Medicinal plants in traumatic brain injury: Neuroprotective mechanisms revisited

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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 other organs especially kidneys, gastrointestinal tract, and heart function. In this review, the search terms were TBI, fluid percussion injury, cold injury, weight drop impact acceleration injury, lateral fluid percussion, cortical impact injury, and blast injury. Studies with Actaea racemosa, Artemisia annua, Aframomum melegueta, Carthamus tinctorius, Cinnamomum zeylanicum, Crocus sativus, Cnidium monnieri, Curcuma longa, Da Chuanxiong Formula, Erigeron breviscapus, Panax ginseng, Salvia tomentosa, Satureja khuzistanica, Nigella sativa, Drynariae cochinchenensis, Polygonum cuspidatum, Rosmarinus officinalis, Rheum tanguticum, Centella asiatica, and Curcuma zedoaria show a significant decrease in neuronal injury by different mechanisms such as increasing superoxide dismutase and catalase activities, suppressing nuclear factor kappa B (NF-κB), interleukin 1 (IL-1), glial fibrillary acidic protein, and IL-6 expression. The aim of this study was to evaluate the neuroprotective effects of medicinal plants in central nervous system pathologies by reviewing the available literature.

KEYWORDS
brain, medicinal plants, signaling mechanisms, TBI, trauma

Abbreviations: AChE, Acetylcholinesterase; AE, Aqueous extract; AEE, Aqueous ethanolic extract; AQP-1, Aquaporin-1; BBB, Blood brain barrier; Bcl-2, B-cell lymphoma 2; BDNF, Brain-derived neurotrophic factor; BrdU, 5-Bromo-2-deoxy-uridine; CAT, Catalase; CCl, Cortical impact injury; CI, Cold injury; Conc, Concentration; EO, Essential oil; Exp, Experimental; Ext, Extract; FPI, Fluid percussion injury; GDNF, Glial cell line-derived neurotrophic factor; GFAP, Glial fibrillary acidic protein; GPx, Glutathione Peroxidase; GSH, Glutathione; GSH/GSSG, Glutathione /Glutathione disulfide; GTS, Ginseng total saponins; HIF-1α, Hypoxia-inducible factor-1α; HO-1, Heme oxygenase 1; HSYA, Hydroxysafflor yellow A; IkB, Inhibitor of κB; IL-1β, Interleukin-1β; LDH, Lactate dehydrogenase; LFP, Lateral fluid percussion; MDA, Malondialdehyde; miR-155, microRNA-155; MMP-9, Matrix metalloprotein-9; NCAM, Neural cell adhesion molecule; NF-κB, Nuclear factor kappa B; NGF, nerve growth factor; NO, nitric oxide; Nogo-A, Neurite outgrowth inhibitor A; NOSs, Nitric oxide synthases; Nrf2, Nuclear factor erythroid 2-related factor 2; NRG-1, Neuregulin-1; NSCs, Neural stem/progenitor cells; NSS, Neurological severity score; RANTES, Regulated on activation normal T cell expressed and secreted; Ref, Reference; ROS, Reactive oxygen species; SalB, Salvianolic acid B; SOD, Superoxide dismutase; TBI, Traumatic brain injury; TGF-β1, Transforming growth factor beta 1; TN-C, Tenascin-C; TNF-α, Tumor necrosis factor-α; TLR4, Toll-like receptor 4; TQ, Thymoquinone; TUNEL, Terminal deoxynucleotidyl transferase dUTP nick end labeling; VEGF, Vascular endothelial growth factor; WDIAl, Weight drop–impact acceleration injury.

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1 | INTRODUCTION

One of the major causes 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 deficits 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 with the pathophysiology of TBI. In addition, myelin and multifocal axonal abnormalities are also attributed to posttraumatic cognitive impairments.\(^3,6\)

