Medicinal plants in traumatic brain injury: neuroprotective mechanism(s)

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Running head: Medicinal plants and traumatic brain injury

Compliance with Ethical Standards:

Funding: Because this article is review article, thus there is no fund resource.

Conflict of Interest: both of authors don’t have any conflict of interest

Ethical approval: the kind of this article is reviewing other articles. Thus we don’t need ethical approval.

This is the peer reviewed version of the following article: Keshavarzi, Z, Shakeri, F, Barreto, GE, Bibak, B, Sathyapalan, T, Sahebkar, A. Medicinal plants in traumatic brain injury: Neuroprotective mechanisms revisited. BioFactors. 2019; 45: 517- 535, which has been published in final form at https://doi.org/10.1002/biof.1516. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.
Abstract:

Traumatic brain injury (TBI) is the most prevalent health problem affecting all age groups, and leads to many secondary problems in the other organs especially kidneys, gastrointestinal tract and heart function. In this review, the search terms were traumatic brain injury (TBI), fluid percussion injury (FPI), cold injury (CI), weight drop–impact acceleration injury (WDIAI), lateral fluid percussion (LFP), ortical impact injury (CCI) and blast injury. Studies with Actaea racemosa, Artemisia annua, Aframomum melegueta, Carthamus tinctorius, Cinnamomum zeylanicum, Crocus sativus, Cnidium monnierii, Curcuma longa, Gastrodia elata, Malva sylvesteri, Da Chuanxiong Formula, Erigeron breviscapus, Panax ginseng, Salvia tomentosa, Satureja khuzistanica, Nigella sativa, Drynaria fortune, Dracaena cochinchinensis, Polygoni Cuspidati, Rosmarinus officinalis, Rheum tanguticum, Centella asiatica and Curcuma zedoaria, show significant decrease in neuronal injury by different mechanisms such as increasing superoxide dismutase (SOD) and catalase (CAT) activities, suppressing nuclear factor kappa B (NF-κB), IL-1, glial fibrillary acidic protein (GFAP) and IL-6 expression. The aim of this study was to evaluate the neuroprotective effects of medicinal plants in central nervous system (CNS) pathologies by reviewing the available literature.

Keywords: TBI, medicinal plants, rat, possible mechanisms
1. Introduction

One of the major cause of morbidity and mortality in both developed and developing countries is traumatic brain injury (TBI) especially people under the age of 45 years. TBI attributes to approximately 10 million deaths and/or hospitalizations annually. Biomechanical and neurochemical damage following TBI, usually leads to a deficit in behavioral, cognitive, neuropsychiatric, and physical functions (1, 2).

Systemic insults of TBI include both hypoxia and hypotension mechanistically. In addition, acute cell death and delayed apoptosis have a relative contribution. Mechanisms of cell damage in TBI include free radical production, excitotoxicity, oxidative stress, inflammation and apoptosis. Genetic factors are also associated to the pathophysiology of TBI. In addition, myelin and multifocal axonal abnormalities are also attributed to posttraumatic cognitive impairments (3-6).

Various aspects of human TBI have been studied in a variety of animal models over the decades to have a better understanding of the pathophysiology and potential treatments. These models of TBI include cortical impact injury (CCI), fluid percussion injury (FPI), blast injury and weight drop–impact acceleration injury (Table 1), (7).

Various traditional supplements and herbal medicine therapies for TBI have been developed recently. These include both crude extracts and isolated compounds from plants and has shown to have neuroprotective effects due to their antioxidant and anti-inflammatory action on nerve function. The medicinal plants included in this review are *Aframomum melegueta*, *Carthamus tinctorius*, *Cinnamomum zeylanicum*, *Crocus sativus*, *Da Chuanxiong Formula*, *Erigeron breviscapus*, *Panax ginseng*, *Salvia tomentosa*, *Nigella sativa*, *Dracaena cochinchinensis*, *Polygoni Cuspidati*, *Rosmarinus officinalis*, *Centella asiatica*, *Curcuma zedoaria*. To date, there
are no reviews about the neuroprotective function of medicinal plants in TBI. In view of increasing number of studies conducted in the recent years, we reviewed the literature to assess the potential neuroprotective role of herbal plants in TBI including active components, experimental methodologies and mechanisms of action.

2. Method

Online literature resources were searched using search engines such as ISI Web of Knowledge, Pub Med, Medline, Scopus and Google Scholar from 1976 to August 2018 to identify studies, editorials, and reviews about the effect of medicinal plants on TBI and their possible mechanisms. We used appropriate keywords such as traumatic brain injury (TBI), medicinal plants, fluid percussion injury (FPI), cold injury (CI), cortical impact injury (CCI), lateral fluid percussion (LFP), weight drop–impact acceleration injury (WDIAI), and blast injury. All of these keywords were searched for each of these plants and its constituents.

3. Results

3.1. *Actaea racemosa*

*Actaea racemosa* (*A. racemosa*) commonly called black cohosh, is a perennial rhizomatous forest herb with white to yellow flowers, belonging to the Ranunculaceae. The chemical constituents of *A. racemosa* are caffeic acid, ferulic acid, phenylpropanoids, triterpenoids, cimigenol and formononetin (8). This plant has been shown to have several therapeutic effects including anti-inflammatory (9), antioxidant (10), antidepressant (11) and immunomodulatory (12) effects.

The effect of formononetin orally was evaluated for 7 days after the induction TBI by WDIAI model in rat. There was a significant improvement in neurological severity score (NSS) and increased cortical neuronal numbers in Nissl-special and DAPI-labeled stains with formononetin.
Formononetin also reduced the levels of IL-6 and TNF-alpha and increased the IL-10 levels in serum and cerebral cortex (13). In another study, intra-peritoneal injection of formononetin for 5 days after the induction TBI by WDIAI model in rat showed formononetin improved NSS, reduced brain edema and inhibited the neuronal apoptosis. Additionally, formononetin up-regulated the expression of microRNA-155 (miR-155) and haeme oxygenase 1 (HO-1) and down-regulated the expression of BACH1 in the brain tissue of TBI rats (14).

3.2. *Aframomum melegueta*

*Aframomum melegueta* (*A. melegueta*), commonly known as grains of paradise, ossame, alligator pepper, Melegueta pepper, fom wisa, Guinea grains, or Guinea pepper, is a flowering plant belonging to the family Zingiberaceae. It has been used traditionally in African folk medicine to treat several conditions including stomach ache, diarrhea, hypertension and is also used as a purgative, galactogogue, anthelmintic, and hemostatic agent (15). The main components of this plant include cardiac glycosides, alkaloids, sterols, tannins, triterpenes, flavonoids, and oils (16). This plant also has various pharmacological effects including antimicrobial (17), anti-ulcer and cytoprotective (18), antioxidant (19), antidiabetic (20), antifungal (21) and antihypertensive (22) activities actions.

