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

Zakieh Keshavarzi Farzaneh Shakeri George E. Barreto Bahram Bibak Thozhukat Sathyapalan Amirhossein Sahebkar

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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 monnieri, Curcuma longa, Gastrodia elata, Malva sylvestris, 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 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-pertonieal 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 ß-pinene, alpha-pinene, camphor, camphene, 1,8-cineole, artemisia ketone, myrcene, borneol, linalool and ß-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 artemisin, 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-1ß, TNF-α and iNOS levels (44).

3.5.*Carthamus tinctorius*

Carthamus tinctorius (*C. tinctorius*), also known as Safflower, is s 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 tinctoriu*s, 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 When

administered orally in experimental allergic encephalomyelitis in mice, cinnamon powder suppressed the expression of iNOS and IL-1ß *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. *Cnidium monnieri*

Cnidium monnieri (*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 *C. monnieri* are osthole, bergapten, isopimpinellin, xanthotoxol, xanthotoxin, sesquiterpenes, cnidimonal, cnidimarin, imperatorin and glucosides (66). The pharmacological effects of *C. monnieri* include its anticonvulsant (67), memory improvement (68), anti-inflammatory and immunomodulatory (69) activities.

Administration of osthole a coumarin compound isolated from *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 eupeptic, 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, (84), antioxidant (85) and 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).

3.14. *Rheum tanguticum*

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 antispasmolytic, 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, caryphyllene 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. cochinchinenesis*), belongs to the Asparagaceae family and is widely cultivated in different provinces of China. The main components of *D. cochinchinenesis* 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 Huzhang 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 (AQPs), including AQP-1, AQP-4 and AQP-9, 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 neuroprote ctive 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 Umbellifere 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, ß-turmerone, ß-elemene, 1,8-cineole

and zingiberene (175). Different therapeutic effects including anti-peptic ulcer (176), anti-inflammatort, 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-1ß, 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-1ß and TNF-a 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 Lamiaceae 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 artesunate 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 the antioxidant effect of *C. tinctorius* was studies, 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 astrocytosis, 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 tha 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

1. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. The Journal of head trauma rehabilitation. 2006;21(5):375-8.
2. Masel BE, DeWitt DS. Traumatic brain injury: a disease process, not an event. Journal of neurotrauma. 2010;27(8):1529-40.
3. Andriessen TM, Jacobs B, Vos PE. Clinical characteristics and pathophysiological mechanisms of focal and diffuse traumatic brain injury. Journal of cellular and molecular medicine. 2010;14(10):2381-92.
4. Keshavarzi Z, Khaksari Hadad M, Zahedi MJ, Bahrami A. The effects of female sex steroids on gastric secretory responses of rat following traumatic brain injury. Iranian Journal of Basic Medical Sciences. 2011;14(3):231-9.
5. Keshavarzi Z, Khaksari M. The effects of female sexual steroids on gastric function and barrier resistance of gastrointestinal tract following traumatic brain injury. Journal of pharmacy & bioallied sciences. 2015;7(1):75.
6. Khaksari M, Razmi Z, Hekmat AS, Naderi V, Rostami S. The effects of cyclooxygenase inhibitors on the brain inflammatory response following traumatic brain injury in rats. Iranian journal of basic medical sciences. 2012;15(5):1102.
7. Xiong Y, Mahmood A, Chopp M. Animal models of traumatic brain injury. Nature Reviews Neuroscience. 2013;14(2):128.
8. Al-Amier H, Eyles SJ, Craker L. Evaluation of Extraction Methods for Isolation and Detection of Formononetin in Black Cohosh (Actaea racemosa L.). Journal of Medicinally Active Plants. 2012;1(1):6-12.
9. Rathore R, Rahal A, Mandil R, Prakash A, Asokan K, Sarkar S, et al. Comparative anti-inflammatory activity of Cimicifuga racemosa and Mimosa pudica. Asian Journal of Animal and Veterinary Advances. 2002;9(6):65-71.
10. Szymczak G, Wójciak–Kosior M, Sowa I, Zapała K, Bogucka-Kocka A. Comparison of phenolic content and antioxidant activity of Actaea racemosa L. and Actaea cordifolia DC. Natural product research. 2015;29(12):1149-52.
11. Winterhoff H, Spengler B, Christoffel V, Butterweck V, Löhning A. Cimicifuga extract BNO 1055: reduction of hot flushes and hints on antidepressant activity. Maturitas. 2003;44:S51-S8.
12. Smith MJ, Germolec DR, Frawley RP, White Jr KL. Immunomodulatory effects of black cohosh (Actaea racemosa) extract in female B6C3F1/N mice. Toxicology. 2013;308:146-57.
13. Li Z, Zeng G, Zheng X, Wang W, Ling Y, Tang H, et al. Neuroprotective effect of formononetin against TBI in rats via suppressing inflammatory reaction in cortical neurons. Biomedicine & Pharmacotherapy. 2018;106:349-54.
14. Li Z, Wang Y, Zeng G, Zheng X, Wang W, Ling Y, et al. Increased miR-155 and heme oxygenase-1 expression is involved in the protective effects of formononetin in traumatic brain injury in rats. American journal of translational research. 2017;9(12):5653.
15. Kokwaro J. Medicinal plants of East Africa. East African Literature Bureau, Nairobi. Korea. 1976;243251.
16. Okoli C, Akah P, Nwafor S, Ihemelandu U, Amadife C. Anti-inflammatory activity of seed extracts of Aframomum melegueta. Journal of herbs, spices & medicinal plants. 2007;13(1):11-21.
17. Galal AM. Antimicrobial activity of 6-paradol and related compounds. International journal of Pharmacognosy. 1996;34(1):64-9.
18. Rafatullah S, Galal A, Al-Yahya M, Al-Said M. Gastric and duodenal antiulcer and cytoprotective effects of Aframomum melegueta in rats. International journal of pharmacognosy. 1995;33(4):311-6.

19. Onoja SO, Omeh YN, Ezeja MI, Chukwu MN. Evaluation of the in vitro and in vivo antioxidant potentials of Aframomum melegueta methanolic seed extract. Journal of tropical medicine. 2014;2014.
20. Gbolade AA. Inventory of antidiabetic plants in selected districts of Lagos State, Nigeria. Journal of Ethnopharmacology. 2009;121(1):135-9.
21. Ikegbunam M, Ukamaka M, Emmanuel O. Evaluation of the antifungal activity of aqueous and alcoholic extracts of six spices. American Journal of Plant Sciences. 2016;7(01):118.
22. Lawal B, Aderibigbe A, Essiet G, Essien A. Hypotensive and antihypertensive effects of Aframomum melegueta seeds in humans. Int J Pharmacol. 2007;3:311-8.
23. Umukoro S, Ashorobi RB. Further studies on the antinociceptive action of aqueous seed extract of Aframomum melegueta. Journal of ethnopharmacology. 2007;109(3):501-4.
24. Ilic NM, Dey M, Poulev AA, Logendra S, Kuhn PE, Raskin I. Anti-inflammatory activity of grains of paradise (Aframomum melegueta Schum) extract. Journal of agricultural and food chemistry. 2014;62(43):10452-7.
25. Umukoro S, Ashorobi R. Further Evaluation of the Anti–inflammatory Activity of Aframomum Melegueta Seed Extract and its Possible Mechanism of Action. Nigerian Journal of Health and Biomedical Sciences. 2005;4(1):35-9.
26. Kumar A, Kennedy-Boone D, Weisz HA, Capra BA, Uchida T, Jennings K, et al. Neuroprotective effects of Aframomum melegueta extract after experimental traumatic brain injury. Natural Products Chemistry & Research. 2015.
27. Yamasaki T, Li L, Lau BH. Garlic compounds protect vascular endothelial cells from hydrogen peroxide-induced oxidant injury. Phytotherapy Research. 1994;8(7):408-12.
28. Jayanthi M, Jyoti M. Experimental animal studies on analgesic and anti-nociceptive activity of Allium sativum (garlic) powder. IJRRMS. 2012;2(1):1-6.
29. Advani U, Anwar A, Menghani E. Anticonvulsant potentials of Sesamum indicum and Allium sativum oil alone and in combination in animal models. Int J Pharm Pharmaceut Sci. 2011;3(Suppl. 4).
30. Schafer G, H Kaschula C. The immunomodulation and anti-inflammatory effects of garlic organosulfur compounds in cancer chemoprevention. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents). 2014;14(2):233-40.
31. Rahman M, Fazlic V, Saad N. Antioxidant properties of raw garlic (Allium sativum) extract. 2012.
32. Chen W, Qi J, Feng F, Bao G, Wang T, Xiang M, et al. Neuroprotective effect of allicin against traumatic brain injury via Akt/endothelial nitric oxide synthase pathway-mediated anti-inflammatory and anti-oxidative activities. Neurochemistry international. 2014;68:28-37.
33. Efferth T, editor From ancient herb to modern drug: Artemisia annua and artemisinin for cancer therapy. Seminars in cancer biology; 2017: Elsevier.
34. Chevallier A. The Encyclopedia of Medicinal Plants Dorling Kindersley. London 1996. There is no corresponding record for this reference.
35. Him-Che Y. Handbook of Chinese herbs and formulas. Institute of Chinese Medicine, Los Angeles. 1985;1:S219-S24.
36. Stuart G. Chinese Materia Medica Taipei, Southern Materials Centre. A translation of an ancient Chinese herbal. 1984.
37. Foster S, Duke JA. A field guide to medicinal plants: eastern and central North America: Boston: Houghton Mifflin Company xii, 366p. ISBN; 1990.
38. Simon JE, Charles D, Cebert E, Grant L, Janick J, Whipkey A. Artemisia annua L.: A promising aromatic and medicinal. Advances in new crops. 1990:522-6.
39. Engeu PO, Omujall F, Agwaya M, Kyakulaga H, Obua C. Variations in antimalarial components of Artemisia annua Linn from three regions of Uganda. African health sciences. 2015;15(3):828-34.