Various aspects of human TBI have been studied in a variety of animal models over the decades to have a better understanding of pathophysiology and potential treatments. The models of TBI include cortical impact injury (CCI), fluid percussion injury (FPI), blast injury, and weight drop impact acceleration injury (WDIAI) (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 have shown to exert neuroprotective effects due to their antioxidant and anti-inflammatory actions on nerve function. The medicinal plants included in this review are *Aframomum melegueta* (*A. melegueta*), *Carthamus tinctorius* (*C. tinctorius*), *Cinnamomum zeylanicum* (*C. zeylanicum*), *Crocus sativus* (*C. sativus*), Da Chuanxiong Formula (DCXF), *Erigeron breviscapus* (*E. breviscapus*), *Panax ginseng* (*P. ginseng*), *Salvia tomentosa* (*S. tomentosa*), *Nigella sativa* (*N. sativa*), *Dracaena cochinchinensis* (*D. cochinchinensis*), *Polygonum cuspidatum* (*P. cuspidatum*), *Rosmarinus officinalis* (*R. officinalis*), *Centella asiatica* (*C. asiatica*), and *Curcuma zedoaria* (*C. zedoaria*). To date, there are no reviews about the neuroprotective function of medicinal plants in TBI. In view of the 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 (Table 2).

2 | METHODS

Online literature resources were searched using search engines such as ISI Web of Knowledge, PubMed, 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 TBI, medicinal plants, FPI, cold injury (CI), CCI, lateral fluid percussion (LFP), WDIAI, and blast injury. All of

| 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 affect 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. |
| Plant           | Ext./cons. | Dose                          | Exp. model | Effect                                                  | References |
|----------------|------------|-------------------------------|------------|--------------------------------------------------------|------------|
| A. racemosa    | Formononetin | 10 and 30 mg/kg              | WDIAI      | Improved NSS score                                     | 8          |
|                | Formononetin | 10 and 30 mg/kg              | WDIAI      | Increased cortical neuronal numbers and IL-10 decreased IL-6 and TNFα | 9          |
|                |             |                               |            | Reduced brain edema and inhibited neuronal apoptosis upregulated the expression levels of mir-155 and HO-1 and downregulated the protein expression of BACH1 |            |
| A. melegueta   | AEE         | 10, 100, 250, 500, and 1,000 mg/kg | FPI        | Reduced neuronal injury and microglial activation      | 10         |
| A. sativum     | Allicin     | 1, 10, and 50 mg/kg          | CCI        | Reduced contusion volume, water content, Bcl-2/Bax ratio, MDA, protein carbonyl, TNFα, and IL-1β | 11         |
|                |             |                               |            | 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-1β, TNFα, iNOS, BDNF, VEGF, GDNF, and inflammasome components (NLRP3, ASC, and caspase-1) | 12         |
| C. tinctorius  | HSYA        | 10 and 30 mg/kg              | CCI        | Increased SOD, CAT, GSH, and GSH/GSSG ratio            |            |
|                | Polyphenol E | 10 mg/kg                      | CI         | Decreased MDA and GSSG                                | 13         |
| C. zeylanicum  |             |                               |            | Reduced infarct and edema formation suppressing the expression of NF-κB, IL-1, IL-6, GFAP, NCAM, and Nrf2 |            |
| C. montnieri   | Osthole     | 10, 20, and 40 mg/kg         | WDIAI      | Reduced neurological deficits, cerebral edema, and hippocampal neuron loss | 14         |
|                |             |                               |            | 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                  | 15         |
|                |             |                               |            | Reduced microglial activation, cell apoptosis, and release of IL-1β and TNFα |            |
|                |             |                               |            | Improved NSS and brain edema                           |            |
| DCXF           | AE          | 520.6 and 2,603.0 mg/kg       | CCI        | Improved behavioral tests                              | 16         |
|                |             |                               |            | Reduced BBB permeability, brain edema, microglia and astrocyte activation, and neurons loss |            |
| E. breviscapus | Breviscapine | 75 μg                        | CCI        | Improved NSS score                                    | 17         |
|                |             |                               |            | Reduced expression of IL-6 in the injured cortex and IL-6-positive cell number in injured brain tissue |            |
| G. elata       | AE          | 505 and 1,515 mg/kg          |            | Improved locomotor functions                           | 18         |
|                |             |                               |            | Reduced the number of astrocyte and the expression of IL-6 and TNFα |            |
| P. ginseng     | AE          | 50, 100, and 200 mg/kg       | WDIAI      | Improved neurological deficits                         | 19         |
|                |             |                               |            | Reduced levels of MDA, nitrite, AChE, TNFα, and IL-6 increased GSH, SOD, and CAT |            |
|                | GTS         | 100 and 200 mg/kg            | CCI        | Reduced neuronal loss in the hippocampal regions of CA1, CA2, and CA3, contusion volume, and percentage of contusion | 20         |
|                |             |                               |            | Improved neurological deficits                         |            |