*A. melegueta* seeds possess significant anti-inflammatory and anti-nociception activity. The anti-nociceptive activity of this plant has been investigated using the Randall–Selitto paw pressure, formalin-induced paw edema, and hot plate models of nociception. This plant extract showed anti-inflammatory effect with the formalin test, and reduced response to nociceptive stimuli evoked by squeezing of the inflamed hind paw of rats (23). *A. melegueta* seeds’ ethanolic extract and pure compounds of its including [6]-paradol, [6]-shogaol, [6]-gingerol have been studied in vitro on pro-inflammatory gene expression and inflammatory enzymes such as lipoxygenases
(LOX) and cyclooxygenase-2 (COX-2) and they are found to have an anti-inflammatory effect (24). Aqueous seed extract of *A. melegueta* (50–200 mg/kg, i.p.) have been investigated in vivo by formaldehyde and nystatin induced sub-chronic inflammatory conditions in rats and is found to have an anti-inflammatory effect (25).

The effect of hydroethanolic extract of *A. melegueta* seed on male rat was evaluated in FPI model of TBI. Eleven days after injury, rats were sacrificed and their brains were collected for assessment of microglial activation. Immunohistochemical analysis of injured rat brain sections using an antibody to CD11b (a marker of activated microglia) showed that this extract reduced microglial activation in the rat cortex and hippocampus. It also showed that the administration of *A. melegueta* extract after injury reduced the number of Fluoro-Jade (a marker for neuronal injury) positive neurons in the CA1/2 and CA3 regions on the hippocampus of ipsilateral side (26).

### 3.3. Allium sativum

*Allium sativum* (*A. sativum*) or garlic, is a bulbous plant belonging to the Amaryllidaceae family. In Ayurvedic medicine, this is used to treat respiratory conditions, dyspepsia, colic and flatulence (27). This plant is also shown to have anti-nociceptive (28), anticonvulsant (29), anti-inflammatory, immunomodulatory (30) and antioxidant (31) properties.

The effect of allicin (an organosulfur compound obtained from garlic), on CCI model of TBI showed that allicin reduced contusion volume and water content of brain, neurological deficit scores, Bcl-2/Bax ratio, MDA, protein carbonyl, TNF-α and IL-1β levels. It increased the activities of CAT, SOD and GST levels of IL-10 and transforming growth factor beta 1 (TGF-β1). It also activated Akt and endothelial nitric oxide synthase (eNOS) as well as inhibited the activation of caspase-3 and PARP (32).
3.4. *Artemisia annua*

*Artemisia annua* (*A. annua*), or sweet wormwood, is an annual, aromatic herb, belonging to the Asteraceae and has been used in China to treat fevers for centuries (33). It is often used in the Tropics as an affordable and effective anti-malarial (34). Leaves of *A. annua* has been used as antiseptic, digestive and febrifuge (35, 36). A leaf infusion of this plant is used as a remedy for colds, fevers and diarrhea (35, 37). The main ingredients of the essential oil of *A. annua* are β-pinene, alpha-pinene, camphor, camphene, 1,8-cineole, artemisia ketone, myrcene, borneol, linalool and β-caryophyllene (38). The pharmacological effects of *A. annua* include its anti-malarial (39), antioxidant, anti-inflammatory, antimicrobial (40), immunomodulatory (41) and anti-cancer properties (42). A variety of compounds have been isolated from *A. annua* such as coumarins, flavonoids, sesquiterpenoids, triterpenoids, phenolics, and artemisinin (43).

The effect of atesunate, a more stable derivative of its precursor artemisinin, on CCI model of TBI showed that atesunate reduced tissue damage and inflammation in histological studies. Additionally, it reduced the expression of brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), glial cell line-derived neurotrophic factor (GDNF) and inflammasomes components (NLRP3, ASC and Caspase-1) as well as Il-1β, TNF-α and iNOS levels (44).

3.5. *Carthamus tinctorius*

*Carthamus tinctorius* (*C. tinctorius*), also known as Safflower, is a thistle-like annual plant with yellow, orange, or red flowers, belonging to the Compositae or Asteraceae family, cultivated mainly for its seed, which is used as edible oil and as birdseed. Traditionally, the crop was grown for its flowers, used for colouring and flavouring foods and making dyes, and in medicines (45). Several pharmacological effects have been described for *C. tinctorius* such as its anti-
inflammatory (46), cardioprotective (47), antioxidant and neuroprotective (48) and anticancer (49). The standardized safflower flavonoid extract (SAFE), (35 and 70 mg/kg, p.o.) and the compounds isolated from safflower including kaempferol 3-O-rutinoside (K3R), anhydrosafflor yellow B (AYB), (50, 100 and 200 μM) were evaluated for their neuroprotective effects in vitro and in vivo using PD models employing 6-hydroxydopamine (6-OHDA)-lesioning in rats and rotenone-induced damage to differentiated PC12 cells, respectively. The results showed that K3R and AYB inhibited microtubule destabilization and decreased cell area and SAFE improved behavioural performances, partially via the suppression of α-synuclein overexpression or aggregation, as well as the suppression of reactive astrogliosis (50). However, some studies were reported the toxic effect of *C. tinctorius* on renal and brain tissue (51). *C. tinctorius* extract has been shown to reduce the cerebral infarction area and neurological deficits as well as expression of TNF-α and IL-1β in ischemia–reperfusion (I/R) brain injury in rats (52).

The effect of hydroxysafflor yellow A (HSYA), a constituent of the flower petals of *Carthamus tinctorius*, on CCI model of TBI showed that HSYA increased the activities of superoxide dismutase (SOD) and catalase (CAT), the level of glutathione (GSH) and the GSH/glutathione disulfide (GSSG) ratio and decreased the levels of malondialdehyde (MDA) and GSSG (53).

### 3.6. *Cinnamomum zeylanicum*

*Cinnamomum zeylanicum* (*C. zeylanicum*) is commonly known as cinnamon, from the Lauraceae family. The major components of the essential oil of *C. zeylanicum* are trans-cinnamaldehyde, eugenol, linalool (54). *C. zeylanicum* is used as part of Ayurvedic medicine as a remedy for a variety of digestive, respiratory and gynaecological symptoms (55). Various pharmacological effects of cinnamon have been reported including antibacterial (56), antifungal (57), antioxidant (58), anti-diabetic (59), anti-inflammatory (60) and immunomodulatory (61) effects.
administered orally in experimental allergic encephalomyelitis in mice, cinnamon powder suppressed the expression of iNOS and IL-1β \textit{in vivo} in the spinal cord and cerebellum suggesting anti-inflammatory effects (62). In addition, cinnamon suppressed neuronal apoptosis, inhibition of glial activation, and reduced amyloid beta in the hippocampus and protected memory as well as learning in an animal model of Alzheimer’s disease (63). In an animal model of Parkinson’s disease, it also protected the nigrostriatum, normalised striatal neurotransmitters, and improved motor functions (64).

