Review

Efficacy of some non-conventional herbal medications (sulforaphane, tanshinone IIA, and tetramethylpyrazine) in inducing neuroprotection in comparison with interleukin-10 after spinal cord injury: A meta-analysis

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Context: Inflammation after spinal cord injury (SCI) may be responsible for further neural damages and therefore inhibition of inflammatory processes may exert a neuroprotection effect.
Objectives: To assess the efficacy of some non-conventional herbal medications including sulforaphane, tanshinone IIA, and tetramethylpyrazine in reducing inflammation and compare them with a known effective anti-inflammatory agent (interleukin-10 (IL-10)).
Methods: We searched relevant articles in Ovid database, Medline (PubMed) EMBASE, Google Scholar, Cochrane, and Scopus up to June 2013. The efficacy of each treatment and study powers were compared using random effects model of meta-analysis. To our knowledge, no conflict of interest exists.
Results: Eighteen articles entered into the study. The meta-analysis revealed that exogenous IL-10 was more effective in comparison with the mentioned herbal extracts. The proposed pathways for each medication's effect on reducing the inflammation process are complex and many overlaps may exist.
Conclusion: IL-10 has a strong effect in the induction of neuroprotection and neurorecovery after SCI by multiple pathways. Tetramethylpyrazine has an acceptable influence in reducing inflammation through the up-regulation of IL-10. Outcomes of sulforaphane and tanshinone IIA administration are acceptable but still weaker than IL-10.

Keywords: Cytokines, Spinal cord, Pharmacology, Neuroinflammation

Introduction

Neurological improvement in spinal cord injury (SCI) has always been a challenge. The cascade of inflammatory processes that occur after injury has been shown to play an important role in inducing further nerve damage.[1,2] Many treatment strategies have focused on inhibiting these inflammatory processes and some involved pathophysiological pathways have been described so far.[3] After traumatic SCI, morphological changes in tissues may occur due to hemorrhage and edema and is followed by secondary damages by activations of inflammatory responses.[4,5] By considering the important role of inflammation in the induction of neural injuries, anti-inflammatory medications have been proposed to have beneficial effects.[6] Major pro-inflammatory cytokines that are detected widely at the site of lesion are tumor necrosis factor-a (TNF-α), interleukin-1b (IL-1b), and IL-6[7] and the most effective medications function by targeting these agents. Moreover, the deficiency of some factors such as IL-10 has been shown to enhance inflammatory response.[8] So the hypothesis of administration of exogenous

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IL-10 was proposed to induce neuroprotection in SCI through its anti-inflammatory effects.[9] Previously, Kwon *et al.*[10] summarized the neuroprotective effect of many administered medications including erythropoietin, non-steroid anti-inflammatory drugs (NSAIDs), antiCD11d antibodies, minocycline, progesterone, estrogen, magnesium, riluzole, polyethylene glycol, atorvastatin, inosine, and pioglitazone in the animal models. Although this study did not compare the efficacy of these agents, it illustrated a valuable context of medications and their mechanisms in inducing neuroprotection which is an essential and vital achievement after SCI. Here, we assessed the efficacy of some new herbal extracts that have been used in pre-clinical investigations on animal models and have shown promising outcomes. In this field, meta-analysis can perform a proper comparison between these medications and assess the power of each study. Although there are noticeable variations in experimental designs and applied methods in evaluating medications' efficacy, by using random model effects, comparison of heterogeneous studies is possible. In the present study, we tried to compare the effect of some non-conventional medications which are shown to have anti-inflammatory influence and may induce neuroprotection and neurorecovery effects after SCI. The effects of IL-10, tanshinone IIA (TIIA; an important lipophilic diterpene extracted from *Salvia miltiorrhiza*), tetramethylpyrazine (TMP; a pure compound derived from a Chinese herb called *Ligusticum chuanxiong*), and sulforaphane (a potent anti-inflammatory extract of cruciferous vegetables) were compared. IL-10 is a known effective anti-inflammatory agent which blocks T-cells' functions. Our purpose was to compare the anti-inflammatory efficacy of the mentioned herbal extracts with a known effective agent (IL-10) in pre-clinical investigations. By considering the fact that the patients in acute phase of SCI need the most effective anti-inflammatory medication in a gold time interval, it becomes necessary to provide evidences in introducing the most effective agent so that the pharmaceutical processes are focused on developing the most appropriate medication.

The induction of neuroprotection is mediated through many complex pathways that involve antioxidative, anti-apoptotic, and anti-inflammatory processes. Along with comparing the neuroprotective effect of sulforaphane, TIIA, and TMP with a known effective agent (IL-10), here we also summarized the proposed mechanism of each medication.