(Continues)
| Plant               | Ext./cons.          | Dose                             | Exp. model | Effect                                                                 | References |
|---------------------|---------------------|----------------------------------|------------|------------------------------------------------------------------------|------------|
|                      |                     |                                  |            | **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                                          |            |
|                      |                     |                                  |            | Downregulated 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 | 22 |
|                      |                     |                                  |            | Inhibited the expression of Nogo-A, Nogo-B, TN-C, and the number of BrdU/nestin positive NSCs in the hippocampal formation | | |
|                      |                     |                                  |            | **Improved neurological function and histological morphology of brain tissue** | 23 |
| GTS                 | (5, 10, 20, 40, 60, and 80 mg/kg, i.p.) |                                  | Reduced neuronal loss, GFAP-positive cells, ROS production, and levels of LPO, IL-1β, IL-6, and TNF α | 24 |
|                      |                     |                                  |            | Increased SOD level                                                    |            |
| 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, CAT, GSH, and GSH/GSSG ratio | 24 |
|                      |                     |                                  |            | Decreased the MDA and GSSG levels | 24 |
|                      |                     |                                  |            | **Reduced water content and MDA levels** | 25,26 |
|                      |                     |                                  |            | Increased SOD and Na+K+ATPase activity | 25,26 |
| R. tanguticum        | AE                  | 3, 6, and 12 mg/kg              | CCI        | Ameliorated BBB damage and brain edema | 25,26 |
| Polysaccharide       | 100, 200, and 400 mg/kg | WDIAI                           | Reduced water content and MDA levels | Increased SOD and Na+K+ATPase activity | 27 |
| S. tomentosa         | Luteolin            | 20 mg/kg                         | CCI        | Reduced levels of TNF α and IL-1β in blood and brain tissue | 28 |
| N. sativa            | TQ                  | 10 mg/kg                         | WDIAI      | Reduced activity of LDH and plasma copeptin level in brain tissue | 29 |
| 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 | 30 |
|                      |                     |                                  |            | Increased serum SOD activity | 30 |
| P. cuspidatum        | Emodin              | 10 mg/kg                         | WDIAI      | Improved NSS | 31 |
|                      |                     |                                  |            | Reduced BBB permeability and ameliorated brain edema | 31 |
|                      |                     |                                  |            | Inhibited the expression of AQP-1, AQP-4 and AQP-9, HIF-1α, and MMP-9 | 31 |
|                      | Resveratrol         | 100 mg/kg                        | WDIAI      | Improved NSS | 32 |
|                      |                     |                                  |            | Reduced escape latency, brain edema, levels of the autophagic marker proteins, microtubule-associated protein light chain 3-II and Beclin1 in the hippocampus | 32 |
| 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 | 33 |
|                      |                     |                                  |            | Increased time spent in target quadrant and activity of SOD, GPx, and CAT | 33 |
| C. asiatica          | AEE                 | 90 mg/kg                         | WDIAI      | Increased the activation of Krox-20, the expression of NRG-1, and the distribution of phospholipids | 34 |
|                      |                     |                                  |            | (Continues) | 34 |
| Plant         | Ext./cons. | Dose                  | Exp. model | Effect                                                                 |
|--------------|-----------|-----------------------|------------|-------------------------------------------------------------------------|
| *C. longa*   | Curcumin  | 500 ppm               | FPI        | Improved neurological deficits                                          |
|              |           |                       |            | Improved cognitive function in MVM test                                |
|              |           |                       |            | Reduced oxidative stress                                               |
|              |           |                       |            | Increased BDNF levels                                                  |
|              |           |                       |            | Protected synaptophys and mitochondria                                  |
|              | Curcumin  | 50, 100, and 200 mg/kg| WDIAI      | Reduced IL-1β, IL-6, TNFα, MCP-1 and RANTES, TLR4 expression, neuronal and apoptotic cell death, and microglial activation |
|              |           |                       |            | Improved NSS                                                           |
|              | Curcumin  | 75, 150, and 300 mg/kg| CCI        | Reduced cerebral edema, AQP4 expression, NF-κB activation, and IL-1β expression |
|              |           |                       |            | Improved neurological function                                          |
|              | Curcumin  | 50 and 100 mg/kg      | WDIAI      | Reduced cerebral damage and brain levels of MDA improved neurological functions |
| *C. zedoaria*| β-Elemene | 100 mg/kg             | WDIAI      | Improved NSS                                                           |
|              |           |                       |            | Reduced TNFα, IL-1β, TUNEL positive cells, apoptosis index, and expression of TLR4 and caspase-3 |
|              |           |                       |            | Increased expression of IkB                                               |
| *D. Fortune* | AE        | 45 ± 0.05 mL/rat      | WDIAI      | Reduced the level of CD8 T cells                                        |
|              |           |                       |            | No effect on IL-2 and CD4 levels                                       |
|              | 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 increased microglial/macrophage activation |
| *S. miltiorrhiza* | SalB     | 25 mg/kg              | CCI        | Reduced brain water content, lesion volume, PMN, Iba-1, TNFα, and IL-1β |
|              |           |                       |            | Increased IL-10 and TGF-β1                                             |
|              |           |                       |            | Improved neurological function                                          |
| *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 TNFα, IL-1β, IL-6, intracranial pressure, neuronal death, and BBB permeability increased IL-10 level and numbers of viable astrocytes |
| *S. baicalensis* | Baicalein | 30 mg/kg              | CCI        | Reduced the number of degenerating neurons, contusion volume, and mRNA and protein expression of TNFα, IL-1β, and IL-6 |
|              |           |                       |            | Improved neurological functions                                          |

