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Advances in Research on Tibetan Medicine for Improving Cognitive Dysfunction

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Abstract: With the rapid aging of the global population, the incidence of cognitive dysfunction is on the rise. The efficacy of existing clinical medications has been less than satisfactory, leading researchers to explore traditional medicinal practices. Tibetan medicine, a vital segment of traditional medicine, has been extensively utilized for the treatment of mental, psychological, and neurological conditions. Modern clinical and experimental pharmacological studies have shown that *Rhodiola L., Terminalia chebula Retz., Sibiraea laevigata (L.) Maxim., Centella asiatica (L.) Urban, Gymnadeniaconopsea (L.) R. Br., Crocus sativus L., Ganoderma lucidum (Curtis) P. Karst.*, Seventy Flavor Pearl Pills, Twenty-Five Flavor Coral Pills, Ruyi Treasure Pills, and Twenty-Five Flavor Pearl Pills have effects on improving cognitive dysfunction. This review meticulously examines the research progress on these Tibetan medicinal substances for their role in mitigating cognitive dysfunction, with the goal of providing valuable insights for the development of novel therapeutic approaches to cognitive deterioration.

Keywords: cognitive dysfunction; Tibetan medicine; Rhodiola; Seventy Flavor Pearl Pills

1. Introduction

Cognition is the cornerstone of human psychological activity, enabling us to recognize, process, and understand the world. This multifaceted function encompasses a variety of domains, including memory, calculation, executive functions, spatial orientation, language comprehension and expression, and adaptive problem-solving skills. Cognitive dysfunction encompasses a spectrum of impairments that affect these cognitive abilities to varying degrees, stemming from a multitude of causes [1]. The severity of cognitive dysfunction can span from mild cognitive impairment to the more severe condition of dementia. The progression of cognitive dysfunction is typically characterized by three stages: [2]. (1) Preclinical Stage. Here, a specific cognitive domain may exhibit slight impairment without presenting noticeable clinical symptoms. (2) Mild Cognitive Impairment (MCI). This stage sees a progressive decline in several cognitive domains, most notably memory, yet the impact on daily living remains manageable. (3) Dementia Stage. This advanced stage is marked by profound cognitive deficits that significantly disrupt an individual's daily life and social interactions [3]. Among these, MCI is an intermediate state between normal aging and dementia [4], classified into amnestic MCI and non-amnestic MCI [5]. Amnestic MCI is characterized by significant memory impairment, whereas non-amnestic MCI involves impairments in other cognitive domains without prominent memory deficits [6].

There are various causes of cognitive dysfunction, with many diseases showing a positive correlation with cognitive impairment, such as cerebrovascular disease, traumatic brain injury, Huntington's disease, and HIV/AIDS [5]. Other diseases that can lead to cognitive dysfunction include hydrocephalus, brain tumors,

hypothyroidism, alcohol intoxication, and brain injuries [2]. Additionally, conditions like epilepsy [7], Parkinson's disease [8], and Alzheimer's disease (AD) [9,10] can also cause cognitive dysfunction (Figure 1), many of these diseases induce cognitive impairment through neuroinflammation, which subsequently leads to cognitive disorders. The neuroinflammatory response observed in hypothyroidism [11], epilepsy [12], Alzheimer's disease (AD), and Parkinson's disease [13] results in neural damage that further compromises cognitive function. Additionally, Huntington's disease [14] is associated with neuroimmunity, contributing to cognitive dysfunction.

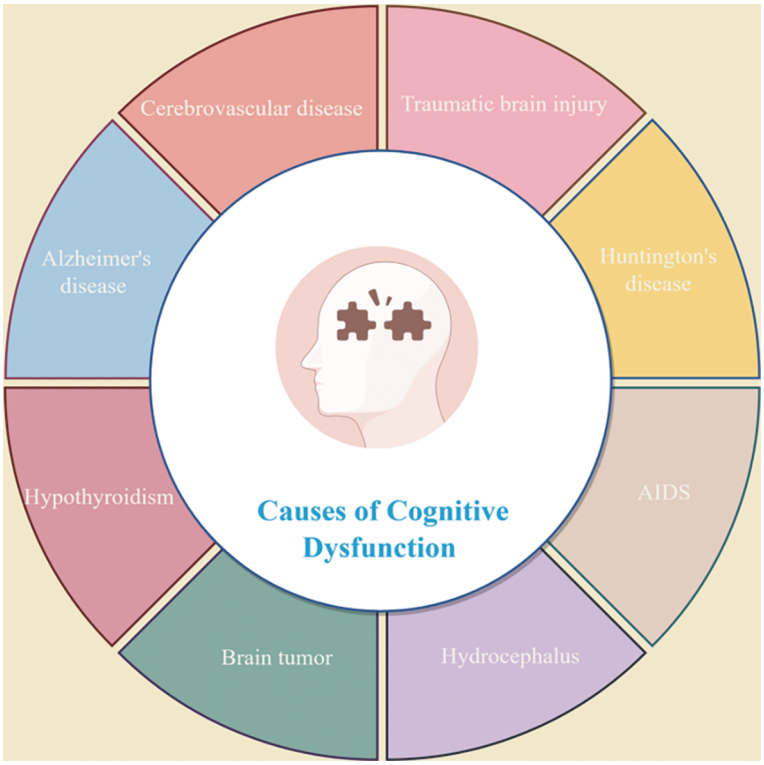

Figure 1. Causes of Cognitive Dysfunction. The causes of cognitive impairment include Traumatic brain injury, Huntington's disease, AIDS, Hydrocephalus, Brain tumor, Hypothyroidism, Alzheimer's disease, Cerebrovascular disease, by Figdraw.

