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Repair of the nervous system by dihydromyricetin and the treatment of diseases

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Abstract: *Dihydromyrictin (DHM) is a dihydroflavonoids, which has many functions such as free radical removal, antioxidant and anti-inflammatory. Because its rich biological activity is widely used in the medical and health care fields, this paper reviews relevant studies on the neuroprotective effects of DHM to analyze its mechanisms and effects in the nervous system. Integrating the existing research results, including the effects of DHM on neurodevelopment, neuroprotection, neuroinflammation and neurodegenerative diseases, aims to summarize the potential application of DHM in the nervous system.*

Keywords: *DHM, neuroinflammation, oxidative stress, Alzheimer's disease (AD), Parkinson's disease (PD)*

1. Introduction

The nervous system is one of the most important physiological systems in the human body. It is responsible for transmitting, processing and storing information, as well as regulating the physiological activities of the human body. However, the nervous system is prone to lesions and dysfunction in the face of external and internal stress and injury. Therefore, finding effective treatments and drugs is important to protect and repair the nervous system. DHM, as a kind, is a dihydroflavonoids compound, chemical formula C15H12O8, with a variety of biological active compounds, widely found in the grape family snake grape plant, the content in up to about 35%). DHM has very low solubility and bioavailability in humans, and has recently been found to have protective and regulatory effects on the nervous system. DHM is almost non-toxic and harmless, and it is widely used in clinical treatment. It has a positive effect on neuroprotection and has a significant cure effect on neuroinflammation and neurodegenerative diseases. This paper will deeply explore the protective and regulatory effects of DHM on the nervous system and its possible mechanisms, and provide a reference for research in related fields.

2. Chemical structure and origin of the DHM

2.1 Chemical structure of the DHM

DHM is a polyphenolic hydroxydihydroflavanol.[1].The chemical formula of C15H12O8 and a molar mass of 320.25 g/mol[2]. The Physicochemical properties of the DHM are shown in table 1.

Table 1: Physicochemical properties of the DHM

molecular formula	C15H12O8
formula weight	320.25
surface	White or like white powder
Physical solubility	Easy soluble in water, hot ethanol and acetone; soluble in ethanol and methanol; Very slightly soluble in ethyl acetate;
heat endurance	good
melting point	245-246℃
boiling point	780.7℃
storage condition	—20℃

It was shown that the adjacent hydroxyl groups on the B loop of the DHM are important for the antioxidant activity, while the single bond at position 2,3 in the C loop causes the stabilization of the

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DHM structure. DHM has oxygen atoms and spatial configurations suitable for the coordination of molecular structure, which can show good biological activity when coordinated with metal ions. Due to the irregular substitution of carbon atoms at positions 2 and 3, DHM can exist in four stereoisomers [3], which are most common at room temperature with readily extracted compounds flavonols and chalcones [4].

Due to the structural differences, the enantiomers may exhibit significant differences in some properties. For example, researchers have found that enantiomers act better in concert with receptor molecules, thereby reducing adverse effects[5].This structure allows DHM to have several beneficial pharmacological activities, such as antioxidant, anti-inflammatory, hepatoprotective effects, and antihypertensive activity [6].Based on this DHM (DHM) shows a range of therapeutic potential, including anti-diabetic, cardioprotective, neuroprotective, and antitumor properties [7].Its mode of action is believed to involve the reduction of oxidative stress (OS), the inhibition of neuroinflammation to reduce inflammatory factors to the nerves[8]. The free radical scavenging and antioxidant capacity of DHM was first demonstrated and applied by Shen et al [9,10].Studies have shown that DHM also has anti-aging effects, improving learning disorders, and improving behavior disorders. The mechanism is related to DHM to improve the synaptic structure of hippocampal neurons, promote mitochondrial biogenesis, reduce lipid peroxidation, and inhibit the production of ROS.

In conclusion, thanks to the oxygen atoms and spatial configuration suitable for molecular structure coordination, DHM can regulate neural response activity by binding to a variety of neural cytokines.

