neurofilament(NF) and glial fibrillary acid protein(GFAP) [27].

Tonify Qi and activate blood circulation

"The YuanQi was deficiency, will not reach the blood vessels, eventually lead to the stagnation of blood and the formation of blood stasis." The method of tonifying qi and activating blood circulation has been commonly used in clinic for treatment of nervous system diseases such as central infarction, cerebral hemorrhage and so on. Recently, scholars have studied Chinese medicine and the extracts in inducing the differentiation of bone marrow MSCs to neurocyte-like cells and acquired some outcomes. Nie et al. [28] observed and evaluated the effect of transdifferentiation of MSCs into nerve cells by ultrafiltration membrane extract mixture from *Angelica sinensis* and *Hedysarum polybotrys*. Results demonstrated that BMSCs changed neural-morphologically after induction. The expression levels of NSE, nestin, NFP, MAP2, GFAP were highest in the positive control group ($P < 0.05$), followed by the ultrafiltration membrane extract mixture group ($P < 0.05$). *Buyang Huanwu Tang* combined with MSCs transplantation could repair the injured blood vessels and lesion tissues, the mechanism study showed that VEGF and Ki-67 expressions were significantly up-regulated in the MSCs group and the combination group, with significant differences as compared with the model group and the sham operation group ($P<0.05$), and with the most strongest effect in the combination group [29]. *Naomai Yihao Capsule* has the function of tonifying qi, activating blood circulation, and resolving phlegm so as to regulate the "sea of blood in brain". The observation of *Naomai Yihao Capsule* combined with BMSCs transplantation showed that *Naomai Yihao Capsule* could promote the angiogenesis and neurological impairment recovery by increasing the expression of CD31 in the brain tissue in focal cerebral ischemia rats which were administered with BMSCs transplantation, and the effect was reinforced with the extension of treatment time [30]. Zhang et al. [31] induced bone marrow MSCs using *Yiqihuoxue recipe* and found that *Yiqihuoxue recipe* could express NSE, a marker of neurons, GFAP, a marker of glial cells, and nestin, a marker of neural stem cells. These evidences indicate that *Yiqihuoxue recipe* can induce the differentiation of bone marrow MSCs *in vitro*.