40. Kim W-S, Choi WJ, Lee S, Kim WJ, Lee DC, Sohn UD, et al. Anti-inflammatory, Antioxidant and Antimicrobial Effects of Artemisinin Extracts from Artemisia annua L. The Korean Journal of Physiology & Pharmacology. 2015;19(1):21-7.
41. Noori S, Naderi G-A, Hassan ZM, Habibi Z, Bathaie SZ, Hashemi SMM. Immunosuppressive activity of a molecule isolated from Artemisia annua on DTH responses compared with cyclosporin A. International immunopharmacology. 2004;4(10-11):1301-6.
42. Michaelsen F-W, Saeed ME, Schwarzkopf J, Efferth T. Activity of Artemisia annua and artemisinin derivatives, in prostate carcinoma. Phytomedicine. 2015;22(14):1223-31.
43. Bhakuni R, Jain D, Sharma R, Kumar S. Secondary metabolites of Artemisia annua and their biological activity. Current science. 2001:35-48.
44. Gugliandolo E, D'Amico R, Cordaro M, Fusco R, Siracusa R, Crupi R, et al. Neuroprotective Effect of Artesunate in Experimental Model of Traumatic Brain Injury. Frontiers in neurology. 2018;9.
45. Emongor V. Safflower (Carthamus tinctorius L.) the underutilized and neglected crop: A review. Asian J Plant Sci. 2010;9(6):299-306.
46. Masterjohn C. The anti-inflammatory properties of safflower oil and coconut oil may be mediated by their respective concentrations of vitamin E. Journal of the American College of Cardiology. 2007;49(17):1825-6.
47. Han S-Y, Li H-X, Ma X, Zhang K, Ma Z-Z, Tu P-F. Protective effects of purified safflower extract on myocardial ischemia in vivo and in vitro. Phytomedicine. 2009;16(8):694-702.
48. Hiramatsu M, Takahashi T, Komatsu M, Kido T, Kasahara Y. Antioxidant and neuroprotective activities of Mogami-benibana (safflower, Carthamus tinctorius Linne). Neurochemical research. 2009;34(4):795-805.
49. Loo WT, Cheung MN, Chow LW. The inhibitory effect of a herbal formula comprising ginseng and carthamus tinctorius on breast cancer. Life Sciences. 2004;76(2):191-200.
50. Ren R, Shi C, Cao J, Sun Y, Zhao X, Guo Y, et al. Neuroprotective effects of a standardized flavonoid extract of safflower against neurotoxin-induced cellular and animal models of Parkinson's disease. Scientific reports. 2016;6:22135.
51. Liu Z, Li C, Li M, Li D, Liu K. The subchronic toxicity of hydroxysafflor yellow A of 90 days repeatedly intraperitoneal injections in rats. Toxicology. 2004;203(1-3):139-43.
52. Fu P-K, Pan T-L, Yang C-Y, Jeng K-C, Tang N-Y, Hsieh C-L. Carthamus tinctorius L. ameliorates brain injury followed by cerebral ischemia-reperfusion in rats by antioxidative and anti-inflammatory mechanisms. Iranian journal of basic medical sciences. 2016;19(12):1368.
53. Wang Y, Zhang C, Peng W, Xia Z, Gan P, Huang W, et al. Hydroxysafflor yellow A exerts antioxidant effects in a rat model of traumatic brain injury. Molecular medicine reports. 2016;14(4):3690-6.
54. Chericoni S, Prieto JM, Iacopini P, Cioni P, Morelli I. In vitro activity of the essential oil of Cinnamomum zeylanicum and eugenol in peroxynitrite-induced oxidative processes. Journal of agricultural and food chemistry. 2005;53(12):4762-5.
55. Ranasinghe P, Pigera S, Premakumara GS, Galappaththy P, Constantine GR, Katulanda P. Medicinal properties of 'true'cinnamon (Cinnamomum zeylanicum): a systematic review. BMC complementary and alternative medicine. 2013;13(1):275.
56. Wang Y, Zhang Y, Shi Y-q, Pan X-h, Lu Y-h, Cao P. Antibacterial effects of cinnamon (Cinnamomum zeylanicum) bark essential oil on Porphyromonas gingivalis. Microbial pathogenesis. 2018;116:26-32.
57. Ranasinghe L, Jayawardena B, Abeywickrama K. Fungicidal activity of essential oils of Cinnamomum zeylanicum (L.) and Syzygium aromaticum (L.) Merr et LM Perry against crown rot and anthracnose pathogens isolated from banana. Letters in Applied Microbiology. 2002;35(3):208-11.