In Tibetan medicine, the understanding of cognitive dysfunction is grounded in a unique worldview that emphasizes the balance of three fundamental energies: "Loong", "Tripa", and "beygen". Cognitive dysfunction is often attributed to an imbalance in Loong, which manifests as mental unrest, forgetfulness, and decreased concentration. Within this framework, Loong functions analogously to the nervous system in Western medicine, facilitating energy flow and information transmission. Cognitive dysfunction is viewed as a consequence of disturbances in Loong, which adversely affect emotional stability, sleep, memory, and cognitive abilities [15].

Regarding the mechanisms underlying cognitive dysfunction, theories include immune dysregulation [16], apoptosis [17], oxidative stress[18], and other studies indicating that glucose metabolism [19], neuroendocrine dysregulation [20], and central nervous system inflammation [21] also play roles. Thus, cognitive dysfunction is a general term for a group of diseases with complex and diverse mechanisms, presenting significant challenges for drug development.

Tibetan medicine has a long history of over 2300 years and is one of the four major traditional medicines in the world, also part of traditional Chinese medicine. Tibetan medical classics, such as the "Four Medical Tantras" and the "Jingzhu Materia Medica," record many traditional Tibetan medicines and classical Tibetan medicine formulas, many of which have significant effects on improving cognitive dysfunction, such as the Seventy-Flavored Pearl Pill [22–24] and Rhodiola [25]. In recent years, research on Tibetan medicine for neurological diseases has deepened, with more Tibetan medicines proven to improve cognitive

dysfunction in humans or animals, providing a potential avenue for prevention and treatment. This paper reviews the research progress to provide a reference for the study of prevention and treatment strategies for cognitive dysfunction.

2. Single Herb of Tibetan Medicines for Improving Cognitive Function

In contemporary clinical and experimental pharmacological studies, several individual Tibetan medicinal substances have demonstrated the capacity to enhance cognitive function. Among these, Rhodiola, Terminalia chebula, Sibraea angustata, Centella asiatica, Gymnadenia conopsea, Ganoderma lucidum, and Crocus sativus have shown particular promise. The following sections detail the findings for each substance (Table 1).

2.1. Rhodiola

Rhodiola (Rhodiola rosea L.), a resilient perennial herb of the Crassulaceae family, thrives in the lofty altitudes of 2800 to 5600 m, ofen nestled among mountainous shrubbery and rock crevices. This hardy plant is renowned for its neuroprotective properties, which not only bolster physical stamina and safeguard cardiac health but also invigorate reproductive capabilities and exhibit antidepressant effects [26]. The main active compounds of Rhodiola rosea are Rosavin, salidroside (also known as rhodioloside) [27,28].

Emerging research highlights the neuroprotective prowess of rhodioloside, a key constituent of Rhodiola rosea, which shows promise in the prevention and treatment of Alzheimer's disease (AD) by mitigating cognitive impairments associated with the condition [29,30]. In a study involving oral administration of rhodioloside to male Sprague-Dawley rat models induced by $A\beta_{1-42}$ over 28 days, the Morris water maze test revealed that rhodioloside significantly shortened the latency period, increased the retention time in the target quadrant, elevated acetylcholine (ACh) levels in the hippocampus, enhanced acetylcholinesterase (ChAT) activity, reduced the expression of phosphorylated tau at Ser396 and Ser404, and increased the expression of phosphorylated GSK-3β (Ser9) [31]. Furthermore, rhodioloside treatment improved superoxide dismutase (SOD) activity in the parietal cortex and reduced malondialdehyde (MDA) content. Additionally, intraperitoneal injection of rhodioloside in normal C57BL/6J wild-type mice extended their freezing time in the fear conditioning test [29]. Further evidence supporting the cognitive-enhancing effects of rhodioloside comes from another study, where Rhodiola rosea extract was found to shorten the latency period during the training phase of the Morris water maze in male Sprague-Dawley rats with streptozotocin-induced Alzheimer's disease. This was accompanied by an increase in the time spent in the target quadrant during the test phase [25]. Collectively, these findings underscore the potential of rhodioloside as a therapeutic agent for improving cognitive dysfunction in Alzheimer's disease.

2.2. Terminalia chebula

Terminalia chebula (Terminalia chebula Retz.) refers to the dried mature fruit of Terminalia chebula or Terminalia chebula var. Tomentella, which belongs to the Combretaceae family. The main production areas in China include Guangdong, Guangxi, Fujian, and Yunnan. This fruit is recognized for its astringent properties, as well as its benefits for the intestines, lungs, and throat. Beyond its traditional uses, modern clinical and pharmacological studies has unveiled a myriad of therapeutic potentials for Terminalia chebula, including neuroprotection, antioxidant activity, antibacterial properties, detoxification, cardiotonic effects, anti-tumor capabilities, and the promotion of tracheal smooth muscle contraction [32,33]. The various components of the terminalia chebula, including the fruit, seeds, gum, and bark, contain a range of bioactive compounds, such as gallic acid, ellagic acid, and other phenolic acids. These compounds are recognized for their potential health benefits and pharmacological effects [34].

