Review

The Effect of Traditional Chinese Medicine on Neural Stem Cell Proliferation and Differentiation

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ABSTRACT: Neural stem cells (NSCs) are special types of cells with the potential for self-renewal and multi-directional differentiation. NSCs are regulated by multiple pathways and pathway related transcription factors during the process of proliferation and differentiation. Numerous studies have shown that the compound medicinal preparations, single herbs, and herb extracts in traditional Chinese medicine (TCM) have specific roles in regulating the proliferation and differentiation of NSCs. In this study, we investigate the markers of NSCs in various stages of differentiation, the related pathways regulating the proliferation and differentiation, and the corresponding transcription factors in the pathways. We also review the influence of TCM on NSC proliferation and differentiation, to facilitate the development of TCM in neural regeneration and neurodegenerative diseases.

Key words: Neural stem cells, proliferation, differentiation, traditional Chinese medicine

Both embryonic and adult neural stem cells (NSCs) are widely distributed in the nervous system. Embryonic NSCs are widely distributed in the brain, while adult NSCs are mainly distributed in the subventricular zone (SVZ) of the lateral ventricle wall and the subgranular zone (SGZ) of the hippocampus dentate gyrus [1, 2]. NSCs go through different stages of neural progenitor cells (NSPCs), neural precursor cells (NPCs), and neuroblasts in the process of proliferation and differentiation into neural cell lineage [3-7]. In the research on NSCs, their identification and differentiation in these stages are related to whether they can be accurately induced, differentiated, and migrated. The corresponding markers of NSCs at different stages have been identified and confirmed, and are summarized in this study.

NSCs can differentiate into different types of neural cells under specific conditions, which can provide new methods of cerebral injury repair and neurological disease treatment. Numerous studies have shown that NSCs have a therapeutic effect on nervous system injuries and degenerative diseases such as Alzheimer’s disease (AD), Parkinson's disease (PD), spinal injury, amyotrophic lateral sclerosis (ALS), vascular dementia, cerebral hemorrhage, and Huntington’s disease [8-17]. However, the differences between animal models and human diseases mean that the clinical application of stem cell therapy is still some way off.

Traditional Chinese medicine (TCM) has the general advantages of multi-targets, multi-levels, and multi-paths [18-21]. It can regulate NSC proliferation and differentiation by changing the microenvironment of

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NSCs and indirectly regulating endogenous and exogenous factors. Studies have shown that single herbs, herb extracts/Chinese herbal monomers and compounds, and Chinese medicinal preparations have, to some extent, a role in regulating NSC proliferation and differentiation [22-27].

Table 1. Markers of stem cell proliferation and differentiation in different stages.

| Marker | Property | Affected cell type | Function | Refs. |
|--------|----------|--------------------|----------|-------|
| Hopx   | atypical homeodomain only protein | NSCs | regulates hippocampal neurogenesis by modulating Notch signaling | [33] |
| Hes3   | basic helix–loop–helix gene | NSCs | promote the proliferation of NSCs | [34, 35] |
| TRIP6  | zyxin family proteins | NSCs | promote the self-renewal and proliferation of NSCs | [36] |
| CycE   | cyclin | NSCs | regulate neurogenesis in the adult hippocampus | [37] |
| JAM-C  | surface protein | NSCs | maintain the pluripotency of NSCs | [38] |
| PtdGlc | lipid | NSCs | identify, isolate, and differentiate NSCs | [39] |
| CD9    | transmembrane protein | NSPCs | have an impact on the cell adhesion, migration, proliferation and differentiation | [40, 41] |
| CD15   | transmembrane protein | NSPCs | promote the survival of NSCs; | [40, 42] |
| CD81   | transmembrane protein | NSPCs | promote the differentiation of NSCs into oligodendroglia | [40, 43] |
| S100β  | acid calcium binding protein | NSPCs | regulate the proliferation of NSCs | [44] |
| CD133  | transmembrane protein | NPC | promote the expansion of NSCs in vitro and its degree of specialization | [45, 46] |
| CD24   | transmembrane protein | NPC | play an important role in self-renewal; maintain NSCs | [45, 47, 48] |
| Pax2   | paired box gene | NPC | regulate the migration and proliferation of nerve cells | [49] |
| NG2    | proteoglycan intermediate filaments protein cytoskeletal protein | NPC | regulate the migration of the oligodendrocyte precursor cells | [50, 51] |
| Nestin | RNA- binding protein | NSCs and NSPCs | be a marker for proliferating or migrating cells; participate in cytoskeleton formation; remodel cells along with other structural proteins; determine the fate of stem cells; maintain the undifferentiated state of NSCs or NSPCs; | [52-55] |
| Musashi1 | RNA- binding protein | NSCs and NSPCs | reflect the structural changes in the development of the brain | [56-61] |
| Tub-II | cytoskeleton protein | NSCs and NSPCs | play a role in self-renewal and maintenance of NSCs; prevent the apoptosis of NSCs. | [56, 64, 65] |
| SOX2   | high-mobility group proteins | NSCs and NSPCs | promote the self-renewal of NSCs | [66-68] |
| SOX1   | high-mobility group proteins | NSCs and NSPCs | maintain the undifferentiated state of NSCs | [69, 70] |
| Sp8    | zinc finger protein | NSCs and NSPCs | promote the neurogenesis in the hippocampus; play an important role in the differentiation and maturation of astrocytes | [71] |
| S100A6i | low-molecular-weight calcium-binding proteins | NSCs and NPC | play an important role in regulating the proliferation and differentiation of NSCs; maintain the intermediate progenitor cells | [72, 73] |
| Prox1  | homeobox transcription factor | neuroblasts | promote the proliferation of NSCs; inhibit their differentiation | [74, 75, 204] |
| Cyc D1 | cyclin | neuroblasts | regulate the migration of neural cells | [76, 77] |