Effect cinnamon polyphenol extract on CI model of TBI in mice showed that extract reduced infarct and edema formation in the brain by suppressing the expression of nuclear factor kappa B (NF-κB), IL-1, IL-6, glial fibrillary acidic protein (GFAP), neuronal cell adhesion molecule (NCAM) and nuclear factor erythroid 2-related factor 2 (Nrf2) in brain (65).

3.7. \textit{Cnidium monnieri}

\textit{Cnidium monnieri} (\textit{C. monnieri}), belongs to the Apiaceae family and is one of the most widely used traditional herbal medicine especially it fruits (66). The main components of \textit{C. monnieri} are osthole, bergapten, isopimpinellin, xanthotoxol, xanthotoxin, sesquiterpenes, cnidimonal, cnidimarin, imperatorin and glucosides (66). The pharmacological effects of \textit{C. monnieri} include its anticonvulsant (67), memory improvement (68), anti-inflammatory and immunomodulatory (69) activities.

Administration of osthole a coumarin compound isolated from \textit{C. monnieri} intraperitoneally, 30 min before TBI, reduced neurological deficits, cerebral edema and hippocampal neuron loss, It also increased SOD activity, GSH and MDA levels, the ratio of Bcl-2/Bax, the expression of active caspase-3 and the number of apoptotic cells in the WDIAI induced TBI in rat (70).
3.8. **Crocus sativus**

*Crocus sativus* (*C. sativus*), or saffron, is a perennial stemless herb belonging to the Iridaceae family. The main components of *C. sativus* are crocin, safranal, isophorone, crocetin, picrocrocin, glycosidic terpenoids and ketoisophorone (71). *C. sativus* has also been used in traditional medicine for its eufepctic, antispasmodic, anti-catarrhal, gingival and nerve-sedating agent. It has also used as an expectorant, diaphoretic, aphrodisiac, emmenagogue and carminative (72). It has various pharmacological effects including anti-inflammatory, antioxidant, and immunomodulatory (73), anxiolytic and hypnotic (74), anticonvulsant (75) and anti-Alzheimer (76) activities.

In a rat model of stroke, administration of crocin during induction of ischemia, showed protective effect against ischemia/reperfusion injury and cerebral edema. It also decreased brain edema and infarct volume (77). In addition, administration of crocin before TBI, activated the Notch signaling pathway by up-regulation Notch intracellular domain (NICD) and bHLH transcription factor 1 (HES1) mRNA. In CCI induced TBI in mice, it also reduced microglial activation, cell apoptosis and release of IL-1β and TNF-α as well as improved brain edema and neurological severity score (NSS) (78).

3.9. **Da Chuanxiong Formula**

*Da Chuanxiong Formula* (DCXF) in Chinese traditional medicine consists of two dried rhizomes of *Ligusticum chuanxiong* and *Gastrodia elata* with the ratio of 4:1 (w/w) (79). Studies have shown that DCXF possesses therapeutic effect on stroke, dementia, vertigo, headache and which is mediated by improvement of blood vessel elasticity and cerebral blood supply, reduction of blood brain barrier (BBB) disruption, intracellular free calcium concentration and edema formation. It also inhibits inflammation and nerve cell apoptosis (80). In LPS-incited RAW 264.7
cells, DCXF inhibited the productions of NO and PGE2 by suppressing COX-2 and iNOS expressions (79).

Treatment with DCXF aqueous extract one week before and 11 days after the induction TBI by CCI model in rat improved the learning ability, memory retention and proliferation of neural stem cells (NSCs). Results also showed that DCXF reduced astrocyte and microglia activation, BBB permeability, brain edema and neuronal loss in the brain with TBI (81).

3.10. *Erigeron breviscapus*

*Erigeron breviscapus* (*E. breviscapus*) known as “Dengzhanxixin”, belonging to the Asteraceae, is a plant species endemic to southwestern China. It has been used in traditional Chinese medicine for various conditions including digestive disorders, heart disease, cerebral infarction and apoplexy (82). The chemical constituents of *E. breviscapus* are flavonoids, triterpenes, caffeoylic derivatives and steroids (83). It has shown to have antifungal, antimicrobial, antioxidant (85), anti-inflammatory (86) activities.

Injection 75 μg breviscapine (a flavonoid extracted from the *E. breviscapus*) via the right lateral ventricle after induction of TBI by CCI model remarkably improved NSS score and reduced expression of IL-6 in the injured cortex and IL-6-positive cell number in injured brain tissue (87).

3.11. *Gastrodia elata*

*Gastrodia elata* (*G. elata*), is a saprophytic perennial herb from Orchidaceae family. The dried rhizome of *G. elata* is used as a traditional Chinese medicine for remedy neurological disorders such as alzheimer, general paralysis, headache, convulsions, vertigo, stroke and tetanus (88). The main components with neuropharmacological properties are 4-hydroxybenzaldehyde (4-HBA), gastrodin, vanillin, and vanillyl alcohol (89). It has shown to have various pharmacological
effects including antimicrobial (90), anti-mutagenic (91) anti-oxidative (92) and anti-inflammatory (93) properties.

The effects of *G. elata* aqueous extract on CCI model of TBI in rat showed that *G. elata* improved locomotor functions in rotarod test and reduced the number of astrocyte in immunohistochemical staining and the expression of IL-6 and TNF-α in the brain tissue (94).

### 3.12. Malva sylvestris

*Malva sylvestris* (*M. sylvestris*), or common mallow, belongs to the Malvaceae family. The main components of *M. sylvestris* are polysaccharides malvin, flavonoids, scopoletin, coumarins, polyphenols, niacin, folic acid, tannins and vitamin A, C and E (95). *M. sylvestris* is used as bacteriostatic, anti-nociceptive anti-inflammatory, antioxidant and anticholinesterase agent in Chinese medicine (96).

The preventive effect of *M. sylvestris* methanolic extract orally on TBI induced CCI model in rat showed improved cognitive function in MVM test and reduced neuronal loss and GFAP positive cells in hippocampus. Additionally, it also increased levels of SOD and decreased ROS production as well as LPO, IL-1β, IL-6, and TNF-α levels in the brain tissue (96).

### 3.13. Panax ginseng

*Panax ginseng* (*P. ginseng*) is a perennial herb from Araliaceae family, native to Korea and China. Ginseng, the root of *P. ginseng* has been traditionally used as an herbal remedy (97). The main components of ginseng are ginseng oils, phytosterol, saponins, organic acids, nitrogenous substances, enzymes, vitamins and minerals (98). Its shown to have antimicrobial (99), antifungal (100), antioxidant (101), antiviral (102), anti-inflammatory and antifatigue (103) and anti-asthmatic activities (104).
Oral administration of ginsenoside Rb1, which is the main bioactive components in ginseng significantly increased cell survival in the dentate gyrus (DG) and hippocampus which could be potentially related to its effects on memory and learning (105). In addition, ginsenoside Rg down regulated calpain I and caspase-3 and attenuated neuronal apoptosis induced by cerebral ischemia-reperfusion injury (106).