Methods

This paper is a systematic review using meta-analysis to determine the difference between some medications' effect in the induction of neuroprotection after SCI in pre-clinical studies. We like to mention that no individuals and organizations beyond the mentioned authors and affiliations have contributed in the analysis and writing this manuscript. The searching process of relevant articles was performed by using keywords of "IL-10", "interleukin-10", "tanshinone IIA", "tetramethylpyrazine", "sulforaphane", and "spinal cord injury" in various databases including Medline (Pubmed), EMBASE, Google Scholar, Ovid, Cochrane, and Scopus. The references of retrieved articles were also scanned to detect any relevant articles. All potential relevant articles published up to July 2013 were reviewed. The searching process was conducted by two different reviewers separately and no language limitation was applied.

Study selection

Inclusion criteria consisted of: exogenous administration of IL-10, TIIA, TMP, and sulforaphane, studies on animal subjects with SCI in acute phase, assessment of the neurological recovery, and existence of a control group for proper comparison. Exclusion criteria were: evaluation of endogenous changes of IL-10 (and not exogenous administration), lack of comparable data, and evaluating other medication effects other than neurological assessment.

In this systematic review, only studies on animal models were selected. Studies on patients with SCI are mostly in chronic phase of SCI. SCI is usually accompanied with multiple trauma and these patients experience critical conditions usually in intensive care unit. Because of vast variability in degree of injuries and critical conditions of these patients, studies on acute phase of SCI in human face difficulties (whether ethical complications or complexity in study designs as it is difficult to define two matched groups because of broad diversities in severity of injuries and clinical conditions among these patients). When we take a look at the literatures evaluating the efficacy of new drugs, barely, we observe a study on human models in acute SCI. The majority of the literatures are performed on the animal models and as we know, the existence of adequate literatures is essential in running a meta-analysis. Moreover, by considering the peak level of inflammation in acute phase, it is expected that these medications show their maximum efficacy at this phase but studies on human models mostly involve patients in chronic phase in which the coincidental complications are controlled and patients experience a stable phase.

Study selection was also performed by two independent reviewers and the rate of agreement was described

with Cohen kappa. Basic information which was drawn from literatures included: the type of the study subject, existence of the control group, the type of used medications, a brief explanation of methods, P-values which indicated significant difference between the case and the control groups, the method of neurological assessment, and major findings.

Statistical analysis

All the analysis was performed by using PASW Statistics for Windows version 18 (SPSS, Inc., Chicago, IL, USA) and Comparative Meta-analysis version 2 (Biostat, Englewood, NJ, USA). Statistical homogeneity was checked by χ^2 test and I^2 using Cochran heterogeneity statistic as Q.[11] As I^2 was higher than 75%, random effects model was used to calculate the weighted mean difference and 95% confidence interval (CI). The effect size was determined by using comparison of P-values and identifying study powers which was expressed as z score. By considering the various experimental designs and different assessment methods in each study, we used random effects model. A random effects model involves an assumption that the effects being estimated in the different studies are not identical, but follow some distribution. However, in this process, the establishment of validity is difficult which is a common criticism of random effects model in the meta-analyses but still simulations have shown that this method is reliable even under extreme distributional assumptions in estimating the heterogeneity.[12] When the procedures of assessed investigations are different, the proper comparison is possible only when the control group in each study exists. The medications which have induced more significant difference between the treatment and the control groups (with a more significant P-value) are considered as "more effective", regardless of applied evaluation and measurement methods.

Results

Among literatures indicating effects of IL-10, seven articles illustrated the neurological improvement after SCI. While some other investigations were close to our purpose, they were removed from the analysis as they met our exclusion criteria. The most important excluded literatures were Milligan *et al.* studies[13–15] which mostly illustrated the anti-inflammatory effect of IL-10 in subjects without SCI. It is noticeable that the dosage and the method of IL-10 administration were vastly different between these studies as some of them used insertion of genetic vectors to release IL-10 while some others used direct intra-spinal or intravenous injections. The basic characteristics of the involved studies are summarized in Table 1. Three studies on sulforaphane, two studies on TIIA, and six literatures on TMP were selected based on the inclusion and exclusion criteria and were entered into analysis. Total of 18 articles went through the process of meta-analysis and the Cohen kappa coefficient was acceptable (0.8).