The table lists the markers of NSCs proliferation and differentiation, the property of the markers, the cell type they affect, and their function in NSC proliferation and differentiation: Tub-II, tubulin beta II; SOX2, sex-determining region Y-box2; SOX1, sex-determining region Y-box1; Sp8, specificity protein 8; PAX2, paired box protein 2; Hopx, homeodomain only protein X; Hes3, hairy and enhancer of split 3; TRIP6, thyroid receptor-interacting protein 6; CycE, cyclinE; JAM-C, junctional adhesion molecule-C; PtdGlc, phosphatidylinositol; S100β, S100 calcium-binding protein B; NG2, Neuron glia antigen 2; Cyc D1, Cyclin D1; Prox1, prospero homeobox protein 1; DCX, doublecortin; NSCs, neural stem cells; NSPCs, neural progenitor cells; NPCs, neural precursor cells.
In this article, we discuss the regulation of NSC proliferation and differentiation by the relevant pathways and the target genes corresponding to the pathways, and review the effects of TCM on the proliferation and differentiation of NSCs, to further develop the study of NSC proliferation and differentiation by TCM.

Table 2. The main transcription factors and associated signaling pathways in NSC proliferation and differentiation.

| TFs  | Protein family | Pathway | In vivo or in vitro | Effect on NSCs | Affected cell type | Location of expression | Refs. |
|------|----------------|---------|---------------------|----------------|--------------------|------------------------|-------|
| Hes1 | bHLH           | Notch   | In vivo and in vitro| Play a role in maintenance of NSCs; Inhibit the differentiation of NSCs into neurons; Have an effect on the maintenance and self-renewal of NSPCs | NSCs and NSPCs | SVZ, SGZ | [81-87] |
| Hes5 | bHLH           | Notch   | In vitro            | promote the proliferation of NSCs | NSCs and NSPCs | SVZ | [88-90] |
| Mash1| bHLH           | Notch   | In vivo and in vitro| Promote the differentiation of NPCs | NSPCs and NPCs | SVZ, SGZ | [91-96] |
| NeuroD| bHLH         | Notch   | In vivo and in vitro| Determine the fate and differentiation of cells; Determine the survival of neurons | NSPCs and NPCs | SGZ, SVZ, VZ | [97-102] |
| zfp488| ZFP           | Notch   | In vivo             | Promote the differentiation of NSCs into the oligodendrocytes; Promote neurogenesis; | NSCs and NSPCs | SVZ | [103, 104] |
| Ngn1 | bHLH           | Notch   | In vivo             | Play a specific role in the maintenance of NSPCs; Promote the differentiation of NPCs in vivo | NSPCs and NPCs | SVZ | [105, 106] |
| Ngn2 | bHLH           | Notch   | In vivo and in vitro| Play a regulatory role in neurogenesis; Control the balance of the maintenance and differentiation of NSPCs | NSPCs | VZ, SVZ | [107, 108] |
| Fezf2 | ZFP           | Notch   | In vivo and in vitro| Has a role in the maintenance and differentiation of NSCs | NSCs, NSPCs and NPCs | SVZ, VZ | [109, 110] |
| Hey1 | bHLH           | Notch   | In vivo             | Play a role in the maintenance of NSCs; Reduce the ability of NSCs to proliferate and self-renew; Reduce the transformation of NSCs into neurons and glial cells | NPCs | VZ, SVZ | [111-113] |
| Gsx2 | HOM            | Notch   | In vivo             | Control the balance of the maintenance and differentiation of NSCs; | NSCs and NSPCs | SVZ, VZ | [114-116] |
| Pax6 | HOM            | Wnt     | In vivo and in vitro| Play an important role in maintenance, self-renewal and multi-directional differentiation of NSCs | NSCs and NSPCs | SVZ, OB, SGZ, VZ | [121-126] |
| Emx2 | HOM            | Wnt     | In vivo and in vitro| Control the proliferation and migration of NPC | NSCs and NSPCs | SVZ, VZ | [127-129] |
| Dix2 | HOM            | Wnt     | In vivo and in vitro| Promote the neurogenesis and proliferation | NPCs | VZ | [130, 131] |
| Pax3 | HOM            | Wnt     | In vivo and in vitro| Regulate the differentiation of NSCs; Determine the fate of cells; Maintain the undifferentiated state of NSCs. | NSPCs | VZ | [132-137] |
| Oct4 | POU            | Wnt     | In vivo and in vitro| Play an important role in the maintenance of the pluripotency of NSCs; Promote the proliferation and self-renewal of NSCs | NSCs | SVZ | [138-140] |
| Prox1| HOM            | Wnt     | In vivo and in vitro| Promote the proliferation of NSCs; Play an important role in the maintenance of intermediate progenitor cells | NSPCs | SGZ | [141, 142] |
| Nkx2.2| HOM           | Shh     | In vivo             | Promote the differentiation of oligodendrocytes | NSPCs and NPCs | SVZ, OB | [152-156] |
1. The stages and related markers of NSC proliferation and differentiation

NSCs go through different stages of NSPCs, NPCs, and neuroblasts in the process of proliferation and differentiation into mature neural cells [28-32]. NSCs can express specific molecular markers in the proliferation and differentiation stages. These markers have the function of selectively binding to signal molecules and are involved in the expression of cell signaling. In addition, transcription factors and cell adhesion molecules are significant for the differentiation of NSCs. The Nestin, Musashi1, sex-determining region Y-box2 (SOX2), Prox1, and CD family proteins are the most common markers.