Oral administration of *P. ginseng* aqueous extract on WDIAI model of TBI in rat improved neurological functions. In addition, *P. ginseng* reduced levels of MDA, nitrite, acetylcholinesterase (AChE), TNF-a and IL-6 and increased GSH, SOD and catalase in hippocampus and cerebral cortex (107).

The major ingredient of *P. ginseng*, ginseng total saponins (GTS) is shown to have neuroprotective effects against TBI. GTS when administered intraperitoneally significantly reduced neuronal loss in hippocampal regions of CA1, CA2, and CA3, contusion volume and percentage of contusion, as well as improved neurological deficits on TBI induced CCI model in rat (108).

In a similar study assess preventive effect of GTS on TBI induced CCI model in rat showed treatment with GTS after induction of TBI improved NSS score and reduced brain water content, neuronal loss in the hippocampus. It increased the activity of SOD, down-regulated IL-1β, IL-6, and TNF-α and upregulated IL-10. It also inhibited the apoptotic cell death and expression of caspase-3, bax and Bcl-2 (109). Similarly, the effect of administration of GTS on CI model of TBI rats was showed improved recovery of neurological functions, including learning and memory and reduced cell loss in the hippocampus (110).

In another study GTS improved NSS score, increased SOD activity and reduced brain water content, level of MDA and expression of IL-1β and TNF-α (111). In addition, administration of
GTS after induction of TBI improved neurological function and histological morphology of brain tissue in rats (112).


*Rheum tanguticum* (*R. tanguticum*), also known as rhubarb in Chinese, belongs to the Polygonaceae family. Traditionally, the roots and rhizomes of *R. tanguticum* have been used as a poultice for their antispasmodic, antineoplastic, antibacterial and antipyretic properties and also to reduce obesity, lipid and blood pressure, (113).

The effect of rhubarb aqueous extract (3, 6 and 12 mg/kg, p.o.) was evaluated after the induction of TBI by CCI model in rat. Rhubarb significantly ameliorated brain edema and BBB injury, increased SOD, CAT activities, GSH level and GSH/GSSG ratio. It also decreased the levels of MDA and GSSG. Rhubarb also prevented gp91^{phox} subunit of NADPH oxidase activation induced ROS production. Additionally, it inhibited ERK/MMP-9 pathway both in vivo and in vitro as well as downregulated GFAP in vitro (114, 115). Oral administration of polysaccharide extracted from *R. tanguticum* (RTP) for 5 days exhibited marked protective effects on oxidative stress and brain edema on WDIAI model of TBI in rats by reduction water content and MDA levels. It also resulted in enhancement SOD and Na+-K+ ATPase activity after injury (116).

3.15. *Salvia tomentosa*

*Salvia tomentosa* (*S. tomentosa*), belongs to the Lamiaceae family. It has used in traditional Chinese medicine to manage various conditions including stomatitis, glossitis, gingivitis, pharyngitis, flatulent dyspepsia, galactorrhea and hyperhydrosis (117). The major components of the essential oil from *S. tomentosa* includes β-pinene, α-pinene, trans-pinocarveol, myrtenol, caryophyllene oxide and d-camphor (118). The reported effects of this herb include antioxidant (119), antibacterial (120) and anticancer (121) activities.
The effect of luteolin which is a flavone isolated from the aromatic flowering plant of *S. tomentosa* on CCI model of TBI in mice showed that it significantly reduced levels of TNFα and IL-1β in blood and brain tissue of mice (122).

### 3.16. *Nigella sativa*

*Nigella sativa* (*N. sativa*), is a grassy plant from the Ranunculaceae family which grows in cold and temperate climates. The seeds of *N. sativa* contain thymoquinone and monoterpenes including p-cymene, a-pinene (123), nigellidine (124), nigellimine (125) and a saponin (126). The seeds have different pharmacological effects including anti-asthmatic, anti-dyspnea (127), anti-nociceptive, anti-diabetes, antihypertensive (128), anti-inflammatory, immunomodulatory (129), anticonvulsant (130), anxiolytic (131) and anti-nociceptive effects (132).

It has been shown that *N. sativa* improved neurological functions and reduced the infarct volume in middle cerebral artery-occluded rats (133). Treatment with thymoquinone (TQ) orally for one week after the induction TBI by WDIAI model in mice reduced activity of lactate dehydrogenase (LDH) and plasma copeptin level in the brain tissue (134).

### 3.17. *Dracaena cochinchinensis*

*Dracaena cochinchinensis* (*D. cochinchinensis*), belongs to the Asparagaceae family and is widely cultivated in different provinces of China. The main components of *D. cochinchinensis* are flavonoids, terpenes, steroids, saponins and phenols (135). Resina Draconis (RD) which is a resin obtained from *D. cochinchinensis*, is a popular traditional Chinese medicine widely used for the management of various conditions including cerebral arterial thrombosis, ischemic heart disease (136), trauma and allergic dermatitis (137, 138). Several therapeutic effects for RD has been described including its anti-tumor (139), anti-diabetes (140), analgesic, anti-inflammatory (141) and immunomodulatory (142) activities.
Administration RD aqueous extract intra-peritoneally for 5 days after the induction TBI by WDIAI model in rat reduced serum levels of MDA, IL-1β, TNF-α and IL-6. It also reduced the amount of neuronal cell apoptosis in brain tissue as well as increased the serum SOD activity (143).

3.18. *Polygoni Cuspidati*

*Polygoni Cuspidati* (*P. Cuspidati*), also known as Hu Zhang in Chinese belongs to the Polygonaceae family. It has been used as a traditional Chinese medicine for the management of inflammatory conditions, infections, jaundice, skin burns and hyperlipidemia (144). The reported therapeutic effects include anti-inflammatory (145), analgesic, antibacterial, antiviral analgesic (146), immunomodulatory (147), and anticancer (148) activities. The major compounds of *P. cuspidati* are polydatin, resveratrol, torachryson-8-O-glucoside, and emodin (149).

The effect of oral administration of emodin after the induction TBI by WDIAI model in rat significantly ameliorated brain edema after TBI, improved neurological severity score (NSS) and reduced BBB permeability. Emodin also inhibited the expression of aquaporins (AQP1, AQP4 and AQP9), hypoxia-inducible factor-1α and matrix metalloprotein-9 (150). Injection of resveratrol intraperitoneally after induction of TBI by WDIAI model remarkably improved NSS and reduced escape latency in MVM, brain edema and levels of the autophagy marker proteins (151).

3.19. *Rosmarinus officinalis*

*Rosmarinus officinalis* (*R. officinalis*), known as rosemary, belongs to the Lamiaceae family. It has been shown to have different therapeutic effects including antibacterial (Huhtanen, 1980), anti-nociceptive, anti-inflammatory (Takaki et al., 2008), antioxidant (Inatani et al., 1983) and vascular smooth muscle relaxant properties (Aqel, 1992b). The main constituents of the essential
oil of *R. officinalis* are gamma-terpinene, p-cymene, linalool, eucalyptol, thymol, alpha-pinene and beta-pinene (152).