All these articles used animal models and tried to find the potential efficacies of tested medication. Major findings of these articles which present the most important mechanisms of anti-inflammatory effects of these medications are summarized in Table 2. It is noticeable that different pathways have been proposed for the efficacy of each medication. In fact, the final influence of the drug is mediated through complex pathways. However, the comparison of given P-values which indicate the strength of association between two factors give us the possibility to compare these pathways to show which one is more powerful and effective in inducing neuroprotection.

Standard deviation differences (SDD) in means of the case and the control groups in each study with CI of 95% are shown in Fig. 1. The total results in four studies on IL-10 showed a SDD of 1.002 (0.521–1.483, z-value: 4.083), which was higher in comparison with other tested medications. Studies on sulforaphane in SCI were so limited or did not contain adequate comparative data and consequently our analysis on sulforaphane was limited to Mao *et al.* investigation (SDD of 0.620 (0.149–1.090, z-value: 2.58)). Because of the lack of available comparative literatures on sulforaphane efficacy in SCI, these results should be interpreted cautiously. TIIA showed a SDD in means of 0.807 (0.317–1.297, z-value: 3.227) and TMP had SDD of 0.501 (0.287–0.714, z-value: 4.59). The comparison of all these medications shows that these herbal extracts have acceptable efficacy in inducing neuroprotection or neurorecovery after SCI (P-values: 0.010, 0.001, and <0.0001 for sulforaphane, TIIA, and TMP, respectively) but still their influence is relatively weaker than IL-10 (Fig. 1).

Various mechanisms have been shown to play a role in the reduction of inflammation. When considering the combined pathways, the interconnections are so complex. This meta-analysis shows that administration of IL-10 was the most powerful anti-inflammatory agent than other tested drugs (Fig. 1). Both methods of releasing IL-10 (inserting genetic vectors or direct intra-spinal/intravenous injection) induced neuroprotection more effectively in comparison with sulforaphane, TIIA, and TMP.

The results over TMP efficacy are controversial, while a very strong power in inflammation reduction was

Table 1 Basic characteristics of involved articles

Study	Medication	Dosage	Subjects	Subjects (no.)	Control	Assessments
Zhou *et al.*[16]	IL-10	2 μl of vector	Female Sprague–Dawley rats	10	Yes	Basso–Beattie–Bresnahan (BBB) motor rating scale[17]
Oruckaptan *et al.*[18]	IL-10	100 mg/kg	Single-strain female Albino rats	32	Yes	6 point lower extremity walking scale[19]
Jackson *et al.*[20]	IL-10	200 pg/ml	Adult mice	20	Yes	Basso–Beattie–Bresnahan (BBB) motor rating scale
Brewer *et al.*[21]	IL-10	5 μg	Female Sprague–Dawley rats	24	Yes	Histological assessment of tissue inflammation
Pearse *et al.*[22]	IL-10	30 mg/kg	Adult rats		Yes	Basso–Beattie–Bresnahan (BBB) motor rating scale
Takami *et al.*[23]	IL-10	15–30 μg/kg	Adult Fischer rats		Yes	Basso–Beattie–Bresnahan (BBB) motor rating scale
Bethea *et al.*[24]	IL-10	5 μg/kg	Adult rats	18	Yes	Basso–Beattie–Bresnahan (BBB)
Mao *et al.*[25]	Sulforaphane	5 mg/kg	Male ICR rats	96	Yes	Measurement of TNF-α and MMP-9 by ELISA
Miller *et al.*[26]	Sulforaphane	5 mg/kg	Young CF-1 mice		Yes	Measurement of Nrf2-ARE-activitating compounds gene expression
Mao *et al.*[27]	Sulforaphane	5 mg/kg	Wild-type mice	288	Yes	Neurological function assessment by Basso open-field motor score (BMS)[28]
Yin *et al.*[29]	TIIA	50 mg/kg	Sprague–Dawley male adult rats	16	Yes	Basso–Beattie–Bresnahan (BBB) motor rating scale
Zhang *et al.*[30]	TIIA		New Zealand rabbits	54	Yes	Assessment of expression of NF-κB and VCAM-1 genes
Fan *et al.*[31]	TMP	30 mg/kg	Male Sprague–Dawley rats	90	Yes	Basso–Beattie–Bresnahan (BBB) motor rating scale
Liang *et al.*[32]	TMP	50 mg/kg	Male Sprague–Dawley rats	24	Yes	Neurological function by Tarlov criteria[33]
Fan *et al.*[34]	TMP	30 mg/kg	Adult male New Zealand white rabbits	36	Yes	Neurological function by Johnson's score[35]
Chen *et al.*[36]	TMP	30 mg/kg	Male New Zealand white rabbits	45	Yes	Neurological function by Tarlov criteria
Xiao *et al.*[37]	TMP		SD rats	110	Yes	Modified Rivilin loxotic plate degree Basso–Beattie–Bresnahan (BBB) motor rating scale Combined behavioral score (CBS)
Shen *et al.*[38]	TMP		Adult Sprague–Dawley rats	80	Yes	Modified Rivilin loxotic plate degree Basso–Beattie–Bresnahan (BBB) motor rating scale