Abbreviations: AChE, acetylcholinesterase; AE, aqueous extract; AEE, aqueous ethanolic extract; AQP-1, aquaporin-1; BBB, blood–brain barrier; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; BrdU, 5-bromo-2′-deoxyuridine; CAT, catalase; CCI, cortical impact injury; Conc, concentration; CI, cold injury; EO, essential oil; Exp, experimental; Ext, extract; FPI, fluid percussion injury; GDNF, glial cell line-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GSH, glutathione; GSH/GSSG, glutathione/glutathione disulfide; GPx, glutathione peroxidase; GTS, ginseng total saponins; HO-1, heme oxygenase 1; HIF-1α, hypoxia-inducible factor-1α; HSYA, hydroxysafflor yellow A; IL-1β, interleukin-1β; IκB, inhibitor of κB; LDH, lactate dehydrogenase; LFP, lateral fluid percussion; MDA, malondialdehyde; miR-155, microRNA-155; MMP-9, matrix metalloprotein-9; NCAM, neuronal cell adhesion molecule; NF-κB, nuclear factor kappa B; NGF, nerve growth factor; NO, nitric oxide; Nogo-A, neurite outgrowth inhibitor A; NOSs, nitric oxide synthases; Nrf2, nuclear factor erythroid 2-related factor 2; NRG-1, neuregulin-1; NSCs, neural stem/progenitor cells; NSS, neurological severity score; ROS, reactive oxygen species; Ref, reference; RANTES, regulated upon activation of normal T cell expressed and secreted; SalB, salvianolic acid B; SOD, superoxide dismutase; TBI, traumatic brain injury; TGF-β1, transforming growth factor beta 1; TLR4, toll-like receptor4; TN-C, tenascin-C; TNFα, tumor necrosis factor alpha; TQ, thymoquinone; TUNEL, terminal deoxynucleotidyl transferase dUTP nick-end labeling; VEGF, vascular endothelial growth factor; and WDIAI, weight drop impact acceleration injury.
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 family. The chemical constituents of *A. racemosa* are caffeic acid, ferulic acid, phenylpropanoids, triterpenoids, cimigenol, and formononetin.\(^7\) This plant has been shown to have several therapeutic effects including anti-inflammatory,\(^9\) antioxidant,\(^5\) antidepressant,\(^5\) and immunomodulatory\(^5\) effects.