The neuroprotective effects of *R. officinalis* in the transient model of focal cerebral ischemia have shown to be related to its ability to decrease sub-cortical and cortical infarct volumes, NSS, cerebral edema and BBB permeability (153). Oral administration of *R. officinalis* after induction of TBI by LFP model reduced the latency to find platform and increased time spent in target quadrant in MWM. Additionally, it reduced neuronal degeneration and glial fibrillary acidic protein (GFAP)-positive cells. It also reduced the levels of TNF-α, IL-1β and IL-6 in hippocampus and increased activity of glutathione peroxidase (GPx), SOD and CAT (154).

### 3.20. *Centella asiatica*

*Centella asiatica* (*C. asiatica*), is a perennial plant belonging to the Umbelliferae family (155). The main components of *C. asiatica* are saponins, brahmoside, brahminoside, glycosides isothankuniside, hankuniside, sterols and flavonoids (156). This plant has been shown to have several pharmacological effects including anti-inflammatory (157), wound healing (158), sedative, anxiolytic (159), antidepressant (160), anticonvulsant (161) and antioxidant (162) activities.

*C. asiatica* when administered orally improved memory and learning flexibility deficits and ameliorated neuronal damage in the dorsal hippocampus when mild chronic cerebral hypoperfusion was induced by right common carotid artery occlusion in rats (163). It has also been shown after the induction TBI by WDIAI model in rat, administration of *C. asiatica* hydroethanolic extract intra-peritoneally increased the activation of Krox-20, the expression of neuregulin-1 (NRG-1) and the distribution of phospholipids and improved neurological functions (164).
3.21. *Curcuma longa*

*Curcuma longa* (*C. longa*), commonly known as turmeric belongs to the family of Zingiberaceae. It’s applied in Ayurvedic medicine for treatment of inflammatory diseases for a long time. This plant has been shown several therapeutic actions including anti-asthmatic (165), oxidant (166), immunomodulatory and anti-inflammatory (167) activities.

The effect of curcumin when evaluated after the induction TBI by FPI model in rat showed that it improved the memory retention and learning ability in MVM test, reduced oxidative stress, increased BDNF levels, as well as, protected synaptic proteins and mitochondria (168-171). Treatment with curcumin intra-peritoneally before the induction TBI by WDIAI model in rat reduced the cerebral damage and brain levels of MDA. It also improved various neurological functions in the rotarod and inclined-plane test (172). In addition, administration of curcumin before TBI and 30 min after TBI, reduced cerebral edema, AQP4 expression within the pericontusional cortex, NF-κB activation and IL-1β expression. It also improved neurological function in rotarod and open-field test in the CCI induced TBI in mice (173). In a similar study assessing the preventive effect of curcumin after the induction TBI by WDIAI model in mice showed that curcumin reduced TNF-α, MCP-1, IL-1β, IL-6, and RANTES (regulated on activation, normal T cell expressed and secreted), TLR4 expression, neuronal and apoptotic cell death. It also reduced microglial activation and improved NSS (174).

3.22. *Curcuma zedoaria*

*Curcuma zedoaria* (*C. zedoaria*), known as zedoary and white turmeric belongs to the Zingiberaceae family. The main ingredients of the essential oil of *C. zedoaria* are curzerenone, germacrone, curdione, 1,8-cineole, cumene, a-phellandrene, β-turmerone, β-elemene, 1,8-cineole
and zingiberene (175). Different therapeutic effects including anti-peptic ulcer (176), anti-inflammatory, antinociceptive (177), antioxidant (178) and anticancer (179).

The effect of curdione after the induction middle cerebral artery occlusion surgery by cerebral ischemia–reperfusion model in rat showed curdione reduced the NSS and infarct size. It also improved cognitive function and neuronal morphologic damages. In addition, it decreased MDA content and enhanced the activities of GSH-PX, CAT and SOD (180). Treatment with β-elemene after the induction TBI by WDIAI model in rat was improved NSS, reduced TNF-α, IL-1β, apoptosis index and expression of Toll-like receptor (TLR4) and casepase 3. It also increased the expression of IkB (inhibitor of kB) (181).

3.23. **Salvia Militorrhiza**

*Salvia Militorrhiza (S. Militorrhiza)*, commonly known as red sage or Chinese sage belongs to the Lamiaceae family. It is used in traditional medicine for prevention and treatment of various cardiovascular diseases such as stroke and myocardial infarction (182). The chemical composition of *S. Militorrhiza* are tanshinone I, tanshinone IIA, salvianolic acid (or salvianolic acid B) and dihydrotanshinone (183).

Injection of salvianolic acid B (SalB) intra-peritoneally after the induction of TBI by CCI model remarkably reduced brain water content, lesion volume, Iba-1, (an activated microglia marker), IL-1β and TNF-α. It also increased TGF-β1 and IL-10 as well as improved neurological function in wire-grip and MVM test (184).

3.24. **Satureja khuzistanica**

*Satureja khuzistanica (S. khuzistanica)* or jamzad, is a herb belonging to the Lamiaceae family. The major constituents of *S. khuzistanica* are p-cymene, carvacrol, and γ-terpinene (185). In folk medicine, *S. khuzistanica* is used as an analgesic and antiseptic (186). Several therapeutic effects
for saffron including antidiarrhea and antispasmodic (187), anti-inflammatory, anti-nociceptive (188) and antioxidant (189) have been described.

It has been shown that after the induction TBI by WDIAI model in rat, administration of *S. khuzistanica* essential oil intra-peritonieally ameliorated veterinary coma scale (VCS) scores, damage to BBB and brain edema. There was a reduction in IL-6, IL-1β and TNF-α levels. There was also a reduction in intracranial pressure, BBB permeability and neuronal death and increased IL-10 level and numbers of viable astrocytes in the treated groups (190).

3.25. *Scutellaria baicalensis*

*Scutellaria baicalensis* (*S. baicalensis*), is a plant belonging to the Lamiacea family. *S. baicalensis* has been used in traditional medicine for managing various inflammatory conditions, hypertension and cardiovascular diseases (191).

Treatment with baicalin (a major bioactive compound of *S. baicalensis*) after the induction TBI by CCI model in rat model reduced the number of degenerating neurons in FJB staining, contusion volume of brain, mRNA and protein expression of IL-1β, IL-6 and TNF-α. It also improved neurological functions in rotarod, tactile adhesive removal and beam walk test (192).

3.26. *Drynaria fortune*

*Drynaria fortune* (*D. fortune*), or gu-sui-bu, is a fern of the Polypodiaceae family. *D. fortune* has been used in traditional medicine for the treatment of various bone conditions (193).