An increasing number of novel markers have also been used to identify NSCs. These include homeodomain-only protein X (Hopx) [33], hairy and enhancer of split 3 (Hes3) [34, 35], thyroid receptor-interacting protein 6 (TRIP6) [36], Cyclin E (CycE) [37], junctional adhesion molecule-C (JAM-C) [38], and phosphatidylinositol-4,5-bisphosphate (PI(4,5)P2) [39], which are mainly expressed in NSCs and can be used as characteristic markers. The expression of CD9 [40, 41], CD15 [40, 42], CD81 [40, 43], and S100 calcium-binding protein B (S100B) [44] are commonly expressed in NSPCs. The same CD family members CD133 [45, 46] and CD24 [45, 47, 48], paired box protein 2 (Pax2) [49] of the paired box gene family, and transmembrane proteoglycan (NG2) [50, 51] are mainly expressed in NPCs. Nestin [52-56], Musashi1 [56-61], cytoskeleton protein (Tub-1) [62, 63], sex-determining region Y-box2 (SOX2) [56, 64, 65], sex-determining region Y-box1 (SOX1) [66-68], specificity protein 8 (Sp8) [69, 70], and low-molecular-weight calcium-binding proteins (S100A6i) [71] are expressed in both NSCs and NSPCs, while prospero homeobox protein 1 (Prox1) [72, 73], Cyclin D1 (CycD1) [74, 75], and doublecortin (DCX) [76, 77] are expressed in the neuroblast. The properties of the related markers, the stage of the labeled cells, and the function of the markers are summarized in Table 1.

2. Signaling pathways and major transcription factors involved in NSC proliferation and differentiation

Multiple signaling pathways regulate the process of NSCs proliferating and differentiating into mature neurons. These pathways determine the fate of NSCs by regulating the expression and activity of different transcription factors, and many pathways are involved. The Notch, Wnt, bone morphogenetic protein (BMP), and sonic hedgehog (shh) signal pathways have been most studied. Downstream of the signal pathway are usually target genes that can be used as transcription factors to regulate the process of proliferation, differentiation, and migration of NSCs, and different signaling pathways and transcription factors can act synergistically to regulate this process. These are summarized in Table 2.

2.1 The Notch signaling pathway

The Notch gene was originally found by Morgan and colleagues in drosophila in 1917 [78]. The partial deletion of this gene function was found to lead to a gap in the wing edge of drosophila. The Notch signaling pathway is a highly conserved pathway, which is widespread in invertebrates and mammals, and it determines the fate of cells by precisely regulating cells growth, differentiation, and apoptosis [79]. Numerous studies have shown that the Notch signaling pathway plays an important role in the proliferation and differentiation of NSCs, particularly for maintaining an undifferentiated state and the ability for self-renewal [80]. The common target genes of the pathway are the hairy and enhancer of split 1 (Hes1), hairy...
and enhancer of split (Hes5), achaete-scute homolog 1 (Mash1), neurogenic differentiation factor-6 (NeuroD), zinc finger protein 488 (zfp488), Neurogenin1 (Ngn1), Neurogenin2 (Ngn2), forebrain embryonic zinc finger 2 (Fezf2), GS Homeobox 2 (Gsx2), hairy/enhancer-of-split related with YRPW motif protein 1 (Hey1), etc. These transcription factors play an important role in the regulation of NSCs proliferation and differentiation. Hes1, Hes5, Mash1, NeuroD, zfp488, Ngn1, Ngn2, and Hey1, are members of the basic helix-loop-helix (bHLH) gene family, which can play a role in the regulation of NSCs in vivo and in vitro. Hes1 is mainly expressed in the SVZ. It can maintain the state of NSCs, inhibit their differentiation into neurons, and also have an effect on the maintenance and self-renewal of NSPCs [81-87]. Hes5 can promote the proliferation of NSCs, which is mainly expressed in SVZ [88-90]. Mash1 is a target gene of the Notch signaling pathway, which can be expressed in SVZ and SGZ during neurogenesis. Mash1 is also a determinant for the differentiation and maturation of neural in vivo and in vitro. Studies have shown that Mash1 promote the differentiation of NSPCs and NPCs [91-96]. NeuroD, a member of the bHLH gene family, can determine the fate and differentiation of cells. It is mainly expressed in SGZ, which regulate neurogenesis in vivo and in vitro [97-102]. zfp488 promotes the differentiation of NSCs into oligodendrocytes [103, 104]. Ngn1 and Ngn2 are the other two bHLH family genes, and Ngn1 can promote neurogenesis and the differentiation of NPCs in vivo. It also plays a specific role in the maintenance of NSPCs [105, 106]. Ngn2 can be expressed in SVZ and the ventricular zone (VZ) during neurogenesis, and plays a regulatory role in neurogenesis in vivo and in vitro. Ngn2 also controls the balance between the maintenance and differentiation of NSPCs [107, 108]. Fezf2 is a zinc finger transcription factor, and research has shown that it can promote the differentiation of NSCs in SVZ. It also influences the maintenance of NSCs [109, 110]. Hey1 has a maintenance effect on NSCs, which is mainly expressed in VZ and SVZ [111-113]. Gsx2 is a homeodomain transcription factor, which is mainly expressed in SVZ. Gsx2 plays an important role in the inhibition of neurogenesis. For example, Gsx2 can reduce the proliferation and self-renewal of NSCs, and inhibit the differentiation of NSCs into neurons and glial cells. Thus, the NSCs and NSPCs can be maintained in a static and undifferentiated state [114-116].

