Potential therapeutic mechanism of traditional Chinese medicine monomers on neurological recovery after spinal cord injury

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Spinal cord injury (SCI) is a common traumatic disease of the central nervous system; it causes serious physical and psychological harm to patients and a huge economic burden on the entire society.[1] The tough situation of SCI treatment requires further exploration of the mechanism and obtaining a new therapeutic strategy.

Traditional Chinese medicine (TCM) is based on syndrome differentiation and treatment and overall concepts, and TCM compounds are used as the main method to treat diseases. However, its specific molecular mechanism has not been elucidated.

In recent years, with the development and rise of Chinese medicine culture, TCM monomer research has become the main method to study the disease resistance mechanism of TCM. Recent studies have shown that multiple TCM monomers, such as triptolide, curcumin, and ginsenoside, play important roles in the treatment of SCI rats. In the present study, we summarized the TCM monomers related to inflammatory response, apoptosis, neuronal autophagy, oxidative stress, and nerve regeneration after SCI and explained the specific molecular mechanism of each TCM monomer. Combined with the results of our previous experiments,[2] we summarized that (1) TCM monomers inhibit the occurrence and development of inflammatory reactions through the Wnt/β-catenin/nuclear factor-kappa B (NF-κB) signaling pathway in SCI rats and (2) the neuronal inflammatory response regulated by the Wnt/β-catenin/NF-κB signaling pathway has a protective effect on neural function recovery in SCI rats [Figure 1]. This innovative hypothesis provides a new molecular mechanism for the application of related TCM monomers after SCI.

Neural inflammation plays an important role in diseases of the central nervous system. Among the TCM monomers, triptolide, sinomenine, paeoniflorin, curcumin, ginsenoside, ginkgolide, baicalin, resveratrol, and saikosaponin exert neuroprotective effect after SCI through anti-inflammatory effects. Their specific molecular mechanisms include inhibiting the activation of microglia and astrocytes, promoting the migration of olfactory ensheathing cells, reducing the release of inflammatory cytokines, regulating microRNA (miRNA) to inhibit the inflammatory response, and mediating the related inflammatory signaling pathways.

After SCI, inflammatory cell infiltration and microglia activation occur at the site of injury, resulting in spinal cord tissue degeneration and neurological dysfunction. Microglia promote inflammatory response by activating and releasing inflammatory cytokines after SCI. Triptolide could inhibit the production of inflammatory factor, tumor necrosis factor (TNF)-α, and interleukin-1β (IL-1β) in the microglia to protect against inflammatory response-mediated neuronal injury and promote spinal cord repair.[3]

Astrocytes could be activated in the body by physical, chemical, and pathological traumas. The activated reactive astrocytes upregulate intermediate filament proteins, which could form obvious glial scar tissues at the injury site, thus affecting neuron-axon regeneration and functional recovery. Triptolide could also inhibit the activation of astrocytes by reducing the expression of intermediate filament proteins and improve the expression of injury-induced mast cells and their cytosolic proteins.[4]

Olfactory ensheathing cells are special glial cells that protect neurons by secreting a neurotrophic factor that inhibits scar formation in the injured spinal cord. They play a crucial role in neuronal protection due to their ability to migrate, proliferate, secrete various neurotrophic factors, and promote axonal regeneration. The TCM monomer ginsenoside Rg1 could promote the migration of olfactory ensheathing cells through the phosphatidylinositol 3 kinase/protein kinase B pathway; reduce the expression of related inflammatory