In a scopolamine-induced amnesia model using C57BL/6N mice, oral administration of Terminalia chebula extract (TCE) significantly prolonged the retention time in the target quadrant during the Morris water maze test [33]. In a sleep deprivation (SD) mouse model established via the Modified Multiple Platform Method (MMPM), polyphenol corilagin (CL) extracted from Terminalia chebula improved object

recognition memory and spatial learning abilities in the Morris water maze test. This effect is likely mediated by the activation of the Nrf2 signaling pathway and the reduction of NOX2 expression [35].These insightful studiescollectively suggest that TCE has the potential to enhance memory, while CL can effectively mitigate learning and memory deficits associated with sleep deprivation, offering promising avenues for further research and therapeutic applications.

2.3. Sibraea angustata

Sibraea angustata (Sibraea angustata (Rchd.)), a distinguished species within the Rosaceae family, is celebrated for its branches and fruit clusters, which are harvested from both Sibraea angustata and its closely related counterpart, Sibraea sinensis [36,37]. It has been shown to regulate lipid metabolism and weight, modulate glucose metabolism, protect liver function, and exhibit antioxidant effects [38]. Sibraea angustata contains a diverse array of chemical components, including triterpenoids, organic acids, and volatile oils [39]. Studies have demonstrated that oral administration of Sibraea angustata extract to normal Kunming mice over 50 days resulted in shorter escape latencies and longer retention times in the target quadrant during the Morris water maze test [40], indicating that Sibraea angustata extract may enhance learning and memory capabilities.

2.4. Centella asiatica

Centella asiatica (Centella asiatica (L.) Urban), a treasured herb from the Umbelliferae family, is renowned for its dried whole plant, which is celebrated for its versatile therapeutic properties. These include the reduction of inflammation, detoxification, and the clearing of damp heat [41]. The main active compounds of Asiaticoside are asiatic acid, madecassic acid, and madecassoside [42].

A clinical study involving 48 patients with post-stroke cognitive impairment demonstrated that after six weeks of treatment with Centella asiatica extract, the Montreal Cognitive Assessment (MoCA) scores improved, indicating that this extract can alleviate symptoms of cognitive dysfunction in patients [43].

Further experimental research [44] has uncovered the cognitive-enhancingf effects of hydroxyasiaticoside, an extract from Centella asiatica, to D-galactose-induced cognitive impairment mouse models for 12 weeks revealed shortened latency periods in the Morris water maze test. Moreover, the treatment was associated with a decrease in hippocampal NF-κB p65 protein levels and $A\beta_{1-42}$ content, inhibited phosphorylation of ERK and p38 MAPK, decreased brain APP and BACE1 mRNA expression, increased NEP and IDE mRNA expression, and reduced NF-κB DNA binding activity. These findings point towards the extract's ability to bolster learning and memory by modulating the NF-κB and ERK/p38 MAPK pathways, thereby mitigating oxidative damage and the accumulation of $A\beta_{1-42}$.

A two-week administration of water extract of Centella asiatica (CAW) to aged C57BL/6 mice resulted in a shortened latency period and extended target quadrant retention time in the Morris water maze test, effects that were not observed in 2-month-old C57BL/6 mice [45]. This indicates that CAW may enhance memory in older individuals. After 14 days of treatment with Centella asiatica water extract in male Wistar rats, the shuttle box test results exhibited a significant increase in the number of successful avoidance responses in the treated group. Additionally, there was a marked decrease in brain MDA levels and a significant increase in glutathione and catalase activities, suggesting that Centella asiatica water extract can improve learning and memory abilities in rats, potentially through mechanisms that reduce oxidative stress in the brain [46]. In another study, three-month-old Swiss albino mice were administered oral Centella asiatica extract for 15 days. Results from the eight-arm maze test indicated that, compared to the control group, the number of correct arm entries significantly increased, and there was enhanced neuronal dendritic branching in the brain, suggesting that Centella asiatica extract can improve memory function and promote neuronal development in mice [47].

2.5. Gymnadenia conopsea

Gymnadenia conopsea (Gymnadenia conopsea R.Br.) is a traditional Tibetan medicine derived from the dried tuber of the Orchidaceae plant, including Gymnadenia conopsea, Gymnadenia crassinervis, and

Chionorchis pauciflora. This plant grows in valleys, shrub layers, forest meadows, and shady slopes across regions such as Tibet, Sichuan, Qinghai, Gansu, Ningxia, Xinjiang, North China, Northeast China, and Inner Mongolia. It is known for its calming effects, intelligence enhancement, salivation and thirst-quenching properties, kidney tonification, essence nourishment, qi regulation, and pain relief [48].