2.2 Wnt signaling pathway

The Wnt signaling pathway is named after its promoter protein Wnt, which is synthesized by the wingless gene of the African drosophila and the proto-oncogene Int1 of the mouse. The four main Wnt signal pathways are the canonical Wnt/β-catenin pathway, the Wnt/polarity pathway, the Wnt/Ca^2+ pathway, and the intracellular pathways that regulate spindle orientation and asymmetric cell division [117]. Of these, the canonical Wnt/β-catenin signaling pathway is important in regulating the proliferation and differentiation of NSCs [118-120]. The target genes regulated by the Wnt signaling pathway are paired box protein 6 (Pax6), paired box protein 3 (Pax3), empty spiracles homeobox 2 (Emx2), distal-less homeobox 2 (Dlx2), Octamer-binding transcription factor 4 (Oct4), Prox1, etc. Pax6, Emx2, Dlx2, Pax3, and Prox1 belong to the zinc finger transcription factor. Pax6 regulates the proliferation and differentiation of NSCs in vivo and in vitro. Studies have shown that Pax6 can be expressed in both SVZ and OB, and can control the balance between the self-renewal and differentiation of NSCs, and is important in their maintenance, self-renewal, and multi-directional differentiation [121-126]. Emx2 is a target gene regulated by the Wnt signaling pathway, which regulates neurogenesis in vivo and in vitro. Emx2 mainly affects NPCs through controlling the migration and differentiation of NPCs [127-129]. Dlx2 is expressed in SVZ and OB, and regulates the proliferation of NPCs in SVZ [130, 131]. Pax3 is a DNA-binding protein, mainly expressed in VZ, and plays a role in the maintenance of NSPCs. The overexpression of Pax3 can inhibit the differentiation of NSCs. But if it is inhibited, it will promote their differentiation [132-137]. Oct4 belongs to the POU protein family, and can be expressed in vivo and in vitro. Oct4 is important in the maintenance of pluripotent stem cells, and promotes the proliferation and self-renewal of NSCs [138-140]. Prospero homeobox protein 1 (Prox1) plays an important role in the maintenance of NSPCs and regulates the differentiation of NSCs in SGZ [141, 142].

2.3 Shh signaling pathway

The hedgehog gene was first found in Drosophila in 1980, and has three homologous genes: sonic hedgehog (Shh), Indian hedgehog (Ihh), and desert hedgehog (Dhh). They encode Shh, Ihh, and Dhh proteins, respectively [143-145]. The Sonic hedgehog is an important developmental regulatory factor produced by the notochord during embryonic development [146]. Shh is important in regulating the migration, survival, and proliferation of NSCs [147-149]. The Shh signaling pathway can regulate the self-renewal of NSCs by increasing their symmetrical division [150, 151]. NK2 homeobox 2 (Nkx2.2) is an important transcription factor involved in the regulation of the Shh pathway. Nkx2.2 can be expressed in both SVZ and OB, and can promote the differentiation of oligodendrocytes and inhibit their self-renewal ability [152-157]. Glioma-associated oncogene-1 (Gli-1) is a...
member of the ZFP protein family and a target gene of the Shh pathway, which can be expressed in vivo and in vitro and promote the proliferation of NPCs [158-162].

Table 3. Effects of single herb and compound Chinese medicinal preparations on NSC proliferation and differentiation.

| Classification | TCM | Affected cell type | Effect on NSCs | Main mechanisms | In vivo or in vitro | Refs. |
|----------------|-----|--------------------|----------------|----------------|--------------------|-------|
| BuyangHuanwu Decoction | NSCs and NSPCs | Promote the proliferation and differentiation of NSCs and NSPCs | Decrease the content of Ca\textsuperscript{2+} in the cells, and increase the expression of NF and GFAP. The expression of nestin, beta-tubulin-III, and fibrillary acidic protein glial were significantly increased | In vivo and in vitro | [177-179] |
| Jiawei Sini San | NPCs | Promote the proliferation of NPCs and inhibit apoptosis | | | In vitro | [180] |
| Compound Chinese medicinal preparations | Shengyu decoction | NSCs and NSPCs | Promote the proliferation of NSCs/NSPCs and their differentiation into neurons | Promote the proliferation of NSPCs; Improve the survival rate of newborn cells | In vivo | [181] |
| FuzhiSan | NSPCs | | | | In vivo | [182] |
| XiehuoBushenDecoction | NSCs | Promote the survival and differentiation of NSCs | | | In vivo and in vitro | [27] |
| PMC-12 | NSPCs | Promote the proliferation of NSPCs in the hippocampus; Improve the survival rate of newborn nerve cells | Increased levels of BDNF, p-CREB and synaptophysin | In vivo | [183] |
| Salvia miltiorrhiza Bge | NSCs | Promote the proliferation of NSPCs and their differentiation into neurons in vitro; Promote the survival, collection and differentiation of NSCs derived from multifunctional stem cell | Increase the expression of nestin and MAP2 | In vivo | [22] |
| Single herb | Sambucus williamsii Hance | NSCs | Promote the differentiation of NSCs into neurons | Up-regulate the expression of Tuj1 and nestin genes, and down-regulate the expression of Oct4 and Sox2 genes | In vitro | [184] |
| | Scutellariaacalensis Georgi, Phelloidendronchinhense Schneid, Ligusticumwallichii Franch | NSCs and NPCs | Promote the proliferation of NSCs and NPCs | Modulate HPA axis and increase the content of corticosterone | In vivo and in vitro | [23] |