2.2 Source and extraction method of DHM

DHM, also known as myricetin, is a flavonoid derived from the stems and leaves of plants.grossedentata. It is also widely found in the Japanese raisin trees (Hovenia dulcis Thunb.) centre.[11], the peel and pulp parts of its fruit contain abundant DHM. In addition, the bud and calyx of honeysuckle (Lonicera japonica), grape (Vitis vinifera) skin and seeds contain considerable content. In addition, the DHM is also present in the fruit of the persimmon (Diospyros kaki). Other plants, such as coptis (Coptis chinensis) and hawthorn (Crataegus pinnatifida) [12], are also very high content in cane tea, usually reaching 30~40%[13]. The Extraction efficiency under the optimal ratio of various techniques is shown in Table 2.

Table 2: Extraction efficiency under the optimal ratio of various techniques

extraction	Reagent physical and chemical environment	Mass ratio of material and liquid	Other necessary conditions	extraction percentage	works cited
Enzyme extraction method	45℃,pH4.46	1:20	Enzyme addition mass fraction was 2.0%	30.65%	[16]
Microwave extraction method	2800W (microwave power)	1:20	Release speed is 40 L/min	28.78%	[17]
Ultrasound technology extraction (Tween-80- - - ultrasound)	54℃	30:1	A Tween concentration of 6.8%	35.58%	[18]
Ultrasound technology extraction (Low-temperature- - Ultrasonic)	50℃,1000W (Ultrasound power)	1:30	It was extracted for 15min	24.37%	[19]
Ultrasound technology extraction (Ethanol- -Ultrasonic)	40℃,65% (Ethanol volume fraction)	1:18	Were extracted for 40min	93.1%	[20]
solvent extraction (aqueous extract)	95℃	1:25	It was extracted for 120min	22.8%	[21]

A comprehensive consideration, grounded in the specific chemical properties and characteristics of DHM, renders it suitable for application in various extraction techniques, including microwave-assisted extraction, ultrasound-assisted extraction, solvent extraction, and enzymatic extraction. Microwave extraction [14], a gradual physical separation method, has yielded the highest extraction efficiency within a shortened timeframe. Ultrasonic-assisted extraction harnesses the mechanical and cavitation effects of ultrasound to facilitate solvent penetration into plant material and enhance the release of solutes, thereby facilitating the rapid extraction of DHM. Due to its simplicity, the solvent extraction method necessitates careful control of the optimal water extraction temperature at 95°C. Lastly, the enzymatic method boasts the fundamental advantages of speed, precision, sensitivity, and simplicity. In recent years, combining

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the characteristics of enzymes with the biological cell structure, the extraction process of biological enzymes in Chinese medicine to improve the extraction rate of Chinese medicine and obtain highly active active ingredients, has achieved great results [15]. The following is the extraction efficiency of various techniques under the optimal ratio. In terms of the DHM extraction efficiency, the highest ultrasonic extraction method was obtained when bound to the surfactant Tween-80.

3. The role of the DHM on neuroprotection

3.1 The inhibitory effect of DHM on nerve cell proliferation and apoptosis

The neural cell level is a landmark indicator of the fast and slow response of the nervous system. Studies have shown that the JAK 2 / STAT3 signaling pathway has a regulatory effect on cellular autophagy, through the activation of this signaling pathway can affect the cell autophagy, and then affect the cell viability. Previous studies have shown that DHM can significantly upregulate the protein expression levels of p-JAK 2 and p-STAT3 and the ratio of p-JAK 2 / t-JAK 2 and p-STAT 3 / t-STAT 3 in cells, thus inhibiting the effect of neural cell proliferation.

In addition, DHM can inhibit renal inflammation and apoptotic cell death by reducing the expression of nuclear factor- κB (NF- κB), TNF-α, and caspase-3 [22]. The underlying mechanism can be attributed to the inhibition of cell proliferation, causing cell cycle arrest or apoptosis [23]. It has been shown that JNK mediates an apoptotic[24] response in microglia. The involvement of JNK in high glucose-induced apoptosis was further confirmed by western blot detection by Lv et al. The final results indicated that DHM was able to antagonize high glucose-induced apoptosis in PC12 neural cells by inhibiting JNK signaling. Meanwhile, Li et al. conducted a study on brain subarachnoid hemorrhage (SAH) by establishing a rat SAH model. There was a positive relationship between the severity of SAH and the Hunt-Hess grade of the patients [25]. By Prx 2 expression protects the brain from oxidative damage and hydrogen peroxide-induced neuronal apoptosis. The results of Li et al. showed that DHM significantly induced Prx 2 expression after SAH and inhibited downstream ask1-dependent activation of pro-death signaling by p38. This implies that DHM may exert its beneficial effects by regulating Prx 2-mediated signaling. The results of Tong et al. showed that DHM could effectively improve cognitive dysfunction in PD model mice, partly reverse the decrease in intrastriatal TH protein expression triggered by MPTP / p, and downregulate inflammation in hippocampal tissue. Factors TNF- α, IL-l β and IL-6 protein expression, reduced the amount of LDH release and upregulated the protein expression of Caspase-8, a negative regulator of necrotizing apoptosis.