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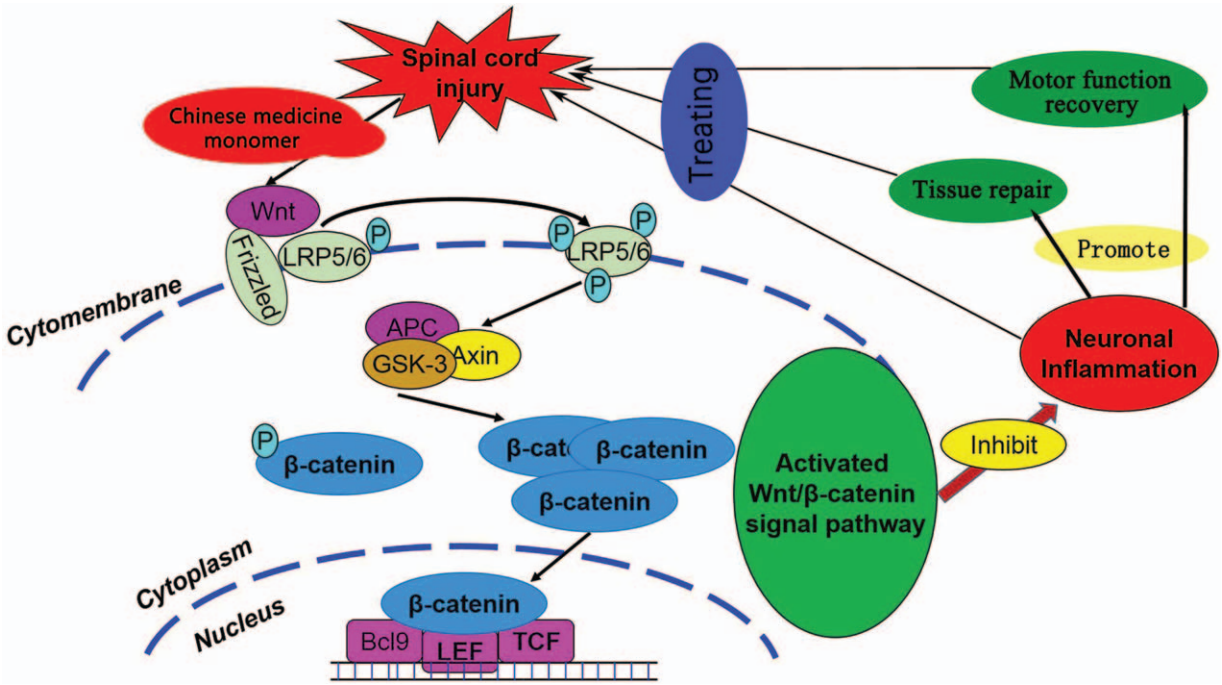

Figure 1: Hypothetical diagram of the effect of TCM monomer on the inflammatory response after SCI and its molecular mechanism via the Wnt/β-catenin/NF-κB signaling pathway. APC: Adenomatous polyposis coli; GSK-3: Glycogen synthase kinase-3; LRP5/6: Low density lipoprotein related protein5/6; LEF: Lymphoid enhancing factor; NF-κB: Nuclear factor-kappa B; P: Phosphorylation; SCI: Spinal cord injury; TCF: T-cell factor; TCM: Traditional Chinese medicine.

cytokines TNF-α, IL-1, and IL-6; and promote the functional repair of SCI in rats.[5]

miRNAs regulate the pathology of inflammation after SCI and are a new target for treatment. miR-96 is related to nerve injury. After peripheral nerve injury in rats, the expression of miR-96 in the ipsilateral dorsal root ganglia was downregulated, and an intrathecal injection of miR-96 could reduce the pathological symptoms caused by nerve injury.[3] Experiments showed that triptolide could reduce the expression of inflammatory cytokines, such as ionized calcium binding adaptor molecule-1, IKKβ, phosphorylated-inhibitory subunit of kappa B alpha, phosphorylated-p65, TNF-α, and IL-1β, by upregulating the expression of miR-96, which promotes exercise recovery in SCI rats.

SCI produces an inflammatory response through the corresponding inflammatory signaling pathway. Among the previously reported TCM monomers, triptolide and ginkgolide regulate the Janus kinase 2/signal transducer and activator of transcription 3 (STAT3) and signal transducer and activator of transcription 1 (STAT1) signaling pathway[6]; curcumin acts on the toll like receptors/transforming growth factor-β activated kinase 1/mitogen activated protein kinase kinase and toll/NF-κB signaling pathway[7]; and paeoniflorin participates in regulating the apoptosis signal-regulating kinase 1/phosphorylated-p38/phosphorylated c-Jun N-terminal kinase (ASK1/p-p38/p-JNK) signaling pathway in SCI rats.[8] By regulating these inflammatory signaling pathways, TCM monomers could downregulate the expression of pro-inflammatory factors (IL-1β, TNF-α, IL-6, IL-8, and Olig2), upregulate the expression of anti-inflammatory factors (IL-4, IL-10, and transforming growth factor-β), and promote the recovery of SCI rats.