58. Ghosh T, Basu A, Adhikari D, Roy D, Pal AK. Antioxidant activity and structural features of Cinnamomum zeylanicum. 3 Biotech. 2015;5(6):939-47.
59. Verspohl EJ, Bauer K, Neddermann E. Antidiabetic effect of Cinnamomum cassia and Cinnamomum zeylanicum in vivo and in vitro. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2005;19(3):203-6.
60. Han X, Parker TL. Antiinflammatory activity of cinnamon (Cinnamomum zeylanicum) bark essential oil in a human skin disease model. Phytotherapy Research. 2017;31(7):1034-8.
61. Niphade SR, Asad M, Chandrakala GK, Toppo E, Deshmukh P. Immunomodulatory activity of Cinnamomum zeylanicum bark. Pharmaceutical biology. 2009;47(12):1168-73.
62. Mondal S, Pahan K. Cinnamon ameliorates experimental allergic encephalomyelitis in mice via regulatory T cells: implications for multiple sclerosis therapy. PLoS One. 2015;10(1):e0116566.
63. Modi KK, Roy A, Brahmachari S, Rangasamy SB, Pahan K. Cinnamon and its metabolite sodium benzoate attenuate the activation of p21rac and protect memory and learning in an animal model of Alzheimer's disease. PloS one. 2015;10(6):e0130398.
64. Khasnavis S, Pahan K. Cinnamon treatment upregulates neuroprotective proteins Parkin and DJ-1 and protects dopaminergic neurons in a mouse model of Parkinson's disease. Journal of Neuroimmune Pharmacology. 2014;9(4):569-81.
65. Yulug B, Kilic E, Altunay S, Ersavas C, Orhan C, Dalay A, et al. Cinnamon polyphenol extract exerts neuroprotective activity in traumatic brain injury through modulation of Nfr2 and cytokine expression. CNS & neurological disorders drug targets. 2018.
66. Li Y-M, Jia M, Li H-Q, Zhang N-D, Wen X, Rahman K, et al. Cnidium monnieri: a review of traditional uses, phytochemical and ethnopharmacological properties. The American journal of Chinese medicine. 2015;43(05):835-77.
67. Luszczki JJ, Andres-Mach M, Cisowski W, Mazol I, Glowniak K, Czuczwar SJ. Osthole suppresses seizures in the mouse maximal electroshock seizure model. European journal of pharmacology. 2009;607(1-3):107-9.
68. Ji H-J, Hu J-F, Wang Y-H, Chen X-Y, Zhou R, Chen N-H. Osthole improves chronic cerebral hypoperfusion induced cognitive deficits and neuronal damage in hippocampus. European journal of pharmacology. 2010;636(1-3):96-101.
69. Zimecki M, Artym J, Cisowski W, Mażol I, Włodarczyk M, Glenśk M. Immunomodulatory and anti-inflammatory activity of selected osthole derivatives. Zeitschrift für Naturforschung C. 2009;64(5-6):361-8.
70. He Y, Qu S, Wang J, He X, Lin W, Zhen H, et al. Neuroprotective effects of osthole pretreatment against traumatic brain injury in rats. Brain research. 2012;1433:127-36.
71. Tarantilis PA, Tsoupras G, Polissiou M. Determination of saffron (Crocus sativus L.) components in crude plant extract using high-performance liquid chromatography-UV-visible photodiode-array detection-mass spectrometry. Journal of Chromatography A. 1995;699(1-2):107-18.
72. Rios J, Recio M, Giner R, Manez S. An update review of saffron and its active constituents. Phytotherapy Research. 1996;10(3):189-93.
73. Boskabady MH, Farkhondeh T. Antiinflammatory, antioxidant, and immunomodulatory effects of Crocus sativus L. and its main constituents. Phytotherapy Research. 2016;30(7):1072-94.
74. Hosseinzadeh H, Noraei NB. Anxiolytic and hypnotic effect of Crocus sativus aqueous extract and its constituents, crocin and safranal, in mice. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2009;23(6):768-74.
75. Sadeghnia H, Cortez M, Liu D, Hosseinzadeh H, Snead OC. Antiabsence effects of safranal in acute experimental seizure models: EEG and autoradiography. Journal of Pharmacy & Pharmaceutical Sciences. 2008;11(3):1-14.

76. Geromichalos GD, Lamari FN, Papandreou MA, Trafalis DT, Margarity M, Papageorgiou A, et al. Saffron as a source of novel acetylcholinesterase inhibitors: molecular docking and in vitro enzymatic studies. Journal of agricultural and food chemistry. 2012;60(24):6131-8.
77. Vakili A, Einali MR, Bandegi AR. Protective effect of crocin against cerebral ischemia in a dose-dependent manner in a rat model of ischemic stroke. Journal of Stroke and Cerebrovascular Diseases. 2014;23(1):106-13.
78. Wang K, Zhang L, Rao W, Su N, Hui H, Wang L, et al. Neuroprotective effects of crocin against traumatic brain injury in mice: Involvement of notch signaling pathway. Neuroscience letters. 2015;591:53-8.
79. Liu Z-K, Ng C-F, Shiu H-T, Wong H-L, Wong C-W, Li K-K, et al. A traditional Chinese formula composed of Chuanxiong Rhizoma and Gastrodiae Rhizoma (Da Chuanxiong Formula) suppresses inflammatory response in LPS-induced RAW 264.7 cells through inhibition of NF-κB pathway. Journal of ethnopharmacology. 2017;196:20-8.
80. Wang L, Zhang J, Hong Y, Feng Y, Chen M, Wang Y. Phytochemical and pharmacological review of da chuanxiong formula: a famous herb pair composed of chuanxiong rhizoma and gastrodiae rhizoma for headache. Evidence-Based Complementary and Alternative Medicine. 2013;2013.
81. Liu Z-K, Ng C-F, Shiu H-T, Wong H-L, Chin W-C, Zhang J-F, et al. Neuroprotective effect of Da Chuanxiong Formula against cognitive and motor deficits in a rat controlled cortical impact model of traumatic brain injury. Journal of ethnopharmacology. 2018;217:11-22.
82. Li X, Song K, Yang J, Yi T. Isolation and characterization of 11 new microsatellite loci in Erigeron breviscapus (Asteraceae), an important Chinese traditional herb. International journal of molecular sciences. 2011;12(10):7265-70.
83. Zahoor A, Hussain H, Khan A, Ahmed I, Ahmad VU, Krohn K. Chemical Constituents from Erigeron bonariensis L. and their chemotaxonomic importance. Records of Natural Products. 2012;6(4):376.
84. Liu H, Yang X, Ding J, Feng Y, Xu H. Antibacterial and antifungal activity of Erigeron breviscapus. Fitoterapia. 2003;74(4):387-9.
85. Wang M, Xie C, Cai R-L, Li X-H, Luo X-Z, Qi Y. Studies on antioxidant activities of breviscapine in the cell-free system. The American journal of Chinese medicine. 2008;36(06):1199-207.
86. Zhang Z, Luo P, Li J, Yi T, Wang J, An J, et al. Comparison of the antiinflammatory activities of three medicinal plants known as “meiduoluomi” in Tibetan folk medicine. Yakugaku Zasshi. 2008;128(5):805-10.
87. Jiang L, Hu Y, He X, Lv Q, Wang T-h, Xia Q-j. Breviscapine reduces neuronal injury caused by traumatic brain injury insult: partly associated with suppression of interleukin-6 expression. Neural regeneration research. 2017;12(1):90.
88. Jang J-H, Son Y, Kang SS, Bae C-S, Kim J-C, Kim S-H, et al. Neuropharmacological potential of Gastrodia elata Blume and its components. Evidence-Based Complementary and Alternative Medicine. 2015;2015.
89. Kim B-W, Koppula S, Kim J-W, Lim H-W, Hwang J-W, Kim I-S, et al. Modulation of LPS-stimulated neuroinflammation in BV-2 microglia by Gastrodia elata: 4-hydroxybenzyl alcohol is the bioactive candidate. Journal of Ethnopharmacology. 2012;139(2):549-57.
90. Duan R, Zhou H, Yang Y, Li H, Dong J, Li X, et al. Antimicrobial meroterpenoids from the endophytic fungus Penicillium sp. T2-8 associated with Gastrodia elata. Phytochemistry Letters. 2016;18:197-201.
91. Chen X, Cao D, Zhou L, Jin H, Dong Q, Yao J, et al. Structure of a polysaccharide from Gastrodia elata Bl., and oligosaccharides prepared thereof with anti-pancreatic cancer cell growth activities. Carbohydrate polymers. 2011;86(3):1300-5.