ROS production is associated with mitochondrial dysfunction and apoptosis in various cell types[26,27].Accumulation of ROS cause prolonged activation of microglia and astrocytes, leading to persistent neuroinflammation, further ROS production [28], and additional cellular damage. While the enhanced LCN2 expression leads to the formation of the LCN 2-SLC3A2 complex, which suppresses the transport activity of the Xcan system leading to the accumulation of ROS. DHM treatment counteracts this process by regulating the expression of LCN 2, thereby inhibiting apoptosis [29]. The diagram of the mechanism of DHM resistance to inflammation is shown in Figure 1.

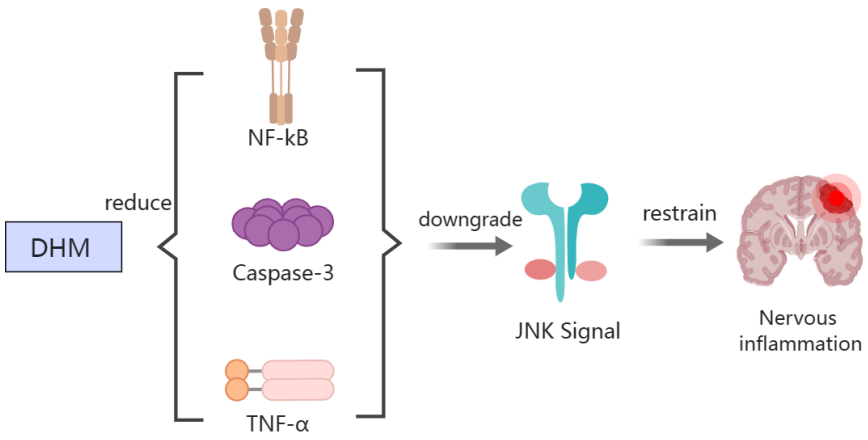

Figure 1: Diagram of the mechanism of DHM resistance to inflammation

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3.2 Regulation of DHM on oxidative stress and neuroinflammation

DHM suppresses oxidative stress and down-regulates inflammatory factor pathway (JNK) signaling pathway in type 2 diabetic (T2DM) mice to improve cognitive dysfunction (CI) and high glucose-induced apoptosis in PC12 cells[30,31] to produce resistance. Wang Zihan et al summarized that these effects are related to the involvement of oxidative stress and activation of JNK signaling in ferroptosis [32].

BDNF is the most abundant neurotrophic factor in the brain and is critical for neuroprotection and neurogenesis [33]. Studies showed that oxidative stress is corassociated with BDNF levels [34]. Therefore, the investigators hypothesize that DHM may improve cerebral ischemic cognitive impairment (DACI) by enhancing BDNF-mediated neuroprotective signaling, and protect neurons from oxidative damage. This speculation is based on the observed upregulated effect of BDNF expression after DHM treatment. This effect may contribute to improve neuronal survival and function to combat cognitive impairment induced by cerebral ischemia[35].

The inflammatory response is a self-protective mechanism of the body, but when it is beyond the appropriate range or duration, it may become a threat, causing more harm to the body than protection. Amanollahi Mobina et al show that neuroinflammation is driven by different immune components, such as activated glia, cytokines, chemokines and reactive oxygen species, which can regulate every step of adult neurogenesis[36]. In the study of (AD), it was found that DHM decreased tissue inflammation and decreased the hippocampus and cortex [37]. Zhang et al. found that the expression of proinflammatory factors (e. g., IL-6, IL-8, and TNF- α) was significantly inhibited in the injured chicken ileum [38].Moreover, it was shown that the expression of IL-16 gene in blood cells decreased when the diet contained DHM protein. In the intestinal tissue of the control group, the expression of TNF- α and IL-16 was significantly increased, and the high dose of dietary DHM may lead to an inflammatory response in the shrimp [39]. In conclusion, DHM reduced the occurrence of neuroinflammatory inflammation by affecting the release of inflammatory factors in the body and reducing the regulation of microglial cells.

