB is predominantly composed of cerebral microvascular endothelial cells, astrocytes, basal lamina, and pericytes. The primary function of BBB is to prevent the diffusion of macromolecules into the brain parenchyma and maintain the stability of the internal environment of the nervous system (Huber et al., 2001; Obermeier et al., 2013; Langen et al., 2019; Alahmari, 2021). After the occurrence of cerebral ischemia, several mediators cause direct damage to the BBB components, which are exacerbated by apoptosis, oxidative stress, and inflammatory reaction, thus increasing the permeability of the BBB and aggravating brain edema and neurologic injury (Jin et al., 2010; Jiang et al., 2018; Kunze and Marti, 2019). Numerous studies have explored the protective role and mechanism of action of curcumin on BBB after ischemic stroke. Curcumin can protect the integrity of BBB and reduce brain edema by the upregulation of aquaporin 4 and tight junction proteins such as zonula occluden 1 (ZO-1), occludin, and claudin-5, and the downregulation of matrix metalloproteinase 9 (MMP-9), intercellular adhesion molecule-l (ICAM-1), and vascular cell adhesion molecule-l (VCAM-1) (Li et al., 2017; Wang et al., 2019a; Wicha et al., 2020; Wu et al., 2021). Furthermore, curcumin attenuates cerebral capillary endothelial cell damage by inhibiting the expression of inducible nitric oxide synthase (iNOS) and the generation of NO(x) (nitrites/nitrates contents), thereby preventing BBB damage (Jiang et al., 2007). The protection of shear rate can also prevent neutrophil adhesion to the cerebrovascular microcirculation and block early microvascular inflammation (Funk et al., 2013). Mo et al. (2021) found that curcumin exhibited a protective effect against cerebral ischemia by reducing the BBB dysfunction through protein kinase C-θ (PKC-θ) signaling. In addition, it was previously reported that curcumin ameliorates the permeability of the BBB during hypoxia by upregulating the expression of HO-1 in brain microvascular endothelial cells (Wang et al., 2013).

Despite many studies demonstrating the protective effect of curcumin on BBB, there are still unanswered questions such as which curcumin formulations and routes of administration can penetrate the BBB more rapidly. What is the main mechanism through which curcumin prevents BBB injury and how to determine the optimal dose and administration interval with favorable safety and efficacy profiles. Further studies are warranted to develop and identify potential treatment strategies for cerebral ischemia.

Curcumin Improves Mitochondrial Dysfunction and Calcium Overload

The mitochondrion is the main structure for regulating cellular calcium homeostasis. Cellular calcium overload can lead to ROS generation, mainly released from mitochondria, and induce oxidative stress (Kirkinezos and Moraes, 2001; Brookes et al., 2004; Peng and Jou, 2010). Mitochondrial permeability transition pore (mPTP) is a ROS-dependent protein complex between the mitochondrial inner and outer membrane. Calcium overload and oxidative stress in mitochondria can induce the opening of mPTP through lipid peroxidation and mitochondrial respiratory chain damage, thus reducing the mitochondrial membrane potential and releasing cytochrome C (Armstrong, 2006; Rottenberg and Hoek, 2017). The latter is a small molecule protein located in the inner membrane of mitochondria, which serves as an electron carrier between the mitochondrial respiratory chain complex III and complex IV. Its release activates caspase-9, which in turn activates the executor of apoptosis protein caspase-3, and ultimately leads to neuronal apoptosis (Kadenbach et al., 2004; Choi et al., 2007). Therefore, the destruction of mitochondrial structural integrity and functional homeostasis is a significant pathological change in cerebral ischemia injury. Protecting the mitochondrial structure and function is the focus of neuroprotection after cerebral ischemia.

Curcumin can alleviate cerebral ischemic injury by preserving the mitochondrial function and minimizing mitochondrial injury, elevating mitochondrial membrane potential, mitochondrial complex I activity, mitochondrial cytochrome c levels, and maintaining the mitochondrial membrane integrity (Rathore et al., 2008; Kakkar et al., 2013; Miao et al., 2016; Zhang Y. et al., 2017; Wang et al., 2019c). Moreover, curcumin may exert neuroprotective effects by increasing mitochondrial biogenesis, including nuclear respiratory factor-1, mitochondrial transcription factor A, and mitochondrial number (Wang et al., 2005; Liu et al., 2014). He et al. (2020) uncovered that curcumin-laden exosomes alleviated cerebral ischemia-reperfusion injury by inhibiting the ROS-mediated mitochondrial apoptosis. In another study, Mondal et al. (2019) discovered that tetrahydrocurcumin epigenetically mitigated mitochondrial dysfunctions by regulating the mitochondrial tissue inhibitor of metalloproteinase 2 (TIMP-2) through hypermethylation of the CpG islands of TIMP-2 promoter. Furthermore, curcumin can relieve Ca^{2+} dysregulation (Shukla et al., 2008), which may be associated with the inactivation of the P2X7 receptor (Wang Z. et al., 2020). However, the crosstalk and interactions of mitochondrial dysfunction, oxidative stress, calcium overload, and apoptosis in cerebral ischemia are complex. Further research is necessary to reveal the specific neuroprotective mechanism of curcumin in this complicated pathological process.