The effect of formononetin orally was evaluated for 7 days after the induction TBI by a 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 interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF\(\alpha\)) and increased the IL-10 levels in serum and cerebral cortex.\(^8\) In another study, intraperitoneal injection of formononetin for 5 days after the induction TBI by WDIAI rat model showed that formononetin improved NSS, reduced brain edema, and inhibited neuronal apoptosis. Additionally, formononetin upregulated the expression of microRNA-155 (miR-155) and heme oxygenase 1 (HO-1) and downregulated the expression of BACH1 in the brain tissue of TBI rats.\(^9\)

3.2 | Aframomum melegueta

*A. melegueta*, commonly known as grains of paradise, ossame, alligator pepper, melegueta pepper, efom wisia, 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, and hypertension, and is also used as purgative, galactagogue, anthelmintic, and hemostatic agents.\(^5\) The main components of this plant include cardiac glycosides, alkaloids, sterols, tannins, triterpenes, flavonoids, and oils.\(^4\) This plant also exhibits various pharmacological effects including antimicrobial,\(^5\) antiulcer and cytoprotective,\(^5\) antioxidant,\(^5\) antidiabetic,\(^5\) antifungal\(^5\) and antihypertensive\(^5\) activities.

*A. melegueta* seeds possess significant anti-inflammatory and antinociceptive activity. The antinociceptive 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.\(^6\) *A. melegueta* seeds' ethanolic extract and pure compounds including 6-paradol, 6-shogaol, and 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 anti-inflammatory effects.\(^6\) Aqueous seed extract of *A. melegueta* (50–200 mg/kg, i.p.) has been investigated in vivo by formaldehyde and nystatin-induced subchronic inflammatory conditions in rats and is found to have anti-inflammatory effects.\(^6\)

The effect of the hydroethanolic extract of *A. melegueta* seeds on male rats was evaluated in an 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.\(^10\)

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.\(^6\) This plant is also shown to have antinociceptive,\(^6\) anticonvulsant,\(^6\) anti-inflammatory, immunomodulatory,\(^6\) and antioxidant\(^6\) properties.

The effect of allicin (an organosulfur compound obtained from garlic) on a CCI model of TBI showed that allicin reduced contusion volume and water content of brain, neurological deficit scores, Bcl-2/Bax ratio, malondialdehyde (MDA), protein carbonyl, TNF\(\alpha\), and IL-1\(\beta\) levels. It increased the activities of catalase (CAT), superoxide dismutase (SOD), and GST levels of IL-10 and transforming growth factor beta 1 (TGF-\(\beta\)1). It also activated Akt and endothelial nitric oxide synthase (eNOS) as well as inhibited the activation of caspase-3 and poly(ADP-ribose) polymerase (PARP).\(^6\)

3.4 | Artemisia annua

*Artemisia annua* (A. annua), or sweet wormwood, is an annual, aromatic herb, belonging to the Asteraceae family and has been used in China to treat fevers for centuries.\(^7\) It is often used in the tropics as an affordable and effective antimalarial agent.\(^7\) Leaves of *A. annua* have been used as antiseptic, digestive, and febrifuge.\(^7\) A leaf infusion of this plant is used as a
remedy for colds, fevers, and diarrhea. The main ingredients of the essential oil of *A. annua* are beta-pinene, alphapinene, camphor, camphene, 1,8-cineole, artemisia ketone, myrcene, borneol, linalool, and beta-caryophyllene. The pharmacological effects of *A. annua* include its antimalarial, antioxidant, anti-inflammatory, antimicrobial, immunomodulatory, and anticancer properties. A variety of compounds have been isolated from *A. annua* such as coumarins, flavonoids, sesquiterpenoids, triterpenoids, phenolics, and artemisinin.

The effect of atesunate, a more stable derivative of its precursor artemisin, on a 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 inflammasome components (NLRP3, ASC, and caspase-1) as well as IL-1β, TNFα, and iNOS levels.

### 3.5 | *Carthamus tinctorius*

*C. tinctorius*, also known as Safflower, is a thistle-like annual plant with yellow, orange, or red flowers, belonging to the Compositae or Asteraceae family, cultivated mainly for its seed, which is used as edible oil and as birdseed. Traditionally, the crop was grown for its flowers, used for coloring and flavoring foods and making dyes, and in medicines. Several pharmacological effects have been described for *C. tinctorius* such as its anti-inflammatory, cardioprotective, antioxidant and neuroprotective, and anticancer properties. The standardized safflower flavonoid extract (SAFE) (35 and 70 mg/kg, p.o.) and the compounds isolated from safflower, including kaempferol 3-rutinoside (K3R), anhydrosafflor yellow B (AYB), (50, 100, and 200 μM), were evaluated for their neuroprotective effects in vitro and in vivo using Parkinson’s disease (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 behavioral performances, partially via the suppression of α-synuclein overexpression or aggregation, as well as the suppression of reactive astrogliosis. However, some studies reported the toxic effects of *C. tinctorius* on renal and brain tissues. *C. tinctorius* extract has been shown to reduce the cerebral infarction area and neurological deficits as well as expression of TNFα and IL-1β in ischemia-reperfusion (I/R) brain injury in rats.