4. The prospect of DHM in neurodegenerative diseases

4.1 Mechanism and progress of DHM in AD

AD is a chronic, progressive neurodegenerative disease that is mainly characterized by progressively deteriorating memory and cognitive dysfunction. The etiology of AD is very complex, and many factors are involved in the pathogenesis of AD [40]. Its pathological features mainly include neuronal loss, including hippocampus and cortex, neurofibrillary tangles and the formation of β amyloid plaques. In addition, neuronal tumors, deposition of other proteins, inflammatory responses, and abnormal neurotransmitters may occur. These pathological features, although still having many details to be further explored and understood, are important for the diagnosis and investigation of AD.

By establishing a mouse aging model, Qian Jianan et al. found that excessive intake of d-galactose (D-Gal) may alter the metabolic process of human D-Gal to produce intermediates such as aldose and hydrogen peroxide [41].Therefore, excessive free radicals and reactive oxygen species (ROS) may be synthesized to accelerate the aging of the nervous system and increase the risk of AD. Low doses of DHM can effectively inhibit neuroinflammatory aging in mice exposed to D-Gal [42]. Thus reversing the cognitive impairment induced by D-Gal.

Inflammatory damage of microglia may trigger neuronal damage and the release of inflammatory mediators, which can aggravate neuroprogressive disease. Its inflammatory response is mainly mediated by TLR 4, and myeloid differentiation protein 2 (MD2) studies have found that MyD 88 also assists in the role of TLR 4 / MD2, and in signal transfer activation[43].At the cellular level, MD2 is the target of DHM, MD2 is a key protein in the activation and mediation of TLR 4 signaling, and an important protein in regulating inflammatory response. Moreover, DHM can inhibit MD2 and inhibit the activation of TLR 4 signaling, and thus play its role [44]. Moreover, Al Omran Alzahra et al. have shown that DHM can regulate mitochondrial function, reduce oxidative stress, maintain antioxidant levels, normalize autophagy, and enhance brain-derived neurotrophic factor (BDNF)[45].

Due to the complex pathogenesis of AD, drug treatment with a single mechanism has limited effect in AD patients. At present, there is no ideal clinical drug options for AD treatment. As a food supplement recognized by some countries, DHM shows its anti-AD effect in many aspects, so it is expected to become an ideal candidate for the treatment of AD. The onset of Alzheimer's disease and the mechanisms of DHM repair is shown in Figure 2.

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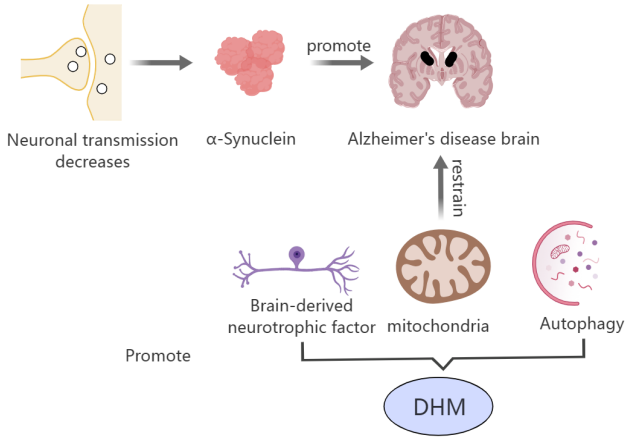

Figure 2: The onset of Alzheimer's disease and the mechanisms of DHM repair

4.2 Application prospects of DHM in China

PD is an age-related neurodegenerative disorder whose major clinical manifestations include limb motor delay, enhanced muscle tone, resting tremor, and postural gait balance disorders. Environmental, genetic and other factors are all related to the development of PD. Show, the occurrence of PD with the selective absence of dopaminergic neurons. These neurons are located in the substantia nigra pars compacta (SNpc) and are responsible for producing dopamine in the brain, an important neurotransmitter critical for the control of movement and coordination of muscle activity.α -Synapnuclein (α SN) is a soluble protein expressed in the presynaptic and perinuclear nucleus of the central nervous system. It is closely related to the pathogenesis and related dysfunction of PD and is the main component of the Lewy body.