After SCI, the levels of pro-apoptotic factors (caspase and Bax families) significantly increased, whereas those of anti-apoptotic factors (Bcl-2 family) significantly decreased, indicating the activation of neuronal apoptosis. Excessive neuronal apoptosis adversely affected the functional recovery after SCI and inhibited the recovery of tissue morphology and behavior. Therefore, neuronal apoptosis is also a potential target for SCI treatment.

Among the TCM monomers reported above, ginsenoside Rb1[9] plays roles in the anti-apoptotic process after spinal cord ischemia-reperfusion injury, and ginkgolide B[10] plays roles in the anti-apoptotic process in SCI rats. After these TCM monomers were used to treat SCI, the expression levels of pro-apoptotic proteins caspase-3, caspase-9, and Bax in the body were significantly reduced. The levels of the anti-apoptotic protein Bcl-2 significantly increased, and the ratio of Bax/Bcl-2 was downregulated, which may be related to STAT3 activation. STAT3 could induce the expression of Bcl-2 and inhibit that of Bax.

Autophagy has neuroprotective effects in neurological diseases. For example, simvastatin treated SCI rats by inhibiting the mammalian target of rapamycin (mTOR) signaling pathway and activating autophagy.[11] Among the TCM monomers introduced in the present article, curcumin and resveratrol could mediate autophagy response after SCI. Resveratrol could regulate the adenosine monophosphate-activated protein kinase (AMPK)/mTOR signaling pathway,[12] a specific autophagic pathway that causes AMPK phosphorylation during signal transduction. Phosphorylated

AMPK could inhibit mTOR activity and eventually activate autophagy and cause the upregulation of protein expression levels, such as beclin-1, microtubule-associated protein 1 light chain 3-II/light chain I (LC3-II/I), and autophagy-related proteins. These proteins promote neural-function recovery in SCI rats. In addition, curcumin mediates autophagy through the AKT/mTOR signaling pathway.[13]

Oxidative stress contributes to a cascade of secondary damage following SCI, which results in inflammatory cell infiltration, neuronal and glial cell destruction, neuronal dysfunction, and cell death. Reducing oxidative stress is helpful for the treatment of SCI. The TCM monomers, such as sinomenine, ginsenoside, and resveratrol, could promote the recovery of neuromotor function by inhibiting oxidative stress in SCI rats. Their mechanisms are related to the levels of nuclear factor 2-related factor 2 (Nrf 2). Nrf 2/heme oxygenase (HO)-1 is an important antioxidant pathway.[14] The activation of this pathway induces the production of corresponding antioxidant enzymes and type II drug metabolizing enzymes, thereby enhancing the ability of the cells to scavenge reactive oxygen species, maintaining redox balance, and reducing oxidative damage.

Neurotrophic factors, such as nerve growth factor (NGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF), play an important role in the development of the nervous system and neuron regeneration. Some TCM monomers could promote the expression of these neurotrophic factors and provide a favorable microenvironment for neuron regeneration after SCI. Research showed that matrine could directly activate extracellular heat shock protein 90, resulting in axonal growth and functional recovery in SCI mice.[15] This finding indicated that matrine could promote the recovery of motor function after SCI. However, the specific molecular mechanism of action has not yet been elucidated. Neuron regeneration and the elaboration of its specific mechanism remain as the current research hotspots.

TCM monomers could protect neurons from SCI by inhibiting inflammatory responses, reducing neuronal apoptosis, and promoting autophagy through different signaling pathways. However, studies on the Wnt/β-catenin signaling pathway have not been conducted. Therefore, we plan to further investigate TCM monomers through the Wnt/β-catenin/NF-κB signal pathway in different neurons and their specific molecular mechanisms. A notable detail that the current research on TCM monomers in SCI is in the stage of animal experiments, and it has not been clinically verified. Therefore, whether all TCM monomer extracts could be converted clinically is still unclear. If this problem could be solved well, the application of TCM monomers in the repair of SCI could play an enhanced role and increase the possibilities for clinical treatment.

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Conflicts of interest

None.