92. Hsieh C-L, Chen C-L, Tang N-Y, Chuang C-M, Hsieh C-T, Chiang S-Y, et al. Gastrodia elata BL mediates the suppression of nNOS and microglia activation to protect against neuronal damage in kainic acid-treated rats. The American journal of Chinese medicine. 2005;33(04):599-611.
93. Hwang SM, Lee YJ, Kang DG, Lee HS. Anti-inflammatory effect of Gastrodia elata rhizome in human umbilical vein endothelial cells. The American journal of Chinese medicine. 2009;37(02):395-406.
94. Ng C-F, Ko C-H, Koon C-M, Chin W-C, Kwong HCST, Lo AW-I, et al. The aqueous extract of rhizome of Gastrodia elata Blume attenuates locomotor defect and inflammation after traumatic brain injury in rats. Journal of ethnopharmacology. 2016;185:87-95.
95. Paul D. A review on biological activities of common mallow (Malva sylvestris L.). Innovare J. Life Sci. 2016;4(5):1-5.
96. Qin H, Qin J, Hu J, Huang H, Ma L. Malva sylvestris attenuates cognitive deficits in a repetitive mild traumatic brain injury rat model by reducing neuronal degeneration and astrocytosis in the hippocampus. Medical science monitor: international medical journal of experimental and clinical research. 2017;23:6099.
97. Coon JT, Ernst E. Panax ginseng. Drug safety. 2002;25(5):323-44.
98. Hou JP. The chemical constituents of ginseng plants. The American Journal of Chinese Medicine. 1977;5(02):123-45.
99. Kachur K, Suntres ZE. The antimicrobial properties of ginseng and ginseng extracts. Expert review of anti-infective therapy. 2016;14(1):81-94.
100. Sung WS, Lee DG. In vitro candidacidal action of Korean red ginseng saponins against Candida albicans. Biological and Pharmaceutical Bulletin. 2008;31(1):139-42.
101. Kim H-G, Yoo S-R, Park H-J, Lee N-H, Shin J-W, Sathyanath R, et al. Antioxidant effects of Panax ginseng CA Meyer in healthy subjects: a randomized, placebo-controlled clinical trial. Food and Chemical Toxicology. 2011;49(9):2229-35.
102. Lee MH, Lee B-H, Jung J-Y, Cheon D-S, Kim K-T, Choi C. Antiviral effect of Korean red ginseng extract and ginsenosides on murine norovirus and feline calicivirus as surrogates for human norovirus. Journal of ginseng research. 2011;35(4):429.
103. Hong M, Lee YH, Kim S, Suk KT, Bang CS, Yoon JH, et al. Anti-inflammatory and antifatigue effect of Korean Red Ginseng in patients with nonalcoholic fatty liver disease. Journal of ginseng research. 2016;40(3):203-10.
104. Jung JH, Kang IG, Kim DY, Hwang YJ, Kim ST. The effect of Korean red ginseng on allergic inflammation in a murine model of allergic rhinitis. Journal of ginseng research. 2013;37(2):167.
105. Liu L, Hoang-Gia T, Wu H, Lee M-R, Gu L, Wang C, et al. Ginsenoside Rb1 improves spatial learning and memory by regulation of cell genesis in the hippocampal subregions of rats. Brain research. 2011;1382:147-54.
106. He B, Chen P, Yang J, Yun Y, Zhang X, Yang R, et al. Neuroprotective effect of 20 (R)-ginsenoside Rg3 against transient focal cerebral ischemia in rats. Neuroscience letters. 2012;526(2):106-11.
107. Kumar A, Rinwa P, Dhar H. Microglial inhibitory effect of ginseng ameliorates cognitive deficits and neuroinflammation following traumatic head injury in rats. Inflammopharmacology. 2014;22(3):155-67.
108. Ji YC, Kim YB, Park SW, Hwang SN, Min BK, Hong HJ, et al. Neuroprotective effect of ginseng total saponins in experimental traumatic brain injury. Journal of Korean Medical Science. 2005;20(2):291-6.
109. Xia L, Jiang ZL, Wang GH, Hu BY, Ke KF. Treatment with ginseng total saponins reduces the secondary brain injury in rat after cortical impact. Journal of neuroscience research. 2012;90(7):1424-36.
110. Hu B-Y, Liu X-J, Qiang R, Jiang Z-L, Xu L-H, Wang G-H, et al. Treatment with ginseng total saponins improves the neurorestoration of rat after traumatic brain injury. Journal of ethnopharmacology. 2014;155(2):1243-55.

111. Xia L, Chen Q, Cheng G. Effects of ginseng total saponin on traumatic brain edema of rats. Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi= Chinese journal of integrated traditional and Western medicine. 2012;32(12):1671-4.
112. Hu B-Y, Jiang Z-L, Wang G-H, Li X, Shen H. Effective dose and time window of ginseng total saponins treatment in rat after traumatic brain injury. Zhongguo ying yong sheng li xue za zhi= Zhongguo yingyong shenglixue zazhi= Chinese journal of applied physiology. 2012;28(2):179-83.
113. Li M, Li L, Liu Y, Liu Y. Study survey on rhubarb in recent years. World Sci Tech/Mod Trad Chin Med. 2006;8:34-9.
114. Wang Y, Fan X, Tang T, Fan R, Zhang C, Huang Z, et al. Rhein and rhubarb similarly protect the blood-brain barrier after experimental traumatic brain injury via gp91 phox subunit of NADPH oxidase/ROS/ERK/MMP-9 signaling pathway. Scientific reports. 2016;6:37098.
115. Xu X, Lv H, Xia Z, Fan R, Zhang C, Wang Y, et al. Rhein exhibits antioxidative effects similar to Rhubarb in a rat model of traumatic brain injury. BMC complementary and alternative medicine. 2017;17(1):140.
116. Wang Z, Liu L, Mei Q-B, Zhang R, Gu J-W, Zhang X, et al. Protective effect of Rheum tanguticum polysaccharides (RTP) on traumatic brain injury in rats. Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi= China journal of Chinese materia medica. 2003;28(10):974-6, 1.
117. Company ME. PDR for herbal medicines: Medical Economics Company; 1998.
118. Ulukanli Z, Karabörklü S, Cenet M, Sagdic O, Ozturk I, Balcilar M. Essential oil composition, insecticidal and antibacterial activities of Salvia tomentosa Miller. Medicinal Chemistry Research. 2013;22(2):832-40.
119. Dinçer C, Tontul I, Cam IB, ÖZDEMİR KS, Topuz A, NADEEM HŞ, et al. Phenolic composition and antioxidant activity of Salvia tomentosa Miller: effects of cultivation, harvesting year, and storage. Turkish Journal of Agriculture and Forestry. 2013;37(5):561-7.
120. Haznedaroglu MZ, Karabay NU, Zeybek U. Antibacterial activity of Salvia tomentosa essential oil. Fitoterapia. 2001;72(7):829-31.
121. Akhtar MS, Swamy MK. Anticancer Plants: Natural Products and Biotechnological Implements. Springer; 2018.
122. Sawmiller D, Li S, Shahaduzzaman M, Smith AJ, Obregon D, Giunta B, et al. Luteolin reduces Alzheimer's disease pathologies induced by traumatic brain injury. International journal of molecular sciences. 2014;15(1):895-904.
123. El–Dakhakhny M. STUDIES ON THE CHEMICAL CONSTITUTION OF EGYPTIAN NIGELLA SATIVA L. SEEDS. II1) THE ESSENTIAL OIL. Planta Medica. 1963;11(04):465-70.
124. Malik S, Hasan SS, Choudhary MI, Ni C-Z, Clardy J. Nigellidine—a new indazole alkaloid from the seeds of Nigella sativa. Tetrahedron letters. 1995;36(12):1993-6.
125. MALIK S, AHMAD S, CHAUDHARY I. Nigellimine N-oxide-a new isoquinoline alkaloid from the seeds of Nigella sativa. Heterocycles. 1985;23(4):953-5.
126. Ansari A, Sadiy H. Structural studies on a saponin isolated from the seeds of Nigella sativa. Phyto Chem. 1989;27:377-9.
127. Boskabady MH, Javan H, Sajady M, Rakhshandeh H. The possible prophylactic effect of Nigella sativa seed extract in asthmatic patients. Fundamental & clinical pharmacology. 2007;21(5):559-66.
128. Ali B, Blunden G. Pharmacological and toxicological properties of Nigella sativa. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2003;17(4):299-305.
129. Majdalawieh AF, Fayyad MW. Immunomodulatory and anti-inflammatory action of Nigella sativa and thymoquinone: A comprehensive review. International immunopharmacology. 2015;28(1):295-304.
130. Hosseinzadeh H, Parvardeh S. Anticonvulsant effects of thymoquinone, the major constituent of Nigella sativa seeds, in mice. Phytomedicine. 2004;11(1):56-64.