reported by Liang *et al.*, Fan LH *et al.*, and Chen *et al.* (Fig. 1), the lower strength of its effect in Fan L *et al.*, Xio *et al.*, and Shen *et al.* studies, led to a moderate total efficacy (SDD in means: 0.501). However, it is noticeable that mechanisms which were evaluated in these literatures were different which shows that TMP efficacy is more powerful in some specific pathways.

Discussion

IL-10 is a powerful agent that can block T-cell function via antigen-presenting cells.[40] Excessive inflammation damages that occur after SCI can be attenuated by proper interventions through inhibition of pro-inflammatory and cytotoxic release. The time interval of initiating these anti-inflammatory medications is also important and it has been shown that cellular events that occur right after SCI are regulated by the expression of pro-inflammatory cytokines including TNF-α and IL-1β at the site of injury.[41] While the absence of IL-10 invigorates neural damage by increasing the expression of iNOS,[8,42] its exogenous consumption leads to significant neurological improvement.[16,18,20–22] The mechanisms of IL-10 efficacy have been well-described up to now. Therefore, IL-10 is a known effective agent in reducing inflammation and subsequently inducing neuroprotection. For instance, TNF-α, which is inhibited by IL-10, is one of the most important agents that induces oligodendrocytic apoptosis;[43] so if IL-10 is initiated immediately after SCI, it can prevent further neural damages. Moreover, its antiapoptotic

Table 2 Major findings in the selected literatures

Study	Year of publication	Medication	P-value	Major findings
Zhou *et al.*[16]	2009	IL-10	<0.05	Improved motor function, increased expression of Bcl-2 and Bcl-xL Inhibition of cytochrome c release and caspase 3 cleavage
Oruckaptan *et al.*[18]	2009	IL-10	<0.026	Decreased lipid peroxidation and myeloperoxidase activity, attenuation of the early ischemic response, and restriction of the tissue damage
Jackson *et al.*[20]	2005	IL-10	<0.05	Greater functional recovery in the first 24 hours after injury
Brewer *et al.*[21]	1999	IL-10	–	Significantly decreased lesion volume, reduction in neuronal damage
Pearse *et al.*[22]	2004	IL-10	–	Improved gross locomotor performance, worsened behavioral outcome
Takami *et al.*[23]	2002	IL-10	–	Improved gross locomotor performance, increased the volume of spared spinal gray matter 3 months after a moderate contusion
Bethea *et al.*[24]	1999	IL-10	–	Reduction of lesion volume by ~49%
Mao *et al.*[25]	2010	Sulforaphane	<0.01	Lower expression and activity of MMP and decreased tumor necrosis factor-α
Miller *et al.*[26]	2013	Sulforaphane	<0.05	Increased expression of hemeoxygenase-1mRNA, attenuation of (4-hydroxy-2-Nonenal) 4-HNE-induced inhibition of mitochondrial respiration for complex I
Mao *et al.*[27]	2011	Sulforaphane	<0.01	Activation of Nrf2, improved hind limb locomotor function assessed by BMS, reduced inflammatory damage, histologic injury, dying neurons count, and spinal cord edema
Yin *et al.*[29]	2012	TIIA	<0.05	Improved motor function, reduced tissue injury (histological score), reduced myeloperoxidase activity, inhibition of NF-κB and MAPK signaling pathways, decreased production of pro-inflammatory cytokines (TNF-α, IL-1b, and IL-6)
Zhang *et al.*[30]	2012	TIIA	<0.01	Reduced expression of NF-κB and VCAM-1
Fan *et al.*[31]	2011	TMP	<0.05	Significant improved neurological outcome, decreased infarct volume, alleviated neutrophil infiltration
Liang *et al.*[32]	2011	TMP	<0.05	Suppressed glutamate level, suppressed the expression of mGluR-1 mRNA, better neurological function
Fan *et al.*[34,39]	2006	TMP	<0.05	Significantly better neurological outcomes, decreased spinal cord malondialdehyde levels, reduced the loss of motoneurons, and reduced apoptotic cell death through Bcl-2 up-regulation parallel to Bax down-regulation
Chen *et al.*[36]	2002	TMP	<0.05	Better neurological status and histopathology, significantly reduced neurological injury
Xiao *et al.*[37]	2012	TMP	<0.05	Significantly higher BBB score, significantly low number of MIF-positive cells
Shen *et al.*[38]	2008	TMP	<0.05	Reduced expression of caspase-3 and increased expression of neurofilament protein (NF-L, NF-H, and NF-M)