The table lists effects of single herb and compound Chinese medicinal preparations on the NSC proliferation and differentiation, and underlying mechanism, and the cell type they affected; PMC-12, polygonummultiflorum Thunberg complex composition-12; Tuj1, tubulin-1; MAP2, microtubule-associated protein 2; HPA, hypothalamus-pituitary-adrenal; NF, neurofilament; GFAP, glial fibrillary acidic protein; TN-C, Tenascin-C; GDNF, glial cell line-derived neurotrophic factor; NVAM, neural cell adhesion molecule; NGF, Nerve growth factor; BDNF, brain derived neurotrophic factor; p-CREB, phosphorylated cAMP-response element binding protein.
### Table 4. Effects of active components of Chinese herbs on NSC proliferation and differentiation.

| Effective components of Chinese herbs | Origin | Categories of Chinese herbs | Affected cell type | Effects | Underlying mechanisms | In vivo or in vitro | Refs. |
|--------------------------------------|--------|-----------------------------|--------------------|---------|----------------------|--------------------|-------|
| Ginsenoside Rg1                      | Panax ginseng C. A. Mey | Tonifying Qi herbs | NSCs and NSPCs | Promote the differentiation of NSCs and NSPCs | Increase the expression of SOX-2 and decrease the expression of IL-1β, IL-6 and TNF-α; Enhance the role of anti-inflammatory and antioxidant | In vivo | [186, 187] |
| Ginsenoside Rd                       | Panax ginseng C. A. Mey | Tonifying Qi herbs | NSCs | Promote the proliferation of NSCs | Regulate the expression of neurotrophic factor 3 and activate the expression of iNOS and NMDA receptors | In vivo | [188] |
| Oleanolic acid                       | Ligustrum lucidum Ait | Tonifying Yin herbs | NSCs and NPCs | Promote the self-renewal and differentiation of NSCs | Increase the expression of tubulin and the ratio of tubulin/DAPI | In vivo | [24] |
| Stilbene glucoside                   | Fallopia multiflora (Thumb.) Harald | Tonifying blood herbs | NSCs | Promote the self-renewal and differentiation of NSCs | Increase the expression of tubulin and the ratio of tubulin/DAPI | In vivo | [24] |
| Resveratrol                          | Fructus Mori | Tonifying Yin herbs | NSCs | Promote the survival and proliferation of NSCs | Up-regulate the expression of Peh-1, Smo, Gli-1 protein and RNA | In vivo | [25, 158] |
| (+)-Cholesten-3-one                  | Chinemys reevesii (Gray) | Tonifying Yin herbs | NSCs | Induce NSCs into dopaminergic neurons | Activate BMP signal; Improve the expression of TH and BMP-IB | In vivo | [189] |
| Psoralen                             | Psoralea corylifolia L. | Tonifying kidney herbs | NSCs | Increase the expression of GFAP protein in NSCs | Increase the expression of GFAP protein | In vivo | [190] |
| Icarin                               | Epimediumgrandiflorum Morr | Tonifying kidney herbs | NSCs | Promote the self-renewal and differentiation of NSCs | Mediate the related kinase signal transduction pathways | In vivo | [191] |
| Salvinianolic acid B                 | Salvia miltiorrhiza Bge | Huoxuehuayu herbs | NSCs and NSPCs | Maintain the self-renewal of NSCs | Regulate PI3K/Akt signaling pathway; Improve the expression of tau mRNA; Down-regulate the expression of mRNAs of neurotrophic factor | In vivo | [192, 193] |
| TMP                                  | Ligusticum wallichii Franch | Huoxuehuayu herbs | NSCs | Promote the proliferation of NSCs | Increase the phosphorylation of erk1/2; Reduce the phosphorylation of p38 | In vivo | [194, 195] |
| PNS                                  | Panax Notoginseng (Burk.) F.H. Chen | Huoxuehuayu herbs | NSCs | Promote the self-renewal, proliferation, and differentiation of NSCs | Improve the expression of tuj1-1, vimentin, and nestin mRNA | In vivo | [196] |
| Bilobalide                           | Ginkgo biloba | Huoxuehuayu herbs | NSCs | Promote the proliferation of NSCs | Increase the phosphorylation of CREB and the level of the neurotrophic factor | In vivo | [197] |
| Berberine                            | Coptis chinensis Franch | Qingrejiedu herbs | NSCs | Inhibit cell cycle arrest | Improve the activity of cell viability-dependent NMDA | In vivo | [198] |
2.4 BMP signaling pathway