Studies [49] have reported that oral administration of 20 mg/kg Gymnadenia conopsea ethanol extract (primarily composed of succinic acid esters) to four-month-old female 5 × FAD transgenic mice resulted in shortened latency and extended target quadrant retention time in the Morris water maze test compared to the model group. Immunohistochemical and immunofluorescence staining techniques revealed significantly reduced $A\beta_{1-42}$ plaque deposition in the cerebral cortex and hippocampal dentate gyrus (DG) area, decreased levels of RIP1, RIP3, and MLKL, reduced GFAP and Iba1 protein expression, and increased TBK1 content. ELISA results indicated significantly reduced levels of inflammatory factors TNF- α, IL-6, and IL-1β in brain tissue compared to the model group, suggesting that the active components of Gymnadenia conopsea can ameliorate learning and memory dysfunction induced by Alzheimer's disease.

2.6. Crocus sativus

Crocus sativus (Crocus sativus L.), commonly known as saffron, is a perennial herbaceous plant in the Iridaceae family, recognized for its effects such as cooling the blood, detoxifying, promoting blood circulation, and alleviating blood stasis [50]. It originated in Southern Europe and Iran and was introduced to China through Tibet during the Tang Dynasty, hence the name "Tibetan saffron." Modern pharmacological research indicates that saffron has anti-cancer [51], anti-diabetic inflammation [52], and learning and memory-enhancing effects [53]. The main active compounds of saffron are Crocin and safranal [54].

A clinical trial encompassing 35 patients with amnesic and multi-domain mild cognitive impairment (aMCImd) over one year found that oral administration of saffron extract significantly improved patients' MMSE scores. While not a double-blind trial, this study hints at the cognitive-enhancing potential of saffron extract in individuals with mild cognitive impairment [55]. Another double-blind clinical study involving 55 patients with mild to moderate Alzheimer's disease (AD) demonstrated that treatment with saffron capsules (containing Safranal and Crocin) led to significant reductions in Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-cog) scores and Clinical Dementia Rating Scale—Sums of Boxes (CDR-SB) scores [56]. The efficacy of saffron was comparable to donepezil. Furthermore, in a subsequent study involving 46 patients with mild to moderate AD, treatment with saffron capsules for 16 weeks resulted in significantly improved cognitive function compared to the placebo group [57]. A double-blind clinical trial involving 68 patients with moderate to severe AD indicated that saffron extract (Crocin) significantly improved patients' MMSE scores [58]. Collectively, these clinical studies suggest that saffron extract has a beneficial effect on cognitive function in AD patients.

In a vascular cognitive impairment model using SD rats, intraperitoneal injection of crocin significantly shortened the escape latency in the Morris water maze test and increased the number of crossings. Furthermore, crocin enhanced superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity, as well as Nrf2 and HO-1 expression, while reducing malondialdehyde (MDA), TNF-α, and IL-1β levels, as well as NF-κB expression. These findings suggest that crocin can enhance learning and memory abilities [59]. In a separate study, intraperitoneal injection of saffron extract in both adult and aged normal Balb/c mice prolonged the latency period in the passive avoidance test and reduced caspase-3 activity and reactive oxygen species (ROS) levels [60]. This indicates that crocin may improve cognitive dysfunction associated with vascular dementia, while saffron extract has the potential to enhance cognitive function. Research [61] has demonstrated that administration of crocin to a mouse model of Alzheimer's disease (AD) induced by aluminum chloride (ALCI3) and D-galactose significantly shortened latency in the Morris water maze test. Additionally, it reduced $A\beta_{1-42}$ levels in the cerebral cortex, increased SOD and GSH-Px levels in serum, cerebral cortex, and hypothalamus, and decreased ROS levels. These findings suggest that crocin can improve cognitive function in AD model mice by alleviating oxidative stress.

2.7. Ganoderma lucidum

Ganoderma lucidum (Ganoderma lucidum), also known as Ganoderma sinense, is a revered fungus from the Polyporaceae family, renowned for its dried fruiting bodies that are traditionally believed to replenish vital energy, calm the mind, soothe coughs, and alleviate asthma. It is commonly used to address various conditions, including palpitations, insomnia, lung deficiency cough, fatigue, and loss of appetite. Modern pharmacological research has uncovered that Ganoderma lucidum exhibits antioxidant, anti-inflammatory, anti-tumor, lipid-lowering, immune-regulating, and central nervous system-regulating effects [62]. The active ingredient of Ganoderma lucidum is Ganoderma lucidum polysaccharide [63].

Experimental research [64] have revealed that Ganoderma lucidum polysaccharides (GLP) can mitigate cognitive decline associated with neurodegenerative diseases such as Alzheimer's disease (AD). Oral administration of GLP for 90 days to 6-month-old APP/PS1 transgenic mice resulted in shortened latency and extended target quadrant retention time in the Morris water maze test. Immunohistochemical staining and immunofluorescence analysis revealed an increase in BrdU/NeuN double-positive cells in the hippocampus of GLP-treated mice, suggesting that GLP can promote neurogenesis and ameliorate spatial learning and memory impairments.