In addition, the occurrence of neuroinflammation will cause nerve cell necrosis and then reduce the release of neurons, triggering the development of PD. The NLRP 3 inflammasome is one of the most well-characterized inflammasomes in the TLR 4-mediated NLR family. When the NLRP 3 signaling pathway is activated, it can recruit both ASC and caspase-1 to form the NLRP 3 inflammasome. The NLRP 3 inflammasome is involved in regulating the maturation and secretion of the proinflammatory cytokine IL-1 β. It was shown that HIF-1a, a protein and downstream signaling protein of the TLR 4 / Akt pathway, is involved in activating the expression of the NLRP 3 inflammasome. DHM significantly inhibited ASC, caspase-1, and NLRP 3 expression induced by LPS treatment in a dose-dependent manner. DHM attenuated the neuroinflammatory response by inhibiting the activation of the TLR 4 / Akt / HIF-1a / NLRP 3 pathway [46] Jia Longgang et al found that DHM inhibited the ability of α SN fiber formation and stabilize mature α SN fibrils. Moreover, DHM effectively fights α SN-induced cytotoxicity by enhancing cell viability[47].

Neuroinflammation and the lack of BDFN are important markers for the development of PD. This shows that in addition to showing effective efficacy in neurotransmission, DHM also exhibits strong neuroprotective effects, capable of reducing the damage of dopamine neurons, and thus is a potential drug for the treatment of PD.

5. Future research directions and challenges

DHM was safe, with acute oral toxicity test [48], long-term toxicity test[49]and genotoxicity test [50] in rats and mice, which were negative.

The solubility and bioavailability of DHM in human body are very low. According to the classification standards of the Biopharmaceutical Classification System (BCS) issued by the World Health Organization, DHM is classified as a class compound due to its low solubility and low permeability. But it has a series of pharmacological effects such as anti-inflammatory, antibacterial, antioxidant and anti-tumor, almost non-toxic and safe, and is widely used in clinical treatment. The optimal clinical dose of DHM ranged from 100 mg to 300 mg daily. However, as a new drug that is difficult to absorb and easy to accept, the optimal dose of DHM should be studied in the future.

The inhibition of apoptosis by DHM may be mediated by clearance of ROS, and activation of

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mitochondrial apoptosis signaling. VitC is a positive drug with significant antioxidant properties. Previous studies have demonstrated the antioxidant properties of VitC under different conditions [51,52]. Using VitCVitC pretreated cells as a control group, the results in the VSMC cells showed that DMY promoted cell viability in a dose-dependent manner. And the 50 μ M concentration[53].

DHM for the anti-aging laboratory of animals by inhibiting apoptosis and rescuing impaired autophagy, Qian et al. showed that low-dose DHM treatment, similar to high-dose DHM treatment, significantly restored serum CAT activity and reduced LPO, AGEs, and content in D-Gal-exposed mice with MDA. DHM supplementation of 168 mg / kg reduced the expression of these aging-related markers in mouse hippocampal neurons. IL-6, IL-2 are both pleiotropic proinflammatory cytokines considered to be closely related to the severity of AD symptoms [54].When cognitive impairment occurs [55,56], an imbalance in serum IL-6 can be found. DHM at a 42-dose dose of mg / kg significantly inhibited the secretion of IL-6 and IL-2 and alleviated oxidative stress in d-gal-exposed aged mice. Qian et al suggested that the dose of 42 mg / kg was significantly lower than previous studies and could be recommended as a safe and effective dose for delaying aging of DHM.

6. Conclusion

DHM as a kind of flavonoids can effectively inhibit nerve cell proliferation and apoptosis, control inflammation and antioxidant effect, comprehensive nearly ten years at home and abroad found that DHM can through multiple targets for the treatment of various neurodegenerative diseases, show its powerful neuroprotective effect in many aspects, is widely used in clinical treatment, especially AD, PD, depression, cerebral ischemia of neurodegenerative diseases. At present, DHM has no obvious toxic effect on human body. Comprehensive studies of the effects of DHM on several diseases have found that only a certain dose of DHM can achieve significant effects. Relevant data showed that DHM had poor stability, low solubility, low bioavailability and low drug availability in human body, which greatly limited its medicinal value. How to solve the problem of low bioavailability of DHM in human body, and the further elaboration of the neuroprotective mechanism of DHM remains to be explored by researchers.

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