Bone morphogenetic protein (BMP) is a type of acidic peptide, and members of the transforming growth factor β (TGF-β) superfamily [163, 164]. BMP is an intercellular signal protein, and is important in the regulation of proliferation, differentiation, and apoptosis of NSCs [165, 166]. The sex-determining region Y-box2 (Sox2) and oligodendrocyte lineage transcription factor 2 (Olig2) are two target genes of the BMP pathway. Sox2 is a high-mobility group box transcription factor gene that can be expressed in the NSCs of SVZ and SGZ, and can also be expressed in the NPCs of VZ. Sox2 can regulate the self-renewal of NSCs and NPCs and prevent the apoptosis of NSCs [167-172]. Olig2 is a helix-loop-helix-transcription factor, mainly expressed in SVZ, and can promote the proliferation of NSPCs, induces the differentiation of NSCs into oligodendrocytes in vitro, and promotes the maturation of differentiated cells [173-175].

3 Effects of TCM on NSCs proliferation and differentiation

Numerous studies have shown that TCM has a regulatory effect on NSC proliferation and differentiation. TCM can improve the microenvironment, promote neurogenesis, repair nerve damage, and provide new treatments for cerebral injury and neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and strokes [176]. Here, we review the effects and underlying mechanisms of Chinese medicinal compounds, single herbs, and herb extract/the Chinese herbal monomer on NSCs proliferation and differentiation. Summarized are shown in Tables 3 and 4.

3.1 Effects of compound Chinese medicinal preparation on NSCs proliferation and differentiation

Experimental studies have found that compound Chinese medicine preparations have important regulatory roles on NSCs proliferation and differentiation. The compound preparations mainly include HuoxueHuyu herbs and Qingsrjiedu herbs; PNS, panax notoginseng saponins; TMP, tramethypyrazine; TNF-a, tumor necrosis factor a; iNOS, inducible nitric oxide synthase; NMDA, N-methyl-D-aspartic acid receptor; TH, tyrosine hydroxylase; BMPR-I, bone morphogenetic protein receptor IB; Patched1; Smoo, Smoothened; PSD95, postsynaptic density proteins 95.

### Table 3. Effects of TCM on NSCs proliferation and differentiation

| Compound | Chinese Name | NSCs Categories | Effect | In vivo | References |
|----------|--------------|----------------|--------|---------|------------|
| Baicalein | Scutellaria baicalensis Georgi | Qingsrjiedu herbs | Promote the differentiation of NPCs into neurons; Inhibit the apoptosis and promote the proliferation of NSCs | In vivo | [199, 200] |
| Baicalin | Scutellaria baicalensis Georgi | Qingsrjiedu herbs | Determine the fate of NSCs; Promote the differentiation of NSCs and NSPCs | In vivo and in vitro | [201, 202] |
| Paeoniflorin | Paeonia lactiflora Pall, Paeonia suffruticosu | Qingsrjiedu herbs | Promote the proliferation of nerve cells and inhibit the apoptosis of cells | In vitro | [203] |

The table lists the effects of active components of Chinese herbs on NSC proliferation and differentiation and the related mechanism, the cell type they affected, the Chinese herbs the components are extracted from, and the categories of Chinese herbs, including tonifying “Qi” herbs, blood herbs, “Yin” herbs, “Yang” herbs, and HuoxueHuayu herbs and Qingsrjiedu herbs; PNS, panax notoginseng saponins; TMP, tramethypyrazine; TNF-a, tumor necrosis factor a; iNOS, inducible nitric oxide synthase; NMDA, N-methyl-D-aspartic acid receptor; TH, tyrosine hydroxylase; BMPR-I, bone morphogenetic protein receptor IB; Patched1; Smoo, Smoothened; PSD95, postsynaptic density proteins 95.

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*Note: The table content is condensed for readability. For full details, see the original document.*

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Gardenia jasminoides Ellis, Radix Rehmanniae, and Abalone. These are weighed according to the ratio of 1:3:1:3:1:4:6, respectively. This Jiaweinisinan prescription can also promote the proliferation of hippocampal NPCs, and inhibit the apoptosis of glial cells and neurons differentiated from Hippocampal-NPCs [180].

Shengyu decoction, a traditional Chinese medicine, has been used to treat diseases that involve a deficit in “qi” and “blood.” Modified Shengyu decoction (MSD) was designed to treat brain injury after head trauma, according to traditional Chinese medicine theories, and is based on the traditional Shengyu. Four additional herbs are in the MSD: Salvia mil-tiorrhiza Bunge, Comniphora myrrha (Nees) Engl., Acorus calamus L, and Curcuma aromatica Salisb. A study on the treatment of traumatic injury in rats using the Shengyu decoction showed that it could increase the expression of nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), neural cell adhesion molecule (NCAM), and Tenascin-C (TN-C) in the cortex and hippocampus of rats. It can also inhibit the expression of Nogo-A and promote the proliferation of NSCs/NSPCs and their differentiation into neurons [181].

Fuzhisan is a traditional Chinese medicine prescription, composed mainly of four Chinese medicinal herbs: Panax ginseng C. A. Mey, Scutellaria baicalensis Georgi, Acorus gramineus Soland, and Glycyrrhiza uralensis Fisch. Experimental studies have shown that Fuzhisan can promote the proliferation of NSPCs and improve the survival rate of newborn cells [182].