Another study [65] indicated that the aqueous extract of Ganoderma lucidum (GLAQ) can prevent memory deficits induced by hypobaric hypoxia. In this study, male Sprague-Dawley (SD) rats were trained in the Morris water maze, and subsequently, a hypobaric hypoxia environment was simulated using a decompression chamber to create a hypobaric hypoxia rat model. The rats were then administered GLAQ via gavage. The Morris water maze experiment demonstrated that the latency period in the GLAQ-treated group was significantly shorter compared to the untreated model group, indicating that GLAQ can improve memory deficits caused by hypobaric hypoxia in rats. Additionally, a study established a memory impairment model in mice through intraperitoneal injection of scopolamine. Following treatment with Gmediosinense extract (GME), a Ganoderma lucidum extract, the latency period in the step-through test was extended, and the preference index for novel objects in the novel object recognition test increased, indicating that GME can ameliorate memory impairment in mice [66]. Another study treated SD rats with D-galactose-induced Alzheimer's disease (AD) using Ganoderma lucidum ethanol extract, which significantly shortened the latency period during the training phase of the Morris water maze and increased the time spent in the target quadrant [67], indicating that the extract improves learning and memory in rats. Furthermore, an experimental study on Ganoderma lucidum extract showed that GL70 significantly mitigated spatial learning and memory deficits in the Morris water maze of an LPS-induced AD rat model. In vitro experiments demonstrated that a galactoglucomannan (GLP70-1-2) isolated from GL70 reduced pro-inflammatory cytokine levels in LPS-activated BV2 cells, suggesting that GL70 may improve learning and memory deficits in LPS-induced rat models, possibly through mechanisms involving the reduction of neuroinflammation [68]. Collectively, these experimental studies underscore that Ganoderma lucidum extracts have the potential to enhance cognitive function in animal models.

Table 1. Single Herb of Tibetan Medicines for Improving Cognitive Function.

Drug Name	Type of Study	Index of Experiment	Results	Reference
Rhodiola	Animal Study	Morris Water Maze	Shortened latency in the test phase, increased time spent in the target quadrant	[31]
		Conditioned Fear	Reduced freezing time	[30]
		Morris Water Maze	Shortened latency in the learning phase, increased time spent in the target quadrant	[69]
Terminalia chebula	Animal Study	Morris Water Maze	Reduced search errors in the learning phase, increased time spent in the target quadrant during the test phase	[70]
			Increased time spent in the target quadrant and platform crossings during the test phase	[35]
Sibraea	Animal Study	Morris Water Maze	Shortened escape latency in the learning phase, increased percentage of time and number of crossings in the target quadrant during the test phase	[40]
Centella asiatica	Clinical Study	MoCA Score	Increased MoCA score	[43]
	Animal Study	Morris Water Maze	Shortened latency in both the learning and test phases, increased search frequency and time in the target quadrant during the test phase	[44]
		Morris Water Maze	Increased time spent in the target quadrant during the test phase	[45]
		Shuttle Box	Increased avoidance responses	[46]
		Eight-arm Maze	Significant increase in the number of correct arm entries	[47]
Gymnadenia conopsea	Animal Study	Morris Water Maze	Shortened latency in the learning phase, increased number of crossings and time spent in the target quadrant during the test phase	[49]
Crocus sativus	Clinical Study	MMSE Score	Increased MMSE score	[55,58]
	Animal Study	ADAS-cog, CDR-SB Scores	Both ADAS-cog and CDR-SB scores decreased	[56]
		Morris Water Maze	Shortened latency in the learning phase, increased number of platform crossings during the test phase	[59]
			Shortened latency	[61]
Ganoderma lucidum	Animal Study	Morris Water Maze	Shortened latency in the learning phase	[64]

3. Tibetan Medicine Formulas for Improving Cognitive Function

Tibetan medicine formulas are compound prescriptions composed of herbs, minerals, and other materials utilized in traditional Tibetan medicine. Clinical research indicates that numerous Tibetan medicine formulas, including Ratanasampil, Coral Formula, Jewel Formula, and Pearl Formula, have the potential to enhance cognitive function. Furthermore, experimental pharmacological studies have substantiated that these formulas can improve learning and memory in animal models, as detailed below (Table 2).

3.1. Ratanasampil

Ratanasampil (RNSP), known in Tibetan as Ranasampei (transliteration), originates from the 15th-century Tibetan medical classic Chhemsnar Sheltri. It is one of the most representative formulas in traditional Tibetan medicine [71,72], exhibiting effects such as calming the mind, regulating qi and blood, and enhancing cognitive function. It is used to treat conditions including “black and white channel disease”, stroke, hemiplegia [73], epilepsy, cerebral hemorrhage, concussion, and various neurological disorders. In Tibetan medicine, the black and white channel represents the nervous system of the human body. The white

channel primarily corresponds to the brain and spinal cord, while the black channel pertains to the peripheral nerves. Consequently, Ratanasampil may have potential therapeutic applications for neurological diseases. Although the precise formula remains confidential, existing literature categorizes its ingredients into several groups: plant-based (e. g., sandalwood, saffron, aloeswood), animal-based (e. g., bezoar, musk, bear bile), gemstone-based (e.g., sapphire, natural pearl), metal-based (e.g., gold, silver), and composite materials such as Zuotai.