ELISA, enzyme-linked immunosorbent assay; MIF, macrophage migration inhibitory factor; MMP-9, metalloproteinase-9; Nrf2-ARE, NF-E2-related factor 2-antioxidant-response element; TNF-α, tumor necrosis factor-α; BMS, Basso open-field motor score.

effect has been shown not only in spinal cord neurons, but also in cerebellar granule cells[44] and ganglion cell line.[45] Many mechanisms have been proposed for this antiapoptotic effect. Zhou *et al.*[16] described that apoptotic cascade is inhibited by IL-10 through cytochrome c release and caspase 3 cleavage along with an increased expression of Bcl-2 and Bcl-xL. Up-regulation of caspase 3 expression along with the activation of caspase 9 were the proposed apoptotic pathways[46,47] which are shown to be efficiently inhibited by IL-10. Clinical investigations did not show any differences in IL-10 level between the patients with SCI and the able-bodied patients while the increased concentration of pro-inflammatory cytokines was observed in the SCI group[48] which shows that despite the neuroprotective effect of IL-10, it is not autonomously released at injury site itself in human bodies and is not in line with animal models of reperfusion injuries.[49,50] By considering the vast majority of literatures showing that IL-10 decreases the infarct size in ischemic damages,[51] it seems that not only the anti-inflammatory effect but also other mechanisms exist that mediate the influence of IL-10 on ischemic/reperfusion tissue damages. In this regard, Oruckaptan *et al.*[18] showed decreased lipid peroxidation and myeloperoxidase activity which was mediated by IL-10.

It is shown that IL-10 leads to the inhibition of cytochrome c release and caspase 3 cleavages while it increases the expression of Bcl-2 and Bcl-xL. Meanwhile, it can also decrease the lipid peroxidation and myeloperoxidase activity. It seems that these pathways are the most powerful and effective pathways of inflammatory reduction. Moreover, worsening of behavioral scores was only reported by treatment with IL-10.

Recently, some new herbal medications (sulforaphane, TIIA, and TMP) have been proposed to be