Xiehuo Bushen Decoction consists of Rheum officinale baill, Paeconia suffruticosa Andr, Paeconia lactiflora Pall, Astragalus membranaceus (Fisch.) Bge, Cuscuta Lam, Viscum coloratum (Kom.), and Nakai. It can promote the survival and differentiation of NSCs transplanted into a brain after cerebral hemorrhage. The possible mechanism is that the Xiehuo Bushen Decoction can enhance the expression of interleukin 4 (IL-4) mRNA and down-regulate the expression of interferon-gamma (IFN-gama) mRNA [27].

Polygonummultiflorum Thunberg complex composition-12 (PMC-12), a mixture of four medicinal herbs, includes Polygonum multiflorum Thunb, Radix Polygala, Rehmanna glutinosa, and Acorus gramineus Soland. PMC-12 was found to promote the proliferation of NSPCs in the hippocampus, increase the survival rate of newborn neurons, and encourage neurogenesis in the hippocampus [183].

Although compounds of Chinese medicine have been found to regulate the proliferation and differentiation of NSCs through experiments, it has not been determined whether one or a combination of the active ingredients influences the proliferation and differentiation of the NSCs, because of the complexity of the active ingredients of the compounds of Chinese medicine. Further experiments are therefore required to establish this.

3.2 Effect of single herbs on NSCs proliferation and differentiation

Extensive research has been conducted on Chinese herbs, such as those used for Huoxuehuayu and Qingrejiedu (clearing away heat and toxic material) in the study of NSC proliferation and differentiation.

Salvia miltiorrhiza Bge is a common traditional Chinese herb for Huoxuehuayu. It has anti-oxidation and anti-inflammatory functions and is often used to treat nervous system diseases. Studies have shown that Danshen can increase the expression of the nestin significantly, promote the differentiation of induced multifunctional NSCs into neurons in vitro, and promote the survival and differentiation of NSCs derived from multifunctional stem cells [22]. Another commonly used herb for Huoxuehuayu, Sambucus williamssii Hance, was also shown in in vitro experiments to promote the proliferation of NSCs, but the study was conducted together with the herbs of Qingrejiedu [184].

The herbal preparation composed of Scutellariaealacensis Georgi, Phellodendron chinense Schneid, and Ligusticumwallichii Franch has been shown to promote the proliferation of NSCs in vitro. In vitro study shows that this herbal medicine can improve the symptoms of depression in mice models, which was mainly achieved through the mechanism of increasing the content of corticosterone and promoting hippocampal precursor cell proliferation [23].

Experiments also showed that the traditional Chinese herb Sambucus williamssii Hance can promote the differentiation of induced pluripotent stem cells (iPSCs) into neurons by up-regulating the expression of tubulin-1 (Tuj1) and nestin, and down-regulating the expression of Oct4 and Sox2 [184].

3.3 Effects of Chinese herbal monomer on NSCs proliferation and differentiation

In recent years, numerous experiments have demonstrated that the extract of Chinese herbal monomer Plays a specific regulatory role in NSC proliferation and differentiation. The current research mainly focuses on the extraction of effective components from the Chinese tonifying herbs HuoxueHuayu and QingreJiedu (Fig.1).
Figure 1. Structures of Chinese herbal monomers
3.3.1 Monomers from Chinese herbs

3.3.1.1 Tonifying Qi herbs

Panax ginseng C. A. Mey is an herb used in TCM for tonifying “Qi”. Recent research has shown that it has roles in anti-anxiety, anti-depression, and cognitive function-enhancing, among others. The numerous active ingredients in Panax ginseng C. A. Mey have the effect of nerve protection [185]. Ginsenoside Rg1 can promote the differentiation of NSCs into neurons and play a neuroprotective role by increasing the expression of SOX-2 and decreasing the expression of interleukin 1β (IL-1β), interleukin 6 (IL-6), and TNF-a. The differentiation of NSCs can be promoted by cAMP protein kinase A (PKA) and PI3K-Akt signaling pathway [186, 187]. Ginsenoside Rd can promote the proliferation of NSCs by regulating the expression of neurotrophic factor 3 and activating the expression of inducible nitric oxide synthase (iNOS) and N-methyl-D-aspartic acid (NMDA) receptors [188].

3.3.1.2 Tonifying Yin herbs

Oleanolic acid extracted from the “Yin”-tonifying Chinese herbal Ligustrum lucidum Ait and stilbene glycoside extracted from Fallopia multiflora (Thunb.) Harald have been found to promote the self-renewal and differentiation of NSCs in vitro. The relevant mechanism may be the increase of the expression of tubulin and the ratio of tubulin/DAPI [24].

Resveratrol is a polyphenolic compound found in various plants, and is an effective component of the Chinese herb Fructus Mori. Experiments have established that it can promote the survival and proliferation of NSCs. In addition, the expression of Patched-1 (Ptch-1), Smoothened (Smo), Gli-1 protein, and RNA were all up-regulated in resveratrol-treated NSCs [25, 158].

The tortoiseshell cholesterol extracted from Chinemys reevesii (Gray), (+)-Cholesten-3-one, can induce NSCs into dopaminergic neurons through a bone morphogenetic protein (BMP) signal, thus providing a possible new treatment for PD [189].