Effect of *Rhizoma drynariae* (*R. drynariae*) aqueous extract from the dried roots of *D. fortune* after the induction TBI by WDIAI model in rat showed *R. drynariae* significantly reduced the level of CD8 T cells without affecting the levels of IL-2 and CD4 cells (194). Administration of *R. drynariae* aqueous extract orally significantly reduced the brain lesion volume and blood levels of IL-6. It also ameliorated anxiety and depression-like behaviors, improved cognitive
function and NSS. In addition, in the CCI model of TBI in rats it increased blood monocyte numbers, IL-10 and the percentage of blood CD3 and CD4 T lymphocytes. It also inhibited macrophage and microglial activation (195).

**Molecular mechanisms underlying the neuroprotective effects on TBI**

It was shown the therapeutic effect of medicinal plants on TBI are mainly mediated by anti-inflammatory, anti-oxidant and immunomodulatory mechanisms. We have reviewed the main molecular mechanisms related to these effects in this section.

The protective effect of formononetin on neurobehavioral disorders after or before TBI may be associated with its inhibition of pro-inflammatory cytokines and oxidative stress as well as activation of Nrf2-dependent antioxidant pathways (13, 14). It has been shown hydroethanolic extract of *A. melegueta* on TBI normalized the genes that are implicated in the chemokine, cytokine, oxidative stress and NF-κB signaling pathways induced by TBI (26). Protective effect of allicin on TBI is potentially associated with its anti-oxidative and anti-inflammatory properties through Akt/eNOS pathway (32). The protective effects of artemesunate in TBI also occur through inhibition of pro-inflammatory cytokines and apoptosis process by reducing the Bax expression and increasing Bcl2 expression, as well as modulation of various neurotrophic factors (44).

When the antioxidant effect of *C. tinctorius* was studied, it was shown that HSYA by reduction of oxidant markers and enhancement antioxidant markers could be a potential neuroprotective medication in cases of TBI (53). In a CI model of TBI, it was shown that cinnamon could be play an important role in reducing of infarct and edema formation through modulation of Nfr2 and cytokine expression. It also reduce oxidative stress and could exert
neuroprotective activity through these mechanisms (65). The protective effect of osthole on TBI may be associated with its antiapoptotic and antioxidative activities (70).

Crocin has also shown to inhibit the production of the pro-inflammatory cytokines and suppresses Notch signaling activation (78). In a CCI model of TBI, it was shown that DCXF aqueous extract improved the proliferation of neural stem cells and reduced the BBB damage as well brain edema. It also alleviated the neuronal loss and improvement in neurological functions including learning, memory and motor abilities mainly through inhibition of inflammation process (81). The protective effect of breviscapine on neurobehavioral disorders after TBI may be associated with its mechanism of improving energy metabolism, free radical scavenging, inhibition of intracellular Ca$^{2+}$, overload, excitatory amino acid toxicity, inflammatory suppression, regulation of brain blood vessel activity, and suppression of IL-6 expression (87, 196, 197). The protective effect of *G. elata* on TBI could be associated to the reduction of proinflammatory cytokines, inflammation and astrocytes accumulation (94). Treatment with *M. sylvestris* prevented neurodegeneration after TBI by reducing astrogliosis, pro-inflammatory cytokines and oxidative stress in the brain tissue (96).

The potential therapeutic effects of *P. ginseng* could be due to inhibition of inflammatory mediators, reactive oxygen species (ROS) production and microglial activation (107). Ginsenosides has been shown to protect neurons from ischemic damage and rescue hippocampal neurons from ischemic damage by free radicals scavenging (108). GTS administration after TBI has been shown to reduce the secondary injury by reduction of oxidative and nitrative stress as well as attenuating the expression of proinflammatory cytokines and apoptotic cell death (109). The protective effect of GTS on neurobehavioral disorders after TBI was related to the regulation of nerve growth-related factors expression and improvement of neural stem/progenitor cells
proliferation (110). The underlying mechanisms of GTS on TBI induced modified Feeney's method could be potentially mediated through various mechanisms including reducing MDA level, expression of TNF-α and IL-1β, generation of reactive oxygen species (ROS), elevating the activity of SOD and inflammatory reactions (111). The *R. tanguticum* have been shown to have neuroprotective effects on TBI through by inhibiting oxidative stress (114-116).

The potential mechanism for protective effects of luteolin could be due to the inhibition of release of inflammatory cytokines (122). The possible mechanisms of TQ on TBI are by improving the redox balance, abating the inflammatory cytokines, and restoring the balance between apoptotic and anti-apoptotic factors (134).

Another study demonstrated the antioxidant and anti-inflammatory effects of *R. draconis* aqueous extract through its effect on SOD, MDA, IL-1β, TNF-α and IL-6 levels in TBI rat (143). It has been shown that emodin attenuated brain edema and BBB disruption after TBI, mediated via inhibition of HIF-1α/AQPs and HIF-1α/MMP-9 pathways (150). The protective effect of resveratrol was shown to have a protective effect on TBI by upregulation of post-synaptic density protein 95, synaptophysin and by suppressing neuronal autophagy (151).

*R. officinalis*, has shown to improve cognitive deficits in TBI by inhibiting inflammation and oxidative stress (154). *C. asiatica* extract has been shown to have a neuroprotective effect on TBI potentially by activation of Krox-20 gene thereby triggering the formation of new phospholipids in nerve cells (164). The proposed mechanism of curcumin on TBI includes inhibition of proinflammatory cytokines, oxidative stress, TLR4 and NF-κB pathway (168-174). β-elemene had a protective effect on TBI which is most likely mediated via reducing the caspase-3 enzyme activity, expression of TLR4 and inflammatory cytokines (181). The neuroprotective effect of
SalB against TBI was associated with its anti-inflammatory activities (184). *R. drynariae* has been shown to have a protective role in TBI-induced brain damage, potentially mediated by its immune-promoting, anti-inflammatory and neuroprotective effects (194, 195). In a WDIAI model of TBI, *S. khuzistanica* has been shown to play a crucial role in reducing edema formation and infarct through its anti-inflammatory action and by reducing neuronal loss (190). The neuroprotective effect of baicalein in TBI-induced brain injury could be potentially mediated via inhibition pro-inflammatory cytokines (192).

**Conclusion**

This review summarized the growing evidence on the protective effects of medicinal plants and their constituents on TBI. Although these studies were mostly conducted in animal models of TBI, potentially similar effects could be expected in human TBI patients. This shows that natural compounds have great therapeutic potential for reducing neurodegeneration and improving functional outcome in TBI patients. However, further studies are required to establish the clinical effects of medicinal plants and their extracts on TBI and their molecular mechanisms.
References


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121. Akhtar MS, Swamy MK. Anticancer Plants: Natural Products and Biotechnological Implements. Springer; 2018.