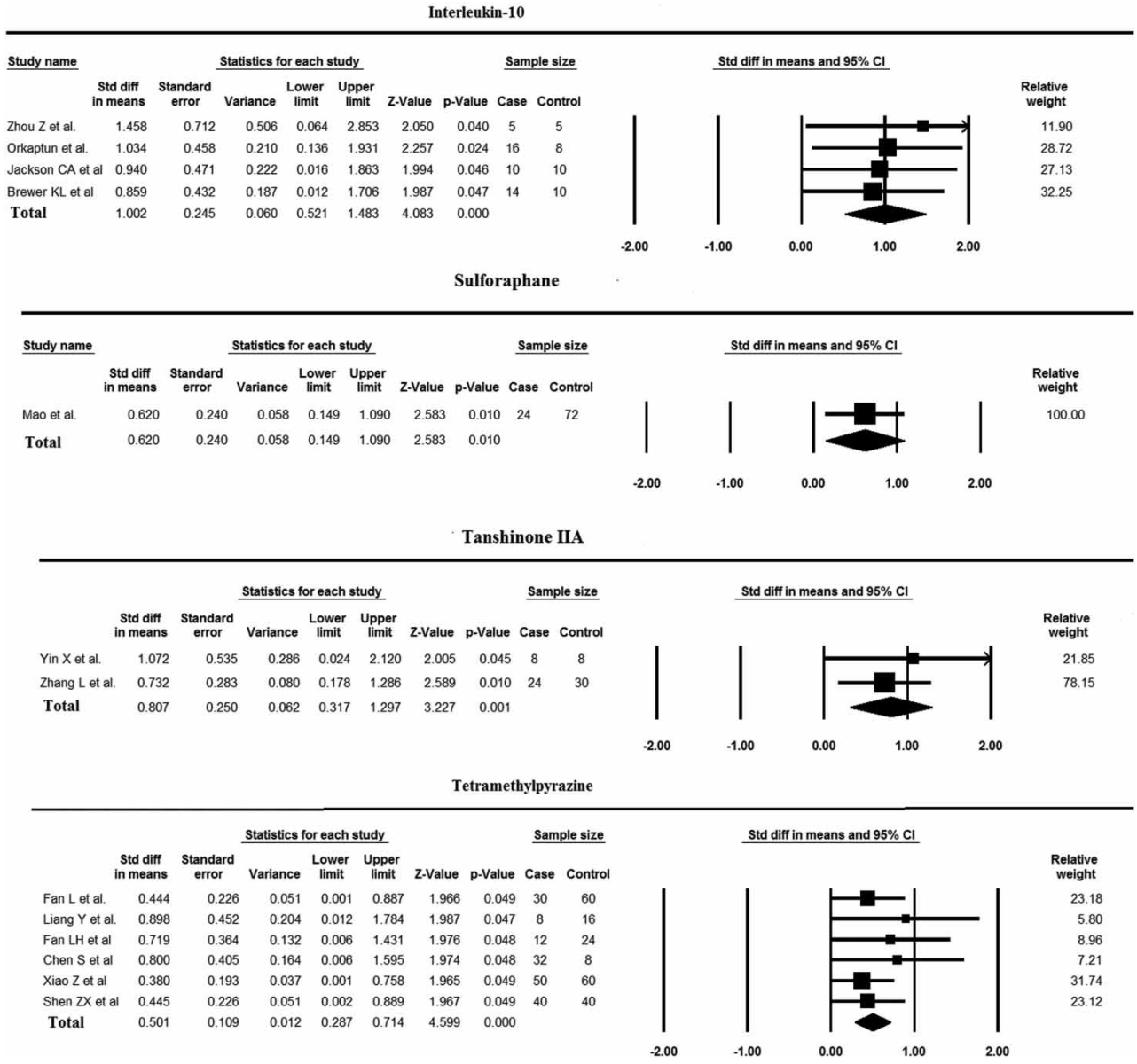

Figure 1 Meta-analysis of several medications' efficacy including IL-10, sulforaphane, TIIA, and TMP on inflammation reduction after SCI. Five studies were excluded due to the lack of comparative data.

effective in reducing inflammation and inhibiting neural damage. Here, we compared IL-10 efficacy in neurological improvement and anti-inflammatory strength with sulforaphane, TIIA, and TMP. Our results show that although these herbal extracts have acceptable efficacy, their influence is still weaker than IL-10. However, it is considerable that worsening of the behavioral outcome was only reported by IL-10 administration.[22] Although this complication was reported in experimental animal models, its clinical administration must be exerted cautiously.

By considering the fact that the inhibition of inflammation results in preventing further neural damage, the administration of some conventional medications such as NSAIDs has been proposed so far. In this regard, Kopp *et al.*[52] showed that ibuprofen which is a Food and Drug Administration-approved NSAID can enhance axonal regeneration by inhibiting the small GTPase RhoA molecule. Furthermore, Kwon *et al.*[10] has expressed the efficacy of various medications including erythropoietin, NSAIDs, antiCD11d antibodies, minocycline, progesterone, estrogen, magnesium, riluzole, polyethylene glycol, atorvastatin, inosine, and pioglitazone as neuroprotective treatments for acute SCI in a systematic review on animal models. Although Kwon did not present any comparison among these medications, the study is considerable as it summarizes the available treatments in inhibiting neural damage after

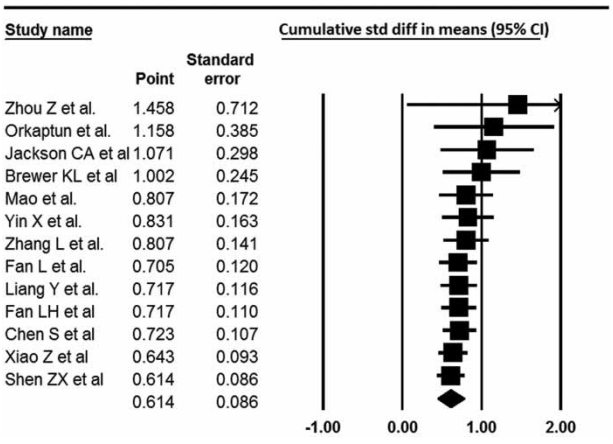

Figure 2 Cumulative study of 13 studies; 5 studies were excluded due to the lack of comparative data.