3.3.1.3 Tonifying kidney herbs

Psoralen is an effective component extracted from the Chinese herb (Psoralea corylifolia L.), and is representative of kidney-tonifying herbs. Psoralen has been found to increase the expression of glial fibrillary acidic protein (GFAP) in NSCs in vitro, thereby promoting the differentiation of NSCs into astrocytes [190]. Icariin, the extract of Epimediumgrandiflorum Morr, which is another well-known Chinese herb for kidney tonifying, can promote self-renewal and differentiation in NSCs. This can be mediated by the related kinase signal transduction pathways [191].

3.3.2 Huoxuehuayu herbs

Salvianolic acid B is the root and rhizome of Salvia miltiorrhiza Bge, a traditional Chinese herb of Huoxuehuayu. It can maintain the self-renewal of NSCs/progenitor cells and promote the proliferation of NSCs though the regulation of the PI3K/Akt signaling pathway [192]. It also promotes the growth of the synapses of NSCs and the differentiation of neurons [193].

Tamethylpyrazine extracted from Ligusticum wallichii Franch can promote the proliferation and differentiation of NSCs under the condition of hypoxia in vitro [194], and also promotes the differentiation of NSCs after cerebral ischemia [195].

Panax notoginseng saponins (PNS), which has the effect of Huoxuehuayu, simultaneously promotes the expression of nestin/BrdU, improves the expression of tubulin-1 (tuJ1), vimentin, and Nestin mRNA, and promote the self-renewal, proliferation, and differentiation of NSCs [196].

Bilobalide extracted from Ginkgo biloba can increase the phosphorylation of the Cyclic AMP response element binding protein (CREB) in NSCs and the level of the neurotrophic factor, and promote the proliferation of NSCs [197].

3.3.3 Qingrejiedu herbs

Berberine is the main active ingredient of Coptis chinensis Franch, a traditional Chinese herb of Qingrejiedu. Studies show that it can inhibit cell cycle arrest and promote the survival and differentiation of NSCs [198]. Baicalein and baicalin are the two main active components of Scutellaria baicalensis Georgi, and baicalin can promote the differentiation of NPCs into neurons. The mechanism may be related to the increase of the expression of presynaptic protein, synapsin I and postsynaptic density proteins 95 (PSD95) [199]. Baicalein can also inhibit apoptosis and promote the differentiation of NSCs [200]. Baicalin, another extract, can determine the fate of NSCs, and promote neurogenesis [201]. It also can regulate the expression of phosphorylated signal transducer transcription3 (p-stat3) and bHLH family proteins, subsequently promoting the differentiation of NSCs/NSPCs [202].

Paeoniflorin is a natural compound extracted from the roots of the Chinese herbs Paeonia lactiflora Pall and Paeonia suffruticosa. It can promote the proliferation and survival of NSCs and precursor cells in vitro and inhibit
the apoptosis of cells. The mechanism may be related to down-regulation of the expression of inhibitor Kb (ixB), nuclear transcription factor-xB (NF-xB), and interleukin-1β (IL-1β)[203].

As mentioned above, the natural compounds extracted from traditional Chinese medicine, which play a regulatory role in the proliferation and differentiation of NSCs, can be divided into the three categories of tonifying (for tonifying Qi, Yin, and kidney), Huoxuehuayu, and Qingrejiedu herbs. The effects of tonifying herbs on NSCs proliferation and differentiation have been studied most. In the theory of TCM, the nerve function damage is often due to kidney deficiency caused by the deficiency of the marrow-reservoir. These tonifying herbs are therefore often used for the treatment of nervous system diseases. In addition, kidney essence is also believed to be critical in maintaining a variety of life activities. The potential function of various organs can be stimulated through the method of tonifying the kidneys, which is interlinked with the method of promoting the proliferation and differentiation of NSCs to repair brain neurons in the treatment of brain damage and neurodegenerative diseases. In addition, the insufficient cerebral blood supply caused by cerebral arteriosclerosis or atherosclerotic plaque inflammatory response is also a common cause of nervous system diseases. Therefore, the heat detoxification practice of TCM is also often applied to treat nervous system diseases, including the clinical use of Huoxuehuayu and Qingrejiedu herbs. Experimental studies also demonstrate that Chinese herbs and their active ingredients can regulate the proliferation and differentiation of NSCs, which provides a broader space for discovering drugs that can regulate the proliferation and differentiation of NSCs.

4. Summary and Perspectives

NSCs pass through the different stages of NSPCs, NPCs, and neuroblasts in the process of proliferation and differentiation into neural cell lineage, and their corresponding markers are found at different stages. In the process of neurogenesis, and in NSC proliferation and differentiation, a variety of internal and external factors precisely regulate NSCs through different protein pathways. Studies have found that single herbs, herb extracts/Chinese herbal monomers, and compounds of Chinese medicine have a certain regulatory role on the proliferation and differentiation of NSCs. However, most of the current studies focus on single pathways. However, the regulation of the NSC proliferation and differentiation is involved in a complex signal network. In addition, NSC research into TCM lacks multi-targeted and multi-channel approaches, which is a systematic deficiency and thus they cannot fully explain the detailed mechanisms underlying regulating NSC by TCM. The effects of TCM promoting neurogenesis are still in the experimental stage, and may not be ready for the clinical application. In short, TCM should be played to its advantages, and in combination with modern medicine used to explore its potential in the regulation of neurogenesis to provide new possibilities for the treatment of brain damage and neurodegenerative diseases.

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