131. Bano F, Ahmed A, Parveen T, Haider S. Anxiolytic and hyperlocomotive effects of aqueous extract of Nigella sativa L. seeds in rats. Pakistan journal of pharmaceutical sciences. 2014;27(5 Spec no):1547-52.
132. Abdel-Fattah A-FM, Matsumoto K, Watanabe H. Antinociceptive effects of Nigella sativa oil and its major component, thymoquinone, in mice. European journal of pharmacology. 2000;400(1):89-97.
133. Akhtar M, Maikiyo AM, Khanam R, Mujeeb M, Aqil M, Najmi AK. Ameliorating effects of two extracts of Nigella sativa in middle cerebral artery occluded rat. Journal of pharmacy & bioallied sciences. 2012;4(1):70.
134. أأج محمد. Potential therapeutic effect of amlodipine and thymoquinone alone or in combination on traumatic brain injury in mice. CU Theses. 2017.
135. Fan J-Y, Yi T, Sze-To C-M, Zhu L, Peng W-L, Zhang Y-Z, et al. A systematic review of the botanical, phytochemical and pharmacological profile of Dracaena cochinchinensis, a plant source of the ethnomedicine "Dragon's Blood". Molecules. 2014;19(7):10650-69.
136. Xin N, Li Y-J, Li Y, Dai R-J, Meng W-W, Chen Y, et al. Dragon's Blood extract has antithrombotic properties, affecting platelet aggregation functions and anticoagulation activities. Journal of Ethnopharmacology. 2011;135(2):510-4.
137. Choy C-S, Hu C-M, Chiu W-T, Lam C-SK, Ting Y, Tsai S-H, et al. Suppression of lipopolysaccharide-induced of inducible nitric oxide synthase and cyclooxygenase-2 by Sanguis Draconis, a dragon's blood resin, in RAW 264.7 cells. Journal of ethnopharmacology. 2008;115(3):455-62.
138. Zheng Q, Chen J, Zhang Y, Yang C. The chemical constituents and pharmaceutical activities of Dragon's blood, a famous traditional medicinal herb. Natur Prod Res Devel. 2005;17:84-95.
139. He L, Liu Y, Shi J, Pei Q. Synthesis and antitumor activity of cholest-4α-methyl-7-en-3β-ol derivatives. Steroids. 2006;71(6):476-83.
140. Gu H-J, Lv J-C, Yong K-L, Chen X, Liu P-P, Zhang X-B. Antidiabetic effect of an active fraction extracted from dragon's blood (Dracaena cochinchinensis). Journal of enzyme inhibition and medicinal chemistry. 2009;24(1):136-9.
141. Li Y-S, Wang J-X, Jia M-M, Liu M, Li X-J, Tang H-B. Dragon's blood inhibits chronic inflammatory and neuropathic pain responses by blocking the synthesis and release of substance P in rats. Journal of pharmacological sciences. 2012;118(1):43-54.
142. Xu J, Xiong T, Yang Y, Li J, Mao J. R esina D raconis as a topical treatment for pressure ulcers: A systematic review and meta-analysis. Wound Repair and Regeneration. 2015;23(4):565-74.
143. Zhang J, Dai K. Anti-neuron apoptosis of Resina Draconis water extracts on rats with traumatic brain injury. Biomedical Research. 2016;27(4).
144. Hu W-H, Chan GK-L, Lou J-S, Wu Q-Y, Wang H-Y, Duan R, et al. The extract of Polygoni Cuspidati Rhizoma et Radix suppresses the vascular endothelial growth factor-induced angiogenesis. Phytomedicine. 2018;42:135-43.
145. Chiou W, Liao J, Huang C, Chen C. 2-Methoxystypandrone represses RANKL-mediated osteoclastogenesis by down-regulating formation of TRAF6–TAK1 signalling complexes. British journal of pharmacology. 2010;161(2):321-35.
146. Fan H, Ding S, Lin H. Pharmacological of Polygoni cuspidati rhizoma. Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi= China journal of Chinese materia medica. 2013;38(15):2545-8.
147. Ghiringhelli F, Rebe C, Hichami A, Delmas D. Immunomodulation and anti-inflammatory roles of polyphenols as anticancer agents. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents). 2012;12(8):852-73.
148. Lin Y-W, Yang F-J, Chen C-L, Lee W-T, Chen R-S. Free radical scavenging activity and antiproliferative potential of Polygonum cuspidatum root extracts. Journal of natural medicines. 2010;64(2):146-52.

149. Cao F, Peng W, Li X, Liu M, Li B, Qin R, et al. Emodin is identified as the active component of ether extracts from Rhizoma Polygoni Cuspidati, for anti-MRSA activity. Canadian journal of physiology and pharmacology. 2015;93(6):485-93.
150. Zeng J-P, Jia L-T, Jin X, Zheng J-P, Zhang X-W, Zhan R-Y. Emodin attenuates brain edema after traumatic brain injury in rats. Int J Clin Exp Med. 2017;10(11):15213-20.
151. Feng Y, Cui Y, Gao JL, Li R, Jiang XH, Tian YX, et al. Neuroprotective effects of resveratrol against traumatic brain injury in rats: Involvement of synaptic proteins and neuronal autophagy. Molecular medicine reports. 2016;13(6):5248-54.
152. Özcan MM, Chalchat J-C. Chemical composition and antifungal activity of rosemary (Rosmarinus officinalis L.) oil from Turkey. International journal of food sciences and nutrition. 2008;59(7-8):691-8.
153. Seyedemadi P, Rahnema M, Bigdeli MR, Oryan S, Rafati H. The neuroprotective effect of rosemary (Rosmarinus officinalis L.) hydro-alcoholic extract on cerebral ischemic tolerance in experimental stroke. Iranian journal of pharmaceutical research: IJPR. 2016;15(4):875.
154. Song H, Xu L, Zhang R, Cao Z, Zhang H, Yang L, et al. Rosemary extract improves cognitive deficits in a rats model of repetitive mild traumatic brain injury associated with reduction of astrocytosis and neuronal degeneration in hippocampus. Neuroscience letters. 2016;622:95-101.
155. Gohil KJ, Patel JA, Gajjar AK. Pharmacological review on Centella asiatica: a potential herbal cure-all. Indian journal of pharmaceutical sciences. 2010;72(5):546.
156. Siddiqui B, Aslam H, Ali S, Khan S, Begum S. Chemical constituents of Centella asiatica. Journal of Asian natural products research. 2007;9(4):407-14.
157. Park JH, Choi JY, Son DJ, Park EK, Song MJ, Hellström M, et al. Anti-inflammatory effect of titrated extract of Centella asiatica in phthalic anhydride-induced allergic dermatitis animal model. International journal of molecular sciences. 2017;18(4):738.
158. Parameshwaraiah S, Shivakumar H. Evaluation of topical formulations of aqueous extract of Centella asiatica on open wounds in rats. Indian journal of experimental biology. 1998;36(6):569-72.
159. Kumar MV, Gupta Y. Effect of different extracts of Centella asiatica on cognition and markers of oxidative stress in rats. Journal of ethnopharmacology. 2002;79(2):253-60.
160. Chen Y, Han T, Qin L, Rui Y, Zheng H. Effect of total triterpenes from Centella asiatica on the depression behavior and concentration of amino acid in forced swimming mice. Zhong yao cai= Zhongyaocai= Journal of Chinese medicinal materials. 2003;26(12):870-3.
161. Hausen B. Centella asiatica (Indian pennywort), an effective therapeutic but a weak sensitizer. Contact dermatitis. 1993;29(4):175-9.
162. Pittella F, Dutra RC, Junior DD, Lopes MT, Barbosa NR. Antioxidant and cytotoxic activities of Centella asiatica (L) Urb. International journal of molecular sciences. 2009;10(9):3713-21.
163. Thong-asa W, Tilokskulchai K, Chompoopong S, Tantisira MH. Effect of Centella asiatica on pathophysiology of mild chronic cerebral hypoperfusion in rats. Avicenna journal of phytomedicine. 2018;8(3):210.
164. Jazmi AF, Alfiantya PF, Nurarifah SAH, Purmitasari EA, Vitania LA, Riawan W. Spade Leaf Extract Phytosome Modulates Krox-20, Neuregulin1-, Phospholipids, and Cognitive Function of Traumatic Brain Injury Model in Rats. Indonesian Journal of Cancer Chemoprevention. 2015;6(3):105-10.
165. Shakeri F, Roshan NM, Kaveh M, Eftekhar N, Boskabady MH. Curcumin affects tracheal responsiveness and lung pathology in asthmatic rats. Pharmacological Reports. 2018;70(5):981-7.
166. Shakeri F, Soukhtanloo M, Boskabady MH. The effect of hydro-ethanolic extract of Curcuma longa rhizome and curcumin on total and differential WBC and serum oxidant, antioxidant biomarkers in rat model of asthma. Iranian journal of basic medical sciences. 2017;20(2):155.
167. Boskabady MH, Shakeri F. Anti-inflammatory, antioxidant and immunomodulatory effects of curcumin in sensitized rat. Eur Respiratory Soc; 2017.