Activate blood and resolve stasis

At the acute phase of cerebral injury, the functions of qi and blood are abnormal, blood stasis appear, which will lead to the necrosis or apoptosis of neurons. The regulatory mechanism of proliferation, immigration, and differentiation of neural stem cells would also be damaged. If blood stasis has not been removed, there would no generation of new blood. Experiments have proved that some Chinese herbs are anti-thrombolysis, they play an important role in differentiating MSCs into nerve cells, so as to improve microcirculation in central nervous system that might improve, repair and rehabilitate from stroke and brain injury [32]. After induction by *Danshensu*, MSCs exhibited the typical form of perikaryon with pyknotic cell body and prominence projected like that of neuron. These cells were positively expressed in NSE, NF-M and nestin, and negatively expressed in GFAP [33]. *Salvianolate* inhibited the proliferation of human umbilical cord mesenchymal stem cells(hUCMSCs) under high concentrations. Cells showed a neuron- like morphology when treated with brain derived neurotrophic factor (BDNF) or salvianolate combined BDNF. The contents of Ach and positive expression rates of Nestin, NES and choline acetytransferase in high-dose and middle-dose combination groups were significantly higher than those in low-dose combination group and BNDF group ($P<0.05$). There was no significant difference between the high- dose and middle- dose combination groups($P>0.05$) [34]. Extract of *Ginkgo biloba*(EGb761) increased the human adipose-derived stem cells (hADSCs) proliferation, especially on 3 d($P<0.05$). EGb761 induced hADSCs to neural differentiation, not to glial cell differentiation [35]. The percentages of NSE-positive neuron-like cells in the different concentrations of *ginkgolide B* were higher than the percentage in the control group. However, there were no significant differences between the different concentrations [36]. Zheng et al. [37] studied the effects of total saponins of *Panax* notoginseng (tPNS) on angiogenesis in rat bone marrow mesenchymal stem cells (rBMSCs). The study showed that tPNS (100 μg/ml) significantly enhanced the mRNA expression level of VEGF-A and Kdr compared to the control group, while they had no obvious effect on the expression of Flt-1. tPNS (1 μg/ml and 100 μg/ml) significantly increased capillary network forming of rBMSCs after endothelial differentiation in Matrigel *in vitro*. tPNS (50 μg/kg, 100 μg/kg and 150 μg/kg) also significantly increased angiogenesis induced by the combination with implantation of rBMSCs and Matrigel *in vivo*. *Sodium Ferulate* (SF), as the main active constituent of *Chuanxiong*, combined with BMSCs administration could facilitate BMSCs migration into the ischemic brain by up-regulation of stromal cell-derived factor-1 alpha (SDF-1α)/chemokine (CXC motif) receptor-4 axis after stroke. The combination treatment of SF and BMSCs could not only promote expression of Glucose transporter 1(Glut1) and Neuron-specific class III beta-tubulin (Tuj1) in the periinfarct area, but also improve BMSCs expression of Glut1, GFAP and Tuj1. Moreover, it showed that combination treatment could enhance the endogenous expression of Tuj-1 in ischemic boundary zone [38]. A novel tissue inducible nerve guide conduit, chitosan microspheres, has better biological compatibility and tissue inducible function. The *ligustrazine* released from the chitosan microspheres could promote MSCs to express NSE and MAP2, the relevant marker molecule of nerve cells [39].

Tonify the kidney to supply essence

The MSCs from bone marrow and NSCs from central nervous system both belong to congenital essence. They can transform into each other. Kidney-tonifying and essence-replenishing method may play an important role to promote MSCs differentiation into NSCs. *Plastrum Testudinis* (PT), as an important CHM to tonify the Kidney, was proved to induce MSCs to differentiate into NSCs *in vitro*, but not into neuron like cells or astrocytes [40]. Other study found that after induced adult rats MSCs 12 h with PT, the positive expression of neuron like cells NF reached the peak [41]. Rehmannia glutinosa polysaccharide (RGP) is one of the effective components of CHM Rehmanniae, with the effect of tonifying the kidney to supply essence. The detection of immunocytochemical stain and RT-PCR method showed that neural cell markers were not expressed in the control group, but expressed in the other groups. Positive cells rate of nestin and NSE in the RGP induction group was higher than the*β*-mercap toethanol(BMT) induction group and the BDNF induction group (P<0.05) and positive cells rate of GFAP lower (P<0.05), but there was no difference between the BMT induction group and the BDNF induction group in nestin, NSE and GFAP positive cells rate. The all cells were Notch 1 protein positive in RGP induction group, which were reduced gradually over time, according to immunocytochemistry. Western blot results showed that the contents of NICD was up-regulated 24 h after RGP induction and decreased gradually, and even fell below the baseline level and significantly lower than control group at 5th day (P<0.05) [42-44]. *Lycium barbarum polysaccharide* also has inductive effect on differentiation of BMSCs into neurons of adult rats *in vitro.* After induction for 4 hours, some BMSCs showed processes extended obviously. Twenty four hours later, the differentiated cells showed significant processes, and the processes were connected to each other, showing typical neural cell morphology. In these cells, the expression of microfilament and nestin was positive, but GFAP was negative [45]. Kuang et al. [46] observed the ability of *Sanjia Fumai Tang* medicated serum in inducing the differentiation of MSCs into neurons *in vitro* in adult rats. The results found that with the extension of the induction time, the cell morphology of MSCs changed obviously, the cell size decreased, the cytoplasm contracted to the nucleus, the morphology changed into circular, forming a network like structure and neuron like cells increased. But the same change did not be observed in the control group. After 12 hours' induction, neuron cell's positive rate reached its peak, and there were still neuron cells survived after 7 days, and the longest survival time was the *Sanjia Fumai Tang* group.