SCI. Here, we tried to assess other new medications. Our vast searches showed the mentioned herbal drugs as potential extracts that are trying to enter into pharmaceutical process. Hence, it was essential to know if these drugs can influence as effective as previous known anti-inflammatory agents (such as IL-10). Besides, we decided not to compare the efficacy of these extracts with conventionally used steroids. The usage of steroids after SCI is not only indicated because of its anti-inflammatory effect, but mostly because of adrenal shock and extremely low blood pressure to maintain circulation. Due to vast indications of steroid administrations after SCI, we did not perform any comparison of the mentioned medications with steroids and we tried to focus only on neuroprotection and anti-inflammatory aspects of some specific drugs.

Sulforaphane (1-isothiocyanato-4-methylsulfinylbutane), which is a member of isothiocyanate family and is derived from cruciferous vegetables, have been shown to exert anti-inflammatory activities.[53,54] The mechanism was first reported in leukemic cell where it was observed that sulforaphane inhibited TNF-α-induced nuclear factor-κB (NF-κB) activation in pathways involving metalloproteinase-9 (MMP-9).[55] Mao *et al.*[25] investigated this effect in individuals with SCI and showed lower expression and activity of MMP-9. MMPs are known to mediate the degradation of gelatin (denatured collagens), collagen IV, V, and XI, and myelin basic protein.[56,57] It has been reported that MMP-9 production can be induced by TNF-α[58,59] and therefore inhibition of MMP-9 may block one of the activity pathways of TNF-α. Moreover, TNF-α and MMP-9 are up-regulated during SCI[60] and although their inhibition may exert beneficial influences, our meta-analysis shows that this effect is weaker than IL-10 efficacy. It is noticeable that sulforaphane acts as an anti-inflammatory agent by activating NF-erythroid 2-related factor 2 (Nrf2)[27,61] and thus it protects cells from oxidative damage by the induction of detoxification enzymes.[62] In conclusion, it seems that administration of sulforaphane in SCI has beneficial effects but other additive medications may be required to invigorate the anti-inflammatory effect. Unfortunately, we could not detect any investigations on combined therapies of sulforaphane and thus we cannot conclude a proper comparison with multidrug regimens efficacy.

TIIA is a lipophilic diterpene extracted from *S. miltiorrhiza* and is used in Chinese traditional herbal medicine. Literatures have shown not only its anti-inflammatory effects[63,64] but also its antiapoptotic[65] and antioxidant[66] activities. Yin *et al.*[29] showed that TIIA leads to improved motor function, reduced tissue injury (histological score), reduced myeloperoxidase activity, and inhibition of NF-κB and MAPK signaling pathways in SCI. TIIA has been shown to have antitoxicity activity and its potential effect in preventing cancer has been described in human;[67,68] however, no clinical investigation on patients with SCI was detected so it is considerable that most of side effects of this medication are not yet known and more citations are needed to recommend this drug in clinical practices in spinal cord injured individuals.

TMP is the main ingredient of a Chinese herb called *Ligusticum wallichii* Franchat (Chuan Xiong) which has been shown to protect tissues from ischemic/reperfusion injuries.[69,70] One of the involved pathways in reducing apoptosis is exerted through the regulation of Bcl-2 and Bax expression.[39] Other proposed mechanisms are: down-regulation of nitric oxide production,[64] blockage of H_2O_2-induced apoptosis,[39] increased transcription of thioredoxin,[70] suppression of glutamate level,[32] inhibition of NF-κB activation in the ischemic tissue,[32] decreased spinal cord malondialdehyde levels,[34] reduced apoptotic cell death through Bcl-2 up-regulation,[34] and scavenging oxygen free radicals.[71] All these mechanisms provide a strong neuroprotection benefit of using this medication. Although its effect in investigations by Fan L *et al.*, Xio Z *et al.*, and Shen *et al.* was statistically significant, it was weaker than IL-10 efficacy. Moreover, it seems that TMP is more effective in SCIs with the underlying mechanism of ischemic/reperfusion damage. In fact, the mechanism of trauma influences on the outcomes of administration of this medication. Plus, it is known that some biochemical pathways are common as it has been reported that TMP up-regulates endogenous IL-10 and both act as inhibitors of NF-κB. It has also been demonstrated that TMP scavenges superoxide anion dose-dependently,