168. Sharma S, Ying Z, Gomez-Pinilla F. A pyrazole curcumin derivative restores membrane homeostasis disrupted after brain trauma. Experimental neurology. 2010;226(1):191-9.
169. Sharma S, Zhuang Y, Ying Z, Wu A, Gomez-Pinilla F. Dietary curcumin supplementation counteracts reduction in levels of molecules involved in energy homeostasis after brain trauma. Neuroscience. 2009;161(4):1037-44.
170. Wu A, Ying Z, Gomez-Pinilla F. Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition. Experimental neurology. 2006;197(2):309-17.
171. Wu A, Ying Z, Schubert D, Gomez-Pinilla F. Brain and spinal cord interaction: a dietary curcumin derivative counteracts locomotor and cognitive deficits after brain trauma. Neurorehabilitation and neural repair. 2011;25(4):332-42.
172. Samini F, Samarghandian S, Borji A, Mohammadi G. Curcumin pretreatment attenuates brain lesion size and improves neurological function following traumatic brain injury in the rat. Pharmacology Biochemistry and Behavior. 2013;110:238-44.
173. Laird MD, Sukumari-Ramesh S, Swift AE, Meiler SE, Vender JR, Dhandapani KM. Curcumin attenuates cerebral edema following traumatic brain injury in mice: a possible role for aquaporin-4? Journal of neurochemistry. 2010;113(3):637-48.
174. Zhu H-t, Bian C, Yuan J-c, Chu W-h, Xiang X, Chen F, et al. Curcumin attenuates acute inflammatory injury by inhibiting the TLR4/MyD88/NF-κB signaling pathway in experimental traumatic brain injury. Journal of neuroinflammation. 2014;11(1):59.
175. Singh P, Singh S, Kapoor I, Singh G, Isidorov V, Szczepaniak L. Chemical composition and antioxidant activities of essential oil and oleoresins from Curcuma zedoaria rhizomes, part-74. Food Bioscience. 2013;3:42-8.
176. Gupta RP, Ali M, Eranna D, Setty RS. Evaluation of anti-ulcer effect of root of Curcuma zedoaria in rats. 2003.
177. Ullah HA, Zaman S, Juhara F, Akter L, Tareq SM, Masum EH, et al. Evaluation of antinociceptive, in-vivo & in-vitro anti-inflammatory activity of ethanolic extract of Curcuma zedoaria rhizome. BMC complementary and alternative medicine. 2014;14(1):346.
178. Hamdi OAA, Ye LJ, Kamarudin MNA, Hazni H, Paydar M, Looi CY, et al. Neuroprotective and Antioxidant Constituents from Curcuma zedoaria Rhizomes. Records of Natural Products. 2015;9(3).
179. Shaikh A, Shrivastava B, Apte K, Navale S. Effect of aqueous extract of Curcuma zedoaria and Gloriosa superba against DMH-Induced colon carcinogenesis in Wistar rats. International Journal of PharmTech Research. 2015;8(10):88-94.
180. Li X-J, Liang L, Shi H-X, Sun X-P, Wang J, Zhang L-S. Neuroprotective effects of curdione against focal cerebral ischemia reperfusion injury in rats. Neuropsychiatric disease and treatment. 2017;13:1733.
181. Meng X, Li N, Zhang Y, Fan D, Yang C, Li H, et al. Beneficial effect of β-elemene alone and in combination with hyperbaric oxygen in traumatic brain injury by inflammatory pathway. Translational neuroscience. 2018;9(1):33-7.
182. Ji X-Y, Tan B, Zhu Y-Z. Salvia miltiorrhiza and ischemic diseases. Acta Pharmacologica Sinica. 2000;21(12):1089-94.
183. Wang B-Q. Salvia miltiorrhiza: Chemical and pharmacological review of a medicinal plant. Journal of Medicinal Plants Research. 2010;4(25):2813-20.
184. Chen T, Liu W, Chao X, Zhang L, Qu Y, Huo J, et al. Salvianolic acid B attenuates brain damage and inflammation after traumatic brain injury in mice. Brain research bulletin. 2011;84(2):163-8.
185. Sefidkon F, Ahmadi S. Essential oil of Satureja khuzistanica Jamzad. Journal of Essential Oil Research. 2000;12(4):427-8.

186. Vosough-Ghanbari S, Rahimi R, Kharabaf S, Zeinali S, Mohammadirad A, Amini S, et al. Effects of Satureja khuzestanica on serum glucose, lipids and markers of oxidative stress in patients with type 2 diabetes mellitus: a double-blind randomized controlled trial. Evidence-Based Complementary and Alternative Medicine. 2010;7(4):465-70.
187. Hajhashemi V, Sadraei H, Ghannadi AR, Mohseni M. Antispasmodic and anti-diarrhoeal effect of Satureja hortensis L. essential oil. Journal of ethnopharmacology. 2000;71(1-2):187-92.
188. Amanlou M, Dadkhah F, Salehnia A, Farsam H, Dehpour AR. An anti-inflammatory and anti-nociceptive effects of hydroalcoholic extract of Satureja khuzistanica Jamzad extract. Journal of pharmacy & pharmaceutical sciences: a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques. 2005;8(1):102-6.
189. Ghazanfari G, Minaie B, Yasa N, Nakhai LA, Mohammadirad A, Nikfar S, et al. Biochemical and histopathological evidences for beneficial effects of Satureja Khuzestanica Jamzad essential oil on the mouse model of inflammatory bowel diseases. Toxicology mechanisms and methods. 2006;16(7):365-72.
190. Abbasloo E, Dehghan F, Khaksari M, Najafipour H, Vahidi R, Dabiri S, et al. The anti-inflammatory properties of Satureja khuzistanica Jamzad essential oil attenuate the effects of traumatic brain injuries in rats. Scientific reports. 2016;6:31866.
191. Romm A. Botanical Medicine for Women's Health E-Book: Elsevier Health Sciences; 2017.
192. Chen SF, Hsu CW, Huang WH, Wang JY. Post-injury baicalein improves histological and functional outcomes and reduces inflammatory cytokines after experimental traumatic brain injury. British journal of pharmacology. 2008;155(8):1279-96.
193. Wong RW, Rabie ABM. Systemic effect of crude extract from rhizome of Drynaria fortunei on bone formation in mice. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2006;20(4):313-5.
194. Wang W-z, Pan Y-z, Wei J-b, Huang L-p, Huang X, Li K. The effects of Rhizoma drynariae on interleukin-2 and T-lymphocyte levels in rats after severe head injury. Journal of ethnopharmacology. 2012;142(1):300-4.
195. Wang W, Li H, Yu J, Hong M, Zhou J, Zhu L, et al. Protective effects of chinese herbal medicine rhizoma drynariae in rats after traumatic brain injury and identification of active compound. Molecular neurobiology. 2016;53(7):4809-20.
196. Wang M, Zhang W-b, Zhu J-h, Fu G-s, Zhou B-q. Breviscapine ameliorates cardiac dysfunction and regulates the myocardial Ca 2+-cycling proteins in streptozotocin-induced diabetic rats. Acta diabetologica. 2010;47(1):209-18.
197. Zheng C, Ou W, Shen H, Zhou Z, Wang J. Combined therapy of diabetic peripheral neuropathy with breviscapine and mecobalamin: a systematic review and a meta-analysis of Chinese studies. BioMed research international. 2015;2015.

Table 1: The summary of animal models [7]

Animal model	description
Fluid percussion injury (FPI) models	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.
Cortical impact injury (CCI) model	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.
Penetrating ballistic-like brain injury (PBBI)	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.
Weight drop models	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.

Table 2. Summary of studies reporting the effects of medicinal plants on TBI.