Table 1: The summary of animal models

<table>
<thead>
<tr>
<th>Animal model</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid percussion injury (FPI) models</td>
<td>The fluid pressure pulse insult is caused by a pendulum striking the piston of a reservoir of fluid to the intact dura through a craniotomy, which is made either centrally around the midline, or laterally over the parietal bone, between bregma and lambda. Brief displacement and deformation of brain tissue produce following the percussion, and the severity of injury depends on the strength of the pressure pulse.</td>
</tr>
<tr>
<td>Cortical impact injury (CCI) model</td>
<td>The exposed intact dura will be under effect of pneumatic or electromagnetic impact device to create a rigid impactor. This method can mimic cortical tissue loss, acute subdural hematoma, axonal injury, concussion, blood–brain barrier (BBB) dysfunction and even coma.</td>
</tr>
<tr>
<td>Penetrating ballistic-like brain injury (PBBI)</td>
<td>A temporary cavity in the brain is produced by transmission of projectiles with high energy and a leading shockwave. The projectile's anatomical path and degree of energy transfer can effect on the outcome in this model.</td>
</tr>
<tr>
<td>Weight drop models</td>
<td>After exposing the skull (with or without a craniotomy), a falling weight guided to it. Injury severity in these models can be altered by adjusting the mass of the weight and the height from which it falls. This model also divided to some subdivisions such as Feeney’s weight-drop model and Marmarou model.</td>
</tr>
</tbody>
</table>
### Table 2. Summary of studies reporting the effects of medicinal plants on TBI.

<table>
<thead>
<tr>
<th>Plant</th>
<th>Ext./Cons.</th>
<th>Dose</th>
<th>Exp. model</th>
<th>Effect</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>A. racemosa</em></td>
<td>Formononetin</td>
<td>10 and 30 mg/kg</td>
<td>WDIAI</td>
<td>Improved NSS score</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Formononetin</td>
<td>10 and 30 mg/kg</td>
<td>WDIAI</td>
<td>Improved NSS score</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased cortical neuronal numbers and IL-10</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Decreased IL-6 and TNF-α</td>
<td></td>
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<tr>
<td><em>A. melegueta</em> seed</td>
<td>AEE</td>
<td>10, 100, 250, 500 and 1000 mg/kg</td>
<td>FPI</td>
<td>Reduced neuronal injury and microglial activation</td>
<td>26</td>
</tr>
<tr>
<td><em>A. sativum</em></td>
<td>Allicin</td>
<td>1, 10 and 50 mg/kg</td>
<td>CCI</td>
<td>Reduced contusion volume, water content, Bcl-2/Bax ratio, MDA, protein carbonyl, TNF-α and IL-1β</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased CAT, SOD, GST, IL-10, TGF-β1, Akt and Enos</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inhibited the activation of caspase-3 and PARP</td>
<td></td>
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<tr>
<td><em>A. annua</em></td>
<td>Atesunate</td>
<td>30 mg/kg</td>
<td>CCI</td>
<td>Reduced tissue damage and inflammation, expression of IL-1β, TNF-α, iNOS, BDNF, VEGF, GDNF and inflammasomes components (NLRP3, ASC and Caspase-1)</td>
<td>44</td>
</tr>
<tr>
<td><em>C. tinctorius</em></td>
<td>HSYA</td>
<td>10 and 30 mg/kg</td>
<td>CCI</td>
<td>Increased the SOD, CAT, GSH and GSH/ GSSG ratio</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decreased the MDA and GSSG</td>
<td></td>
</tr>
<tr>
<td><em>C. zeylanicum</em></td>
<td>polyphenol E</td>
<td>10 mg/kg</td>
<td>CI</td>
<td>Reduced infarct and edema formation suppressing the expression of NF-κB, IL-1, IL-6, GFAP, NCAM and Nrf2</td>
<td>65</td>
</tr>
<tr>
<td><em>C. monnieri</em></td>
<td>Osthole</td>
<td>10, 20 and 40</td>
<td>WDIAI</td>
<td>Reduced neurological deficits, cerebral edema and</td>
<td>70</td>
</tr>
<tr>
<td>Plant</td>
<td>Compound</td>
<td>Dose</td>
<td>Treatment</td>
<td>Effects</td>
<td></td>
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<td>---------------</td>
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<td>-------------------------------------------------------------------------</td>
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<tr>
<td><em>C. sativus</em></td>
<td>Crocin</td>
<td>20 mg/kg</td>
<td>CCI</td>
<td>Activated the Notch signaling pathway, decreased microglial activation, cell apoptosis, and release of IL-1β and TNF-α, improved NSS and brain edema</td>
<td></td>
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<tr>
<td><em>DCXF</em></td>
<td>AE</td>
<td>520.6 and 2603.0 mg/kg</td>
<td>CCI</td>
<td>Improved behavioral tests, reduced BBB permeability, brain edema, microglial and astrocyte activation, and neurons loss</td>
<td></td>
</tr>
<tr>
<td><em>E. breviscapus</em></td>
<td>Breviscapine</td>
<td>75 μg</td>
<td>CCI</td>
<td>Improved NSS score, reduced expression of IL-6 in the injured cortex and IL-6-positive cell number in injured brain tissue</td>
<td></td>
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<tr>
<td><em>G. elata</em></td>
<td>AE</td>
<td>505 and 1515 mg/kg</td>
<td>CCI</td>
<td>Improved locomotor functions, reduced the number of astrocyte and the expression of IL-6 and TNF-α</td>
<td></td>
</tr>
<tr>
<td><em>P. ginseng</em></td>
<td>AE</td>
<td>50, 100 and 200 mg/kg</td>
<td>WDIA</td>
<td>Improved neurological deficits, reduced levels of MDA, nitrite, AChE, TNF-a and IL-6, increased GSH, SOD and CAT</td>
<td></td>
</tr>
<tr>
<td><em>GTS</em></td>
<td>(5, 10, 20, 40, 60 and 80 mg/kg, i.p.)</td>
<td>CCI</td>
<td>Improved NSS score, reduced brain water content, neuronal loss, levels of MDA, NOSs and NO, apoptotic cell death, expression of caspase-3, bax and Bcl-2, increased the activity of SOD</td>
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<tr>
<td>Compound</td>
<td>Dose</td>
<td>Treatment</td>
<td>Effect</td>
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<tr>
<td>GTS</td>
<td>(5, 10, 20, 40, 60) mg/kg, i.p.)</td>
<td>Improved NSS score</td>
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<tr>
<td></td>
<td>and 80 mg/kg, i.p.)</td>
<td>Increased the expression of NGF, GDNF and NCAM</td>
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<td></td>
<td>Inhibited the expression of Nogo-A, Nogo-B, TN-C, and the number of BrdU/nestin positive NSCs in the hippocampal formation</td>
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<tr>
<td>GTS</td>
<td>(10, 20, 40, 60) mg/kg, i.p.)</td>
<td>Improved neurological function and histological morphology of brain tissue</td>
<td></td>
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<tr>
<td>M. sylvestris</td>
<td>250 and 500 mg/kg</td>
<td>Improves cognitive function in MVM test</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Reduced neuronal loss, GFAP positive cells, ROS production and levels of LPO, IL-1β, IL-6, and TNF-α</td>
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<tr>
<td></td>
<td></td>
<td>Increased SOD level</td>
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</tr>
<tr>
<td>R. tanguticum</td>
<td>AE</td>
<td>3, 6 and 12 mg/kg</td>
<td>Ameliorated BBB damage and brain edema</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polysaccharide</td>
<td>100, 200 and 400 mg/kg</td>
<td>Reduced water content and MDA levels</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Increased SOD and Na+/K+ ATPase activity</td>
<td></td>
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<tr>
<td>S. tomentosa</td>
<td>Luteolin</td>
<td>20 mg/kg</td>
<td>Reduced levels of TNFα and IL-1β in blood and brain tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. sativa</td>
<td>TQ</td>
<td>10 mg/kg</td>
<td>Reduced activity of LDH and plasma copeptin level in brain tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. cochinchinensis</td>
<td>AE</td>
<td>40 and 80 mg/kg</td>
<td>Reduced serum levels of MDA, IL-1β, TNF-α and IL-6, and the amount of neuronal cell apoptosis in brain tissue</td>
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<tr>
<td></td>
<td></td>
<td>Increased serum SOD activity</td>
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<tr>
<td>P. cuspidati</td>
<td>Emodin</td>
<td>10 mg/kg</td>
<td>Improved NSS</td>
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<td></td>
<td></td>
<td>Reduced BBB permeability, ameliorated brain edema</td>
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</tbody>
</table>
Inhibited the expression of AQP-1, AQP-4 and AQP-9, HIF-1α and MMP-9