Clinical trials have yielded promising results, such as a study involving 40 patients with cerebral infarction demonstrated that Ratanasampil treatment significantly reduced NIHSS scores, indicating improved neurological function following cerebral infarction [22]. In another investigation [74], 8 patients with high-altitude cerebral edema in the recovery stage experienced a reduction in seizure-like episodes after treatment with Ratanasampil. Additionally, a study involving 48 Alzheimer's disease (AD) patients found that 12 weeks of Ratanasampil treatment markedly improved MMSE scores, suggesting a amelioration of clinical symptoms in AD patients [75].

In a study involving Tg2576 AD model mice, Seventy Flavor Pearl Pills were administered via gavage for 8 weeks period. Notably, the Y-maze light-dark discrimination learning test demonstrated that the training time required to meet the standard was significantly shorter in the treatment group compared to the control group. Additionally, the open field test revealed that the treatment group spent less time in the central grid, along with an increase in the number of standing and crossing events in the treatment group [76]. In another experiment, APP/PS1 AD model mice received Seventy Flavor Pearl Pills via gavage for 12 weeks. Results from the Morris water maze test showed a significant decrease in latency and an increase in the number of ring crossings. The open field test indicated prolonged movement time in the central area and an increased total number of hole pokes [77]. These findings suggest that Seventy Flavor Pearl Pills improve spatial learning, memory, and exploratory motor abilities in AD model mice. In another experiment [78], adult male Sprague Dawley rats were given Seventy Flavor Pearl Pills via gavage for 7 days. On the 7th day. On the 7th day, a cerebral ischemia-reperfusion model was induced using a modified Longa suture method, one hour after gavage. Following 40 min of ischemia and 24 h of reperfusion, the brain water content was measured and found to be significantly lower in the Seventy Flavor Pearl Pills treatment group compared to the model group. This indicates the pills' efficacy in reducing brain edema. Kunming mice received Seventy Flavor Pearl Pills via gavage for 10 days. On the 9th day, 2 h after administration, the mice were intraperitoneally injected with 5 mg/kg anisodamine to establish a memory impairment model. Ten minutes later, step-down training was conducted, followed by another administration the next day. Learning and memory were assessed 2 h later, revealing a significant reduction in errors in the Seventy Flavor Pearl Pills treatment group compared to the model group. These results indicate that Seventy Flavor Pearl Pills can enhance learning and memory abilities in animals with memory acquisition impairments [79]. After 4 weeks of oral administration of RNSP to SD rats with Parkinson's disease (PD) induced by 6-hydroxydopamine (6-OHDA), the Morris water maze test indicated that the escape latency was significantly shorter in the RNSP-treated groups compared to the model group. Furthermore, the number of platform crossings and the time spent in the target quadrant were significantly increased. There was also a notable rise in the number of tyrosine hydroxylase (TH) -positive neurons, as well as elevated levels of reduced glutathione, superoxide dismutase, and dopamine. Conversely, levels of malondialdehyde and the p-JNK/JNK and p-P38/P38 ratios were significantly reduced. These findings suggest that RNSP may enhance cognitive function in PD model animals, potentially through the inhibition of the P38/JNK/ERK signaling pathway, reduction of oxidative stress in the midbrain, decreased loss of dopaminergic neurons, and increased levels of monoamine neurotransmitters in the hippocampus [80].

3.2. Twenty-Five Ingredients Coral Pill

The Twenty-Five Ingredients Coral Pill (TFIC), formulated by the Tibetan physician Dr. Gyeshi Danzeng Puntsok in the 18th century and documented in the 19th-century Tibetan medical text Ji Yao Li Le Ku, is regarded as one of the classic formulas of traditional Tibetan medicine [81]. This pill comprises a diverse array of ingredients, including coral, pearl, mother-of-pearl, cinnabar, dragon bone, lapis lazuli, calamine, amber, magnetite, musk, costus root, clove, safflower, agarwood, orpiment, Terminalia chebula,

gourd, sesame, aster root, picrorhiza, acorus, saffron, benthamidia, chamomile, and licorice [82]. It is recognized for its effects on opening sensory orifices, invigorate blood circulation, and alleviating pain. In Tibetan medicine, it is used to treat "white channel disease," which refers to central nervous system disorders [83]. The recommended dosage is 1 g once daily [84]. Clinically, TFIC is frequently employed to treat neurological and cerebrovascular disorders, encompassing headaches [85], stroke, epilepsy [81], and vascular dementia [86].

In one study [86], involving 90 patients with vascular mild cognitive impairment (MCI) were assigned to three groups: general treatment, nimodipine treatment, and Coral Formula treatment. After 12-weeks, the TFIC group exhibited a marked enhancement in Mini-Mental State Examination (MMSE) scores, underscoring the formula's efficacy in bolstering cognitive function among these patients.

Another study [87] involved male BALB/c mice with dementia induced by aluminum trichloride and D-galactose, which were treated with the Twenty-Five Ingredients Coral Pill via gastric gavage for 28 days. Results from the Morris water maze test demonstrated a reduction in latency period. Furthermore, the treatment resulted in decreased phosphorylation of Tau protein (*p*-tau) in the hippocampus, increased expression of phosphorylated mTOR (*p*-mTOR), and decreased expression of GSK-3β. These findings suggest that the Twenty-Five Ingredients Coral Pill may ameliorate learning and memory deficits in an Alzheimer's disease mouse model induced by D-galactose combined with aluminum trichloride.