Plant	Ext./Cons.	Dose	Exp. model	Effect	Ref.
A. racemosa	Formononetin	10 and 30 mg/kg	WDIAI	Improved NSS score Increased cortical neuronal numbers and IL-10 Decreased IL-6 and TNF-α	[13]
	Formononetin	10 and 30 mg/kg	WDIAI	Improved NSS score Reduced brain edema and inhibited neuronal apoptosis Up-regulated the expression levels of miR-155 and HO-1 and down-regulated the protein expression of BACH1	[14]
A. melegueta seed	AEE	10, 100, 250, 500 and 1000 mg/kg	FPI	Reduced neuronal injury and microglial activation	[26]
A. sativum	Allicin	1, 10 and 50 mg/kg	CCI	Reduced contusion volume, water content, Bcl-2/Bax ratio, MDA, protein carbonyl, TNF-α and IL-1β Increased CAT, SOD, GST, IL-10, TGF-β1, Akt and Enos Inhibited the activation of caspase-3 and PARP	
A. annua	Atesunate	30 mg/kg	CCI	Reduced tissue damage and inflammation, expression of Il-1ß, TNF-α, iNOS, BDNF, VEGF, GDNF and inflammasomes components (NLRP3, ASC and Caspase-1)	[44]
C. tinctorius	HSYA	10 and 30 mg/kg	CCI	Increased the SOD, CAT, GSH and GSH/ GSSG ratio Decreased the MDA and GSSG	[53]
C. zeylanicum	polyphenol E	10 mg/kg	CI	Reduced infarct and edema formation suppressing the expression of NF-κB, IL-1, IL-6, GFAP, NCAM and Nrf2	[65]
C. monnieri	Osthole	10, 20 and 40	WDIAI	Reduced neurological deficits, cerebral edema and	[70]

		mg/kg		hippocampal neuron loss Increased SOD, GSH MDA, Bcl-2/Bax, the expression of active caspase-3, and the number of apoptotic cells	
C. sativus	Crocin	20 mg/kg	CCI	Activated the Notch signaling pathway Reduced microglial activation, cell apoptosis, and release of IL-1β and TNF-α Improved NSS and brain edema	78
DCXF	AE	520.6 and 2603.0 mg/kg	CCI	Improved behavioral tests Reduced BBB permeability, brain edema, microglia and astrocyte activation, and neurons loss	81
E. breviscapus	Breviscapine	75 μg	CCI	Improved NSS score Reduced expression of IL-6 in the injured cortex and IL-6-positive cell number in injured brain tissue	87
G. elata	AE	505 and 1515 mg/kg		Improved locomotor functions Reduced the number of astrocyte and the expression of IL-6 and TNF-α	94
P. ginseng	AE	50, 100 and 200 mg/kg	WDIAI	Improved neurological deficits Reduced levels of MDA, nitrite, AChE, TNF-a and IL-6 Increased GSH, SOD and CAT	107
	GTS	100 and 200 mg/kg	CCI	Reduced neuronal loss in hippocampal regions of CA1, CA2, and CA3, contusion volume and percentage of contusion Improved neurological deficits	108
	GTS	(5, 10, 20, 40, 60 and 80 mg/kg, i.p.)		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	109

				Down-regulated IL-1β, IL-6, and TNF-α and upregulated IL-10	
	GTS	(5, 10, 20, 40, 60 and 80 mg/kg, i.p.)		Improved NSS score Increased the expression of NGF, GDNF and NCAM Inhibited the expression of Nogo-A, Nogo-B, TN-C, and the number of BrdU/nestin positive NSCs in the hippocampal formation	110
	GTS	(10, 20, 40, 60 and 80 mg/kg, i.p.)		Improved neurological function and histological morphology of brain tissue	112
M. sylvestris		250 and 500 mg/kg	CCI	Improved cognitive function in MVM test Reduced neuronal loss, GFAP positive cells, ROS production and levels of LPO, IL-1β, IL-6, and TNF-α Increased SOD level	96
R. tanguticum	AE	3, 6 and 12 mg/kg	CCI	Ameliorated BBB damage and brain edema Increased SOD, CAT, GSH, and GSH/GSSG ratio Decreased the MDA and GSSG levels	114,115
	Polysaccharide	100, 200 and 400 mg/kg	WDIAI	Reduced water content and MDA levels Increased SOD and Na+-K+ ATPase activity	116
S. tomentosa	Luteolin	20 mg/kg	CCI	Reduced levels of TNFα and IL-1β in blood and brain tissue	122
N. sativa	TQ	10 mg/kg	WDIAI	Reduced activity of LDH and plasma copeptin level in brain tissue	134
D. cochinchinenesis	AE	40 and 80 mg/kg	WDIAI	Reduced serum levels of MDA, IL-1β, TNF-α and IL-6, and the amount of neuronal cell apoptosis in brain tissue Increased serum SOD activity	143
P. cuspidati	Emodin	10 mg/kg	WDIAI	Improved NSS Reduced BBB permeability, ameliorated brain edema	150

				Inhibited the expression of AQP-1, AQP-4 and AQP-9, HIF-1α and MMP-9	
	Resveratrol	100 mg/kg	WDIAI	Improved NSS	[151]
				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	[154]
				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	[164]
				Improved neurological deficits	
C. longa	Curcumin	500 ppm	FPI	Improved cognitive function in MVM test	[168-171]
				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	[174]
				Improved NSS	
	Curcumin	75, 150 and 300 mg/kg	CCI	Reduced cerebral edema, AQP4 expression, NF-κB activation and IL-1β expression	[173]
				Improved neurological function	
	Curcumin	50 and 100 mg/kg	WDIAI	Reduced cerebral damage and brain levels of MDA	[172]
				Improved neurological functions	

C. zedoaria	β-elemene	100 mg/kg	WDIAI	Improved NSS Reduced TNF-α, IL-1ß, TUNEL positive cells, apoptosis index and expression of TLR4 and casepase 3 Increased expression of IkB	181
D. fortune	AE	45±0.05 ml/rat	WDIAI	Reduced the level of CD8 T cells No effect on IL-2 and CD4 levels	194
	AE	20 mg/kg	CCI	Decreased brain lesion volume, IL-6 Improved NSS and cognitive function Increased IL-10, blood monocyte numbers and percentage of blood CD3 and CD4 T lymphocytes Inhibited microglial/macrophage activation	195
S. Militorrhiza	SalB	25 mg/kg	CCI	Reduced brain water content, lesion volume, PMN, Iba-1, TNF-α and IL-1β Increased IL-10 and TGF-β1 Improved neurological function	184
S. khuzistanica	EO	50, 100 and 200 mg/kg	WDIAI	Ameliorated brain edema, damage to BBB and veterinary coma scale (VCS) scores Reduced levels of TNF-a, IL-1ß, IL-6, intracranial pressure, neuronal death and BBB permeability Increased IL-10 level and numbers of viable astrocytes	190
S. baicalensis	Baicalein	30 mg/kg	CCI	Reduced the number of degenerating neurons, contusion volume, mRNA and protein expression of TNF-α, IL-1β and IL-6 Improved neurological functions	192

Abbreviations: TBI.: Traumatic brain injury, Exp.: Experimental, Ref.: Reference, Ext.: Extract, Conc.: Concentration, EO.: Essential oil, AE.: Aqueous extract, AEE.: Aqueous ethanolic extract, FPI.: Fluid percussion

injury, HSYA.: Hydroxysafflor yellow A, CCI.: Cortical impact injury, miR-155.: microRNA-155, HO-1.: heme oxygenase 1, BDNF.: Brain-derived neurotrophic factor, VEGF.: Vascular endothelial growth factor, GDNF.: Glial cell line-derived neurotrophic factor, SOD.: Superoxide dismutase , AChE.: Acetylcholinesterase, NOSs.: Nitric oxide synthases , NO.: nitric oxide, CAT.: Catalase, GSH.: Glutathione, GSH/GSSG.: Glutathione /Glutathione disulfide, MDA.: Malondialdehyde, CI.: Cold injury, NF-Kβ.: Nuclear factor kappa B, GFAP.: Glial fibrillary acidic protein, NCAM.: Neuronal cell adhesion molecule, Nrf2.: Nuclear factor erythroid 2-related factor 2, IL-1β.: Interleukin-1β , TNF-α.: Tumor necrosis factor-α, NSS.: Neurological severity score, BBB.: Blood brain barrier , GTS.: Ginseng total saponins, WDIAI.: Weight drop–impact acceleration injury, TQ.: Thymoquinone, LDH.: Lactate dehydrogenase, AQP-1.: Aquaporin-1 , HIF-1α.: , Hypoxia-inducible factor-1α MMP-9.: Matrix metalloprotein-9 , LFP.: Lateral fluid percussion, ROS.: Reactive oxygen species, GPx.: Glutathione Peroxidase, NRG-1.: Neuregulin-1, TUNEL.: Terminal deoxynucleotidyl transferase dUTP nick end labeling, TLR4.: Toll-like receptor4, IkB.: Inhibitor of kB, Bcl-2.: B-cell lymphoma 2, NGF.: nerve growth factor, GDNF.: Glial cell line-derived neurotrophic factor, NCAM .: Neural cell adhesion molecule, Nogo-A.: Neurite outgrowth inhibitor A, TN-C.: Tenascin-C, BrdU.: 5-Bromo-2′-deoxy-uridine, NSCs.: Neural stem/progenitor cells, RANTES.: Regulated on activation, normal T cell expressed and secreted, TGF-β1.: Transforming growth factor beta 1, SalB.: Salvianolic acid B.