Open the orifices to induce resuscitation

The method of opening the orifices to induce resuscitation for the treatment of cerebral infarction has a long history, and the curative effect is exact. Both the method and activated NSCs which are usually in a resting state have particular but similar effect on promoting the nerve regeneration. Xiao et al. [47,48] directly induced 5-10 generation MSCs with culture medium containing *musk polypeptide in vitro*, the results showed that the cells changed into neuron like cells, immunohistochemical sample also showed that the neuronal cell NSE and NF induced, nest protein expressed positively, GFAP expressed negatively. Neuron like cell count analysis found that the percentage of NSE and NF-H positive cells were higher after inducted by *musk polypeptide*. As inducers, *Gastrodia elata* similarly could induce most of MSCs to differentiate into neuron-like cells, revealing cytodendrite. By immunochemical staining, cells showed positive NSE, nestin, and negative of GFAP [49]. *Niupo Zhibao Weiwan*(NZW) was varied from *Zhibaodan*. The study found that NZW medicated serum could enhance the expression of Brdu and NF in MSCs transplantation region, and the enhancement effect can last 6 weeks [50,51].

Induce resuscitation by Fu-unblocking therapy

The method of inducing resuscitation by Fu-unblocking therapy can not only modulate the function of stomach, spleen, lung, liver and other viscera, but also improve permeability of the blood-brain barrier, relieve cerebral edema, and promote nerve regeneration. *Rhubarb aglycone* can decrease the degradation of basal lamina Col Ⅳ and the permeability of brain micrangium in cerebral ischemic rats with BMSCs transplantation by means of regulating the balance of matrix metalloproteinase-9 (MMP-9), increasing the expression of tissue inhibitor of metalloproteinase-1 (TIMP-1) [52]. *Rhubarb aglycone* also can advance the time of protecting neurocytes after BMSCs transplantation. The mechanism may be related to the fact that it can up-regulate the expressions of NGF and glial cell-line derived neurotrophic factor (GDNF) in earlier phase and increase NGF expression in metaphase and anaphase [53]. 100 μmol/L *baicalin* can promote amplification of cord blood MSCs *in vitro*. After culture cultured for 4 weeks, the expression of neuron specific enolase and microtubule associated protein 2 were lower in the blank control group and β-mercaptoethanol group compared to the *baicalin* group (P < 0.01), and no significant difference was found in the co-culture group(P > 0.05). All these indicated that *baicalin* also can induce the differentiation of cord blood MSCs into neuron-like cells [54,55]. *Berberine* was also approved with the same effect of inducing adult rat MSCs to differentiate into neuron-like cells *in vitro* [56].

Views and Prospects

At present, researchers have carried out many theoretical discussions and experimental studies in inducing the differentiation of mesenchymal stem cells into neural-like cells via the use of TCM thoughts from different angles, such as the composition of CHM monomer, single CHM and effective component, and have achieved encouraging results. However, in the process of these current studies, the

focus was usually partial to some effective components of the composition, single herb or the compound, which led to the neglect of the concept of holism of TCM theory. So the theory of medicinal properties and pharmacodynamics of CHM should be combined with the basic theories of TCM. Only by means of getting research ideas from the viewpoint of the holistic concept of TCM theory and combining with modern research methods, could the development of modernization of TCM be better.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

AUTHOR CONTRIBUTIONS

Lijun Qiao drafted the manuscript. Lijun Qiao, Aili Lu, Mei Feng, Caiwen Qian and Lingbo Hou retrieved the literature together. Jun Zhang,Tongxiang Lin,Yuanqi Zhao reviewed this manuscript. All authors approved the final version of this paper.

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