References

1. Shen J, Gao F, Zhao L, Hao Q, Yang YL. MicroRNA-34c promotes neuronal recovery in rats with spinal cord injury through the C-X-C motif ligand 14/Janus kinase 2/signal transducer and activator of transcription-3 axis. Chin Med J 2020;133 18:2177–2185. doi: 10.1097/CM9.0000000000001022.
2. Zhang T, Wang F, Li K, Lv C, Gao K, Lv C. Therapeutic effect of metformin on inflammation and apoptosis after spinal cord injury in rats through the Wnt/β-catenin signaling pathway. Neurosci Lett 2020;739:135440.
3. Huang Y, Zhu N, Chen T, Chen W, Kong J, Zheng W, *et al*. Triptolide suppressed the microglia activation to improve spinal cord injury through miR-96/IKKβ/NF-κB pathway. Spine 2019;44 12: E707–E714. doi: 10.1097/BRS.0000000000002989.
4. Su Z, Yuan Y, Cao L, Zhu Y, Gao L, Qiu Y, *et al*. Triptolide promotes spinal cord repair by inhibiting astrogliosis and inflammation. Glia 2010;58 8:901–915. doi: 10.1002/glia.20972.
5. Tang YY, Guo WX, Lu ZF, Cheng MH, Shen YX, Zhang YZ. Ginsenoside Rg1 promotes the migration of olfactory ensheathing cells via the PI3K/Akt pathway to repair rat spinal cord injury. Biol Pharm Bull 2017;40 10:1630–1637. doi: 10.1248/bpb.b16-00896.
6. Zheng JL, Li BS, Cao XC, Zhuo WK, Zhang G. Alleviation of spinal cord injury by Ginkgolide B via the inhibition of STAT1 expression. Genet Mol Res 2016;15. doi: 10.4238/gmr.15027673.
7. Zhang N, Wei G, Ye J, Yang L, Hong Y, Liu G, *et al*. Effect of curcumin on acute spinal cord injury in mice via inhibition of inflammation and TAK1 pathway. Pharmacol Rep 2017;69 5:1001–1006. doi: 10.1016/j.pharep.2017.02.012.
8. Wang B, Dai W, Shi L, Teng H, Li X, Wang J, *et al*. Neuroprotection by paeoniflorin against nuclear factor kappa B-induced neuroinflammation on spinal cord injury. Biomed Res Int 2018;2018: 9865403. doi: 10.1155/2018/9865403.
9. Zhao D, Zhang M, Yuan H, Meng C, Zhang B, Wu H. Ginsenoside Rb1 protects against spinal cord ischemia-reperfusion injury in rats by downregulating the Bax/Bcl-2 ratio and caspase-3 and p-Ask-1 levels. Exp Mol Pathol 2018;105 3:229–235. doi: 10.1016/j.yexmp.2018.09.001.
10. Song Y, Zeng Z, Jin C, Zhang J, Ding B, Zhang F. Protective effect of ginkgolide B against acute spinal cord injury in rats and its correlation with the Jak/STAT signaling pathway. Neurochem Res 2013;38 3:610–619. doi: 10.1007/s11064-012-0959-y.
11. Gao K, Wang G, Wang Y, Han D, Bi J, Yuan Y, *et al*. Neuroprotective effect of simvastatin via inducing the autophagy on spinal cord injury in the rat model. Biomed Res Int 2015;2015:260161. doi: 10.1155/2015/260161.
12. Meng HY, Shao DC, Li H, Huang XD, Yang G, Xu B, *et al*. Resveratrol improves neurological outcome and neuroinflammation following spinal cord injury through enhancing autophagy involving the AMPK/mTOR pathway. Mol Med Rep 2018;18 2:2237–2244. doi: 10.3892/mmr.2018.9194.
13. Li W, Yao S, Li H, Meng Z, Sun X. Curcumin promotes functional recovery and inhibits neuronal apoptosis after spinal cord injury through the modulation of autophagy. J Spinal Cord Med 2021;441: 37–45. doi: 10.1080/10790268.2019.1616147.
14. Liu X, Gu X, Yu M, Zi Y, Yu H, Wang Y, *et al*. Effects of ginsenoside Rb1 on oxidative stress injury in rat spinal cords by regulating the eNOS/Nrf2/HO-1 signaling pathway. Exp Ther Med 2018;16 2:1079–1086. doi: 10.3892/etm.2018.6286.
15. Tanabe N, Kuboyama T, Tohda C. Matrine directly activates extracellular heat shock protein 90, resulting in axonal growth and functional recovery in spinal cord injured-mice. Front Pharm 2018;9:446. doi: 10.3389/fphar.2018.00446.

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