Figure 1. Neuroprotective effects of medicinal plants on TBI.

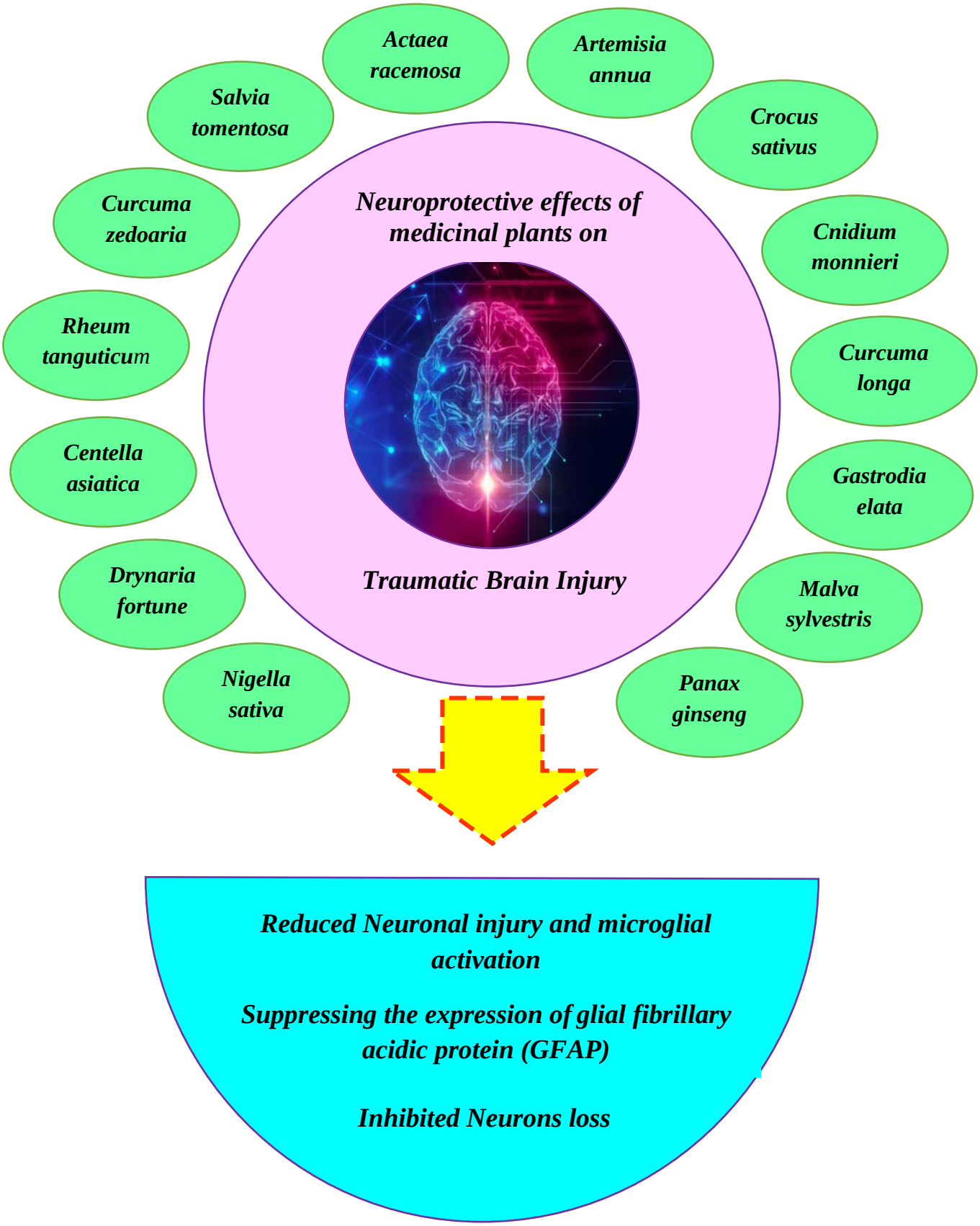
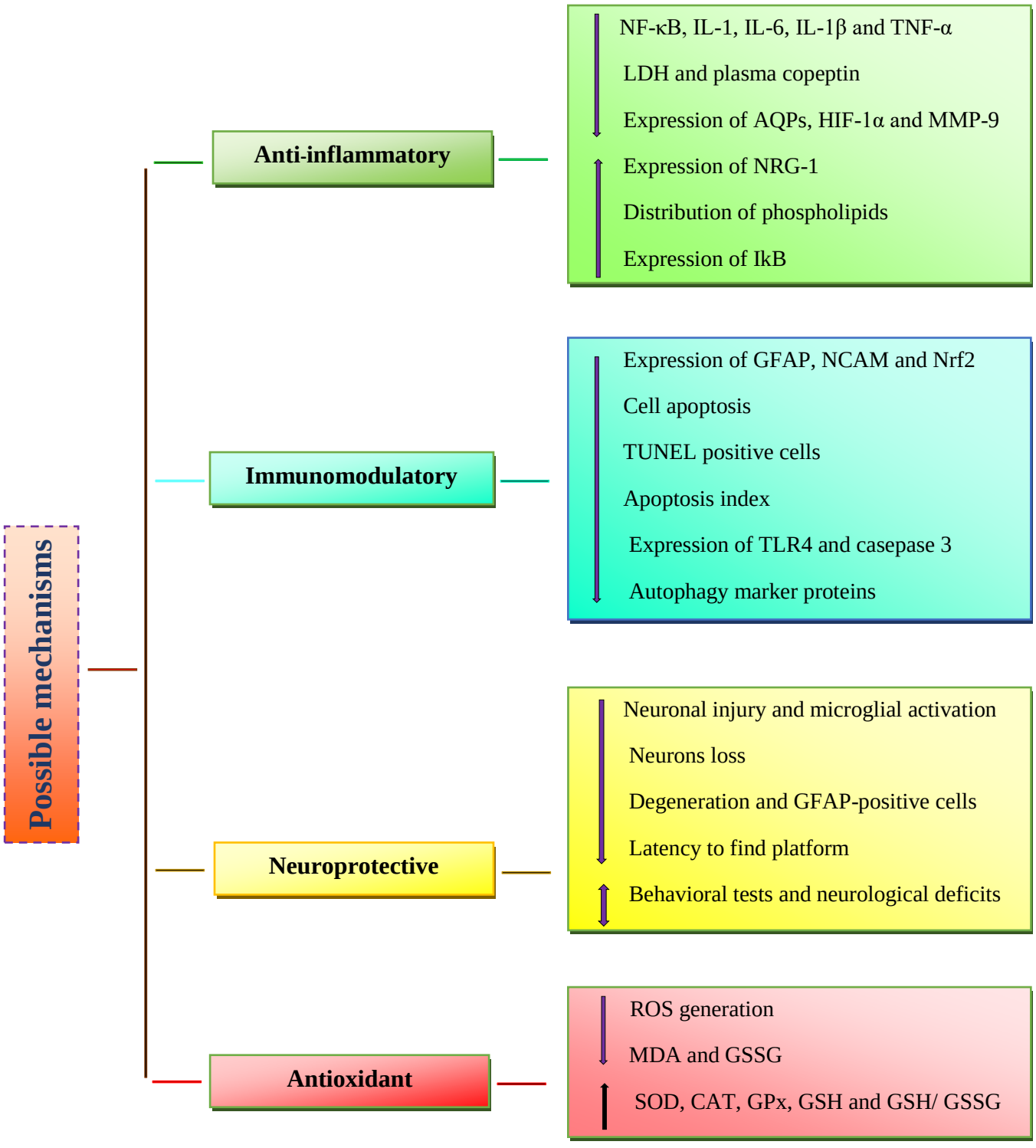


Figure 2. Possible mechanisms of action of medicinal plants on TBI.



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