Curcumin Regulates Autophagy

Autophagy is a ubiquitous occurrence in eukaryotic animals in which cells phagocytose their own cellular components into vesicles and subsequently fuse with lysosomes to form autophagolysosomes, which breakdown to maintain the cell metabolism and organelle renewal (Mizushima et al., 2008; Mizushima and Komatsu, 2011). It is instrumental in maintaining cell survival and intracellular homeostasis under stressful conditions such as ischemia and hypoxia; however, immoderate autophagy may promote cell death (Smith et al., 2011; Kubisch et al., 2013; Choi et al., 2018). So far, the researchers have detected more than 30 autophagy-related genes involved in regulating autophagy. Cerebral ischemia is known to activate autophagy. However, the role and mechanism of autophagy in cerebral ischemia remain elusive (Wang et al., 2021). The influence and effect of autophagy may be dependent on the degree of ischemic injury and duration of ischemia (Sun et al., 2018; Wang et al., 2018; Wolf et al., 2019; Hou et al., 2022).

Curcumin can exert a beneficial impact by mediating autophagy, thereby inducing antitumor (Masuelli et al., 2017), anti-fibrotic (Kong et al., 2020), anti-apoptotic (Chen et al., 2021), and neuroprotective effects (Forouzanfar et al., 2020). Many studies have illustrated that curcumin attenuates cerebral ischemic injury with the involvement of autophagy. Curcumin can exert neuroprotective effects by suppressing the overactivated autophagy, with a diminished LC3-II/LC3-I ratio (Tyagi et al., 2012; Huang L. et al., 2018; Zhang et al., 2018). Conversely, other researchers hypothesize that curcumin attenuates cerebral ischemia-reperfusion injury by improving mitophagy, with an elevated LC3-II/LC3-I ratio (Wang and Xu, 2020). The difference between curcumin on autophagy may be correlated with the administration time point and dosage of curcumin, the stage of ischemic injury, and other factors. The dynamic alterations in autophagy regulated by curcumin in cerebral ischemia need to be explored in further research. Interestingly, Hou et al. (2019) identified that inhibition of autophagy caused a decrease in HIF-1α and an attenuation in HIF-1α induced autophagy suppression under OGD/R conditions, indicating the importance of the interaction of autophagy and HIF-1α underlying curcumin-induced neuroprotection in brain ischemia.

SUMMARY

Turmeric is a traditional Chinese medicine widely used in food and medicine and has been used to treat various diseases for millennia. Akin to many natural products, turmeric has a variety of biological activities with low toxicity. As a critical active component of turmeric, curcumin has been found to play a neuroprotective role in the treatment of cerebral ischemia through various mechanisms, such as antioxidant activity, anti-apoptosis, anti-inflammatory

activity, and BBB protection. However, there are unresolved questions. First, the clinical application of curcumin is challenging. At present, most of the studies are experimental by nature, and related clinical trials are limited. Although basic research has achieved favorable results, it should be noted that animals and humans have significant differences in terms of drug applications, such as drug dosage and frequency, administration route, and treatment time points. In addition, it has a strong desire to further illustrate the effectiveness, safety, and stability of curcumin in the body through clinical trials, and choose the optimal treatment strategy. Second, the effect of curcumin combined with other drugs and treatment methods should be explored to determine the potential mechanism of their synergistic effects in promoting the therapeutic effect of curcumin. Furthermore, curcumin has a wide range of therapeutic targets, making it challenging to focus on just one. Therefore, an effective strategy to maximize the efficacy of curcumin is by accelerating the development of drug delivery systems based on nanoparticles and other carriers and to carry out targeted modification in the new forms of curcumin. Last but not least, it is imperative to further deepen our understanding of the biological and pharmacological activities of curcumin. Considering that curcumin is almost insoluble in water and has a short half-life and low bioavailability, further studies are warranted to determine its application in cerebral ischemic therapy.

AUTHOR CONTRIBUTIONS

FF and ML contributed to the design of the review and revised the manuscript. FF drafted the manuscript. ML revised the manuscript. All the authors read and approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

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