Resveratrol 100 mg/kg WDIAI Improved NSS
Reduced escape latency, brain edema, levels of the autophagic marker proteins, microtubule-associated protein light chain 3-II and Beclin1 in the hippocampus

*R. officinalis* AE 40, 80 and 160 mg/ml LFP Decreased latency to find platform, neuronal degeneration and GFAP-positive cells, ROS generation, levels of IL-1β, IL-6 and TNF-α
Increased time spent in target quadrant and activity of SOD, GPx and CAT

*C. asiatica* AEE 90 mg/kg WDIAI Increased the activation of Krox-20, the expression of NRG-1, and the distribution of phospholipids
Improved neurological deficits

*C. longa* Curcumin 500 ppm FPI Improved cognitive function in MVM test
Reduced oxidative stress
Increased BDNF levels
Protected synaptic proteins and mitochondria

Curcumin 50, 100 and 200 mg/kg WDIAI Reduced IL-1β, IL-6, TNF-α, MCP-1 and RANTES, TLR4 expression, neuronal and apoptotic cell death and microglial activation
Improved NSS

Curcumin 75, 150 and 300 mg/kg CCI Reduced cerebral edema, AQP4 expression, NF-κB activation and IL-1β expression
Improved neurological function

Curcumin 50 and 100 mg/kg WDIAI Reduced cerebral damage and brain levels of MDA
Improved neurological functions
<table>
<thead>
<tr>
<th>Plant</th>
<th>Compound</th>
<th>Dosage</th>
<th>Model</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. zedoaria</em></td>
<td>β-elemene</td>
<td>100 mg/kg</td>
<td>WDIAI</td>
<td>Improved NSS</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Reduced TNF-α, IL-1β, TUNEL positive cells, apoptosis index and expression of TLR4 and caspase 3</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased expression of IkB</td>
</tr>
<tr>
<td><em>D. fortune</em></td>
<td>AE</td>
<td>45±0.05 ml/rat</td>
<td>WDIAI</td>
<td>Reduced the level of CD8 T cells</td>
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<td></td>
<td>No effect on IL-2 and CD4 levels</td>
</tr>
<tr>
<td></td>
<td>AE</td>
<td>20 mg/kg</td>
<td>CCI</td>
<td>Decreased brain lesion volume, IL-6</td>
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<td></td>
<td>Improved NSS and cognitive function</td>
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<td></td>
<td></td>
<td>Increased IL-10, blood monocyte numbers and percentage of blood CD3 and CD4 T lymphocytes</td>
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<td>Inhibited microglial/macrophage activation</td>
</tr>
<tr>
<td><em>S. Militorrhiza</em></td>
<td>SalB</td>
<td>25 mg/kg</td>
<td>CCI</td>
<td>Reduced brain water content, lesion volume, PMN, Iba-1, TNF-α and IL-1β</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Increased IL-10 and TGF-β1</td>
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<td></td>
<td>Improved neurological function</td>
</tr>
<tr>
<td><em>S. khuzistanica</em></td>
<td>EO</td>
<td>50, 100 and 200 mg/kg</td>
<td>WDIAI</td>
<td>Ameliorated brain edema, damage to BBB and veterinary coma scale (VCS) scores</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reduced levels of TNF-α, IL-1β, IL-6, intracranial pressure, neuronal death and BBB permeability</td>
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<td></td>
<td></td>
<td>Increased IL-10 level and numbers of viable astrocytes</td>
</tr>
<tr>
<td><em>S. baicalensis</em></td>
<td>Baicalein</td>
<td>30 mg/kg</td>
<td>CCI</td>
<td>Reduced the number of degenerating neurons, contusion volume, mRNA and protein expression of TNF-α, IL-1β and IL-6</td>
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<td></td>
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<td></td>
<td>Improved neurological functions</td>
</tr>
</tbody>
</table>

Figure 1. Neuroprotective effects of medicinal plants on TBI.

Neuroprotective effects of medicinal plants on

- *Salvia tomentosa*
- *Actaea racemosa*
- *Artemisia annua*
- *Crocus sativus*
- *Curcuma zedoaria*
- *Cnidium monnieri*
- *Curcuma longa*
- *Gastrodia elata*
- *Malva sylvestris*
- *Panax ginseng*
- *Rheum tanguticum*
- *Centella asiatica*
- *Drynaria fortune*
- *Nigella sativa*

Traumatic Brain Injury

Reduced Neuronal injury and microglial activation

Suppressing the expression of glial fibrillary acidic protein (GFAP)

Inhibited Neurons loss
Figure 2. Possible mechanisms of action of medicinal plants on TBI.

**Anti-inflammatory**
- NF-κB, IL-1β, IL-1α, IL-6, IL-1β and TNF-α
- LDH and plasma copeptin
- Expression of AQP5, HIF-1α and MMP-9
- Expression of NRG-1
- Distribution of phospholipids
- Expression of IkB

**Immunomodulatory**
- Expression of GFAP, NCAM and Nrf2
- Cell apoptosis
- TUNEL positive cells
- Apoptosis index
- Expression of TLR4 and caspase 3
- Autophagy marker proteins

**Neuroprotective**
- Neuronal injury and microglial activation
- Neurons loss
- Degeneration and GFAP-positive cells
- Latency to find platform
- Behavioral tests and neurological deficits

**Antioxidant**
- ROS generation
- MDA and GSSG
- SOD, CAT, GPx, GSH and GSH/GSSG

Abbreviations: :: Reduced, :: Increased, :: Improved.