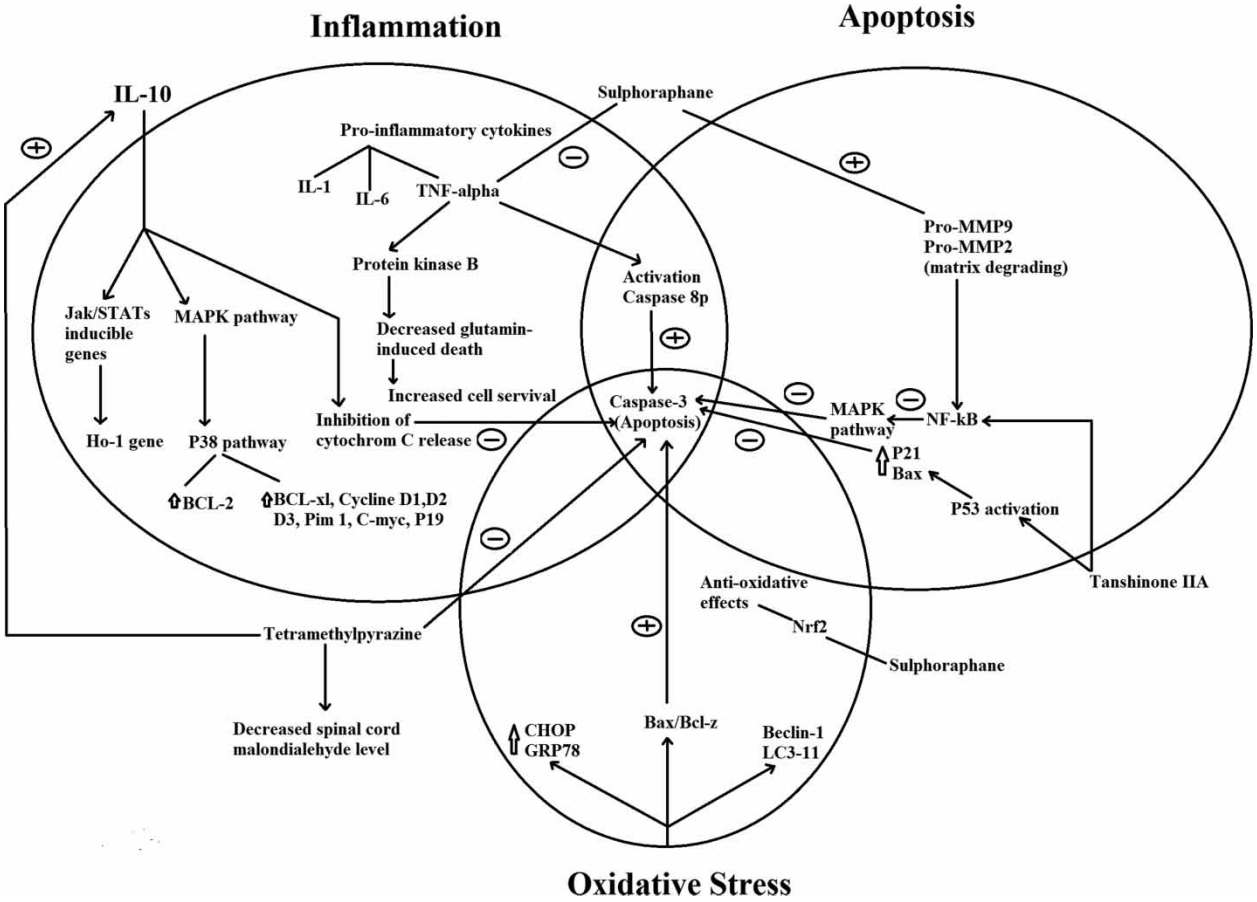

Figure 3 Proposed pathways in which effects of IL-10, sulforaphane, TIIA, and TMP are mediated through.

decreases the production of nitric oxide in human leukocytes[72] and its antiplatelet activity in human has been described as well[73]; however, it seems that although TMP is an effective agent with multiple functions on different human cells, its neuroprotective effect is still weaker than IL-10.

There are complex pathways among inflammatory, apoptotic, and oxidative pathways. It seems that all these medications (IL-10, sulforaphane, TIIA, and TMP) inhibit caspase 3 and subsequently prevent cell apoptosis (Fig. 3). Although the mechanisms of these medications' functions are different, it seems that caspase 3 is the common agent among their pathways. Fig. 3 shows that caspase 3 (which is an apoptotic agent) is inhibited by all these drugs. Although these medications have different efficacy and power, some parts of their function may overlap with each other through inhibition of caspase 3.

Conclusion

IL-10 has a strong effect in the induction of neuroprotection and neurorecovery after SCI by multiple pathways. TMP has an acceptable influence on inflammation reduction through up-regulation of IL-10. The results on sulforaphane and TIIA are acceptable but still weaker than IL-10.

Disclaimer statements

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Ethics approval None.

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