3.3. Twenty-Five Ingredients Pearl Pill

The Twenty-Five Ingredients Pearl Pill is recognized as one of the classic formulas of Tibetan medicine, first documented in the 8th-century Tibetan medical classic, the Four Medical Tantras. This pill consists of a combination of plant-based, animal-based, and mineral-based ingredients. The plant-based components include 19 ingredients: including clove, tsaoko cardamom, nutmeg, cardamom, emblic, sandalwood, cinnamon, costus root, Terminalia chebula, long pepper, malva fruit, celery seed, dalbergia, agarwood, black cumin seed, myrobalan, safflower, saffron, and zhidazasan (a Tibetan herb). The animal-based components consist of four ingredients: artificial musk, crab, cultured bezoar, and concentrated buffalo horn powder. The mineral-based components include four ingredients: pearl, mother-of-pearl, travertine, and mica [72], It promotes blood circulation, opens channels, and improves microcirculation, which contributes to its widespread use in the treatment of brain disorders [88]. Clinically, the pill is commonly used to treat conditions such as stroke [89], sequelae of cerebral hemorrhage [90], coronary heart disease [91], and vascular dementia [92]. The recommended dosage is 1–2 g, administered twice daily.

A clinical study [92] involving 48 patients with vascular dementia (VD) found that after two courses of treatment with the Twenty-Five Ingredients Pearl Pill, the Hasegawa's Dementia Scale (HDS) scores were significantly higher in the treatment group compared to the control group. These results indicate that the Twenty-Five Ingredients Pearl Pill positively affects memory improvement in patients with vascular dementia.

In an experimental study [93], Zhang Jijong and colleagues administered the Twenty-Five Ingredients Pearl Pill via gastric gavage to KM mice for 10 days. On the 10-day period, 1 h after administration, scopolamine (5 mg/kg) was injected intraperitoneally to induce a memory acquisition impairment model. Twenty minutes later, the mice underwent a step-down avoidance test, and their learning and memory were assessed 24 h later. The results demonstrated a significantly extended latency period in the treatment group and a marked reduction in the number of errors compared to the model group, indicating that the Twenty-Five Ingredients Pearl Pill can significantly ameliorate learning and memory in animals with memory acquisition impairments.

3.4. Ruyi Zhenbao Pill

The Ruyi Zhenbao Pill, also known as "Sangpei Nuburibu," was first documented in the 13th century by the Tibetan medical scholar Renqing Jianzhan in his work. The Secret Pearl String [94]. It is recognized for its effects in relaxing muscles and tendons and awakening the brain [95], It is designed to balance "Loong" and "Tripa" energies, emphasizing a combination of medicinal effects that clear heat, promote blood circulation, refresh the mind, enhance sensory perception, and improve meridian flow. It is particularly effective in treating cerebrovascular and nervous system disorders [96]. The pill primarily consists of 30

Tibetan medicinal ingredients, including: Aquilaria (22.69 g), Pearl Shell (22.69 g), Calcitum (22.69 g), Mica Schist (6.81 g), Crab (11.34 g), Safflower (22.69 g), Clove (9.07 g), Amomum Fruit (9.07 g), Nutmeg (9.07 g), Chebulic Myrobalan (22.69 g), Indian Gooseberry (29.49 g), Rhizoma Ligustici (9.07 g), Tsaoko Amomum (6.81 g), Sandalwood (18.15 g), Nigella Seeds (9.07 g), Long Pepper (6.81 g), Dalbergia Wood (74.86 g), Galangal (18.15 g), Myrobalan (29.49 g), Licorice Extract (9.07 g), Frankincense (13.61 g), Cinnamon (11.34 g), Cassia Seeds (13.61 g), Aucklandia (18.15 g), Abelmoschus Seeds (11.34 g), Buffalo Horn (9.07 g), Tibetan Costus Root (18.15 g), Herba Plantaginis (34.03 g), Synthetic Bezoar (0.45 g), and Synthetic Musk (0.45 g) [97]. Studies indicate that this formula is primarily utilized to treat peripheral facial paralysis [98], gout [99], rheumatoid arthritis [100], vascular dementia [97], and it exhibits efficacy in preventing and treating diseases associated with cognitive dysfunction.

In a clinical trial, 124 patients with vascular dementia were divided into an observation group, which received a combination of Ruyi Zhenbao Pills and Oxiracetam, and a control group, which was treated with Oxiracetam alone. Each group comprised 62 patients. After 8 weeks of treatment, the increases in the Mini-Mental State Examination (MMSE) scores and Activities of Daily Living (ADL) scores in the observation group were significantly greater than those in the control group. These results suggest that the combination of Ruyi Zhenbao Pills and Oxiracetam can enhance efficacy and alleviate clinical symptoms in patients with vascular dementia [101].

In an experimental study, SD rats with vascular dementia induced by the modified permanent bilateral common carotid artery occlusion method, were administrated Ruyi Zhenbao Tablets for 3 weeks. The Y-maze test demonstrated that the treated rats had significantly more correct responses (escaping directly from the start zone to the safe zone after being shocked) compared to the model group. This finding underscores the potential of Ruyi Zhenbao Tablets in enhancing cognitive function and navigating escape behaviors in rats with dementia [97].

Table 2. Tibetan Medicine Formulas for Improving Cognitive Function.

Drug Name	Type of Study	Index or Experiment	Results	Reference
Ratanasampi	Clinical Study	NIHSS Score	NIHSS score decreased	[22]
		MMSE Score	MMSE score increased	[75]
	Animal Study	Y-Maze	Reduced training time for light-dark discrimination learning test	[76]
		Morris Water Maze	Shortened latency during learning phase, increased platform crossings, and time spent in target quadrant during testing phase	[77]
		Step-Down Test	Reduced number of errors	[79]
		Morris Water Maze	Shortened escape latency during learning phase, increased time in target quadrant and platform crossings during testing phase	[80]
Twenty-Five Ingredients Coral Pill	Clinical Study	MMSE Score	MMSE score increased	[86]
	Animal Study	Morris Water Maze	Shortened latency during learning phase	[87]
Twenty-Five Ingredients Pearl Pill	Clinical Study	HDS Score	HDS score increased	[92]
	Animal Study	Step-Down Test	Increased latency, reduced number of errors	[93]
Ruyi Zhenbao Pill	Clinical Study	MMSE Score	MMSE score increased	[101]
	Animal Study	Electric Shock Y-Maze	Correct responses increased	[97]

4. Conclusions

This comprehensive review underscores the promising potential of a spectrum of Tibetan medicine in enhancing cognitive function and offering neuroprotection. By examining the research progress on different plant extracts and traditional Tibetan medicine formulas, this paper sheds light on their roles in the prevention

and management of cognitive decline and neurodegenerative disorders.

4.1. Enhancement of Cognitive Function Improvement by Natural Plant Extracts

This review explores the cognitive and neuroprotective potential of a range of natural plants, including Rhodiola rosea, Terminalia chebula, Gentiana macrophylla, Centella asiatica, Gastrodia elata, and Crocus sativus, each of which has demonstrated its own unique capacity to enhance cognitive function and provide neuroprotection. Notably, salidroside, derived from Rhodiola rosea, has revealed its potential therapeutic effects in Alzheimer's disease models by modulating brain cholinergic activity and inhibiting tau protein hyperphosphorylation. Moreover, Centella asiatica extracts have shown beneficial effects on cognitive recovery post-stroke. While Saffron and its primary active constituent, crocin, have been validated in several clinical trials for their ability to improve cognitive function in patients with mild cognitive impairment and Alzheimer's disease.

The collective findings from these studies indicate that natural plant extracts can exert a positive influence on cognitive function through a variety of mechanisms, including antioxidation, anti-inflammation, neurotransmitter regulation, and neuroprotection. However, the majority of these studies are currently confined to animal models or initial clinical trials. To establish their efficacy and safety across a broader population, there is a clear need for additional large-scale, randomized controlled trials involving human participants.

4.2. The Neuroprotective Potential of Traditional Tibetan Medicine Formulas

In the realm of Tibetan medicine, formulas such as Ruyi Zhenbao Pill, Ershiwuwei Shanhu Pill, and Saffron Shisanwei Pill are renowned for their unique combination of ingredients and complex pharmacological effects. Research indicates that the Ruyi Zhenbao Pill exhibits protective effects against neurodegenerative diseases by reducing oxidative stress and preventing the loss of dopaminergic neurons. Similarly, the Ershiwuwei Shanhu Pill has been shown to improve cognitive function following cerebrovascular diseases, hinting at its potential to stimulate neurogenesis and curtail neuroinflammation.

The therapeutic impact of these Tibetan medicine formulas transcends the effects of individual components, harnessing the synergistic interactions among multiple ingredients. Consequently, Tibetan medicine formulas may possess multi-targeted therapeutic effects, simultaneously addressing neuroprotection, anti-inflammation, antioxidation, and blood circulation improvement. However, the complexity of their ingredients and variability in formulations pose challenges for standardization and clinical application. Therefore, further investigation employing contemporary scientific methods is essential to clarify the precise mechanisms, dose-response relationships, and standardization of Tibetan medicine formulas.

4.3. Future Directions and Perspectives

In conclusion, the exploration of various natural compounds and Tibetan medicine formulas reveals considerable promise for enhancing cognitive function and neuroprotection. However, the majority of research remains in preliminary stages, lacking large-scale clinical trials and long-term data on efficacy and safety. Additionally, the complexity of Tibetan medicine formulations necessitates robust standardization and quality control measures.

Future research should be directed towards the following focal points: (1) conducting large-scale, randomized controlled clinical trials to validate the efficacy and safety of these natural compounds and Tibetan medicine formulas. (2) employing modern pharmacological and molecular biology techniques to investigate their specific mechanisms of action and (3) the establishment of scientifically rigorous standardization and manufacturing processes to ensure consistency in the quality and composition of Tibetan medicine formulas.

In conclusion, the fusion of traditional medicinal wisdom with modern scientific advances may provide new approaches for the prevention and treatment of cognitive impairments and neurodegenerative diseases. Enhanced interdisciplinary collaboration is imperative in forthcoming research and clinical practices to fully develop and utilize the potential of these natural compounds and Tibetan medicine formulas.

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