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

### 3.6 | *Cinnamomum zeylanicum*

*C. zeylanicum* is commonly known as cinnamon, belonging to the Lauraceae family. The major components of the essential oil of *C. zeylanicum* are trans-cinnamaldehyde, eugenol, and linalool. *C. zeylanicum* is used as part of Ayurvedic medicine as a remedy for a variety of digestive, respiratory, and gynecological symptoms. Various pharmacological effects of cinnamon have been reported including antibacterial, antifungal, antioxidant, antidiabetic, anti-inflammatory, and immunomodulatory effects. When administered orally in experimental allergic encephalomyelitis in mice, cinnamon powder suppressed the expression of iNOS and IL-1β in vivo in the spinal cord and cerebellum, suggesting anti-inflammatory effects. 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 disease. In an animal model of Parkinson disease, it also protected the nigrostriatum, normalized striatal neurotransmitters, and improved motor functions.

The effect of cinnamon polyphenol extract on the CI model of TBI in mice showed that the 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.

### 3.7 | *Cnidium monnieri*

*Cnidium monnieri* (*C. monnieri*), belongs to the Apiaceae family, and is one of the most widely used traditional herbal medicines, especially its fruits. The main components of *C. monnieri* are osthole, bergapten, isopimpinellin, xanthotoxol, xanthotoxin, sesquiterpenes, cnidimonal, cnidimarin, imperatorin, and glucosides. The pharmacological effects of *C. monnieri* include its anticonvulsant, memory improvement, anti-inflammatory, and immunomodulatory 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.

### 3.8 | *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.\textsuperscript{104} C. sativus has also been used in traditional medicine for its euphoretic, antispasmodic, anticatarhal, gingival, and nerve-sedating agent. It has also been used as expectorant, diaphoretic, aphrodisiac, emmenagogue, and carminative.\textsuperscript{105} It has various pharmacological effects including anti-inflammatory, antioxidant, and immunomodulatory,\textsuperscript{106} anxiolytic and hypnotic,\textsuperscript{107} anti-convulsant,\textsuperscript{108} and anti-Alzheimer\textsuperscript{109} activities.

In a rat model of stroke, administration of crocin during induction of ischemia showed protective effects against I/R injury and cerebral edema. It also decreased brain edema and infarct volume.\textsuperscript{110} In addition, administration of crocin before TBI activated notch signaling pathway by upregulation of notch intracellular domain and basic helix-loop-helix (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 TNFα, as well as improved brain edema and NSS.\textsuperscript{115}

### 3.9 | Da Chuanxiong Formula

DCXF in Chinese traditional medicine consists of two dried rhizomes of \textit{Ligusticum chaunxiong} and \textit{Gastrodia elata} (\textit{G. elata}) at a ratio of 4:1 (w/w).\textsuperscript{111} Studies have shown that DCXF possesses therapeutic effects on stroke, dementia, vertigo, and headache, and 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.\textsuperscript{112} In lipopolysaccharide (LPS)-incitated RAW 264.7 cells, DCXF inhibited the productions of NO and PGE2 by suppressing COX-2 and iNOS expressions.\textsuperscript{111}

Treatment with DCXF aqueous extract 1 week before and 11 days after the induction TBI by a CCI model in rat improved the learning ability, memory retention, and proliferation of neural stem cells (NSCs). Results also showed that DCXF reduced activation of astrocytes and microglia, BBB permeability, brain edema, and neuronal loss in the brain with TBI.\textsuperscript{116}

### 3.10 | \textit{Erigeron brevicaespus}

\textit{E. brevicaespus} known as “Dengzhanxixin,” belonging to the Asteraceae family, 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.\textsuperscript{113} The chemical constituents of \textit{E. brevicaespus} are flavonoids, triterpenes, caffeoyl derivatives, and steroids.\textsuperscript{114} It has been shown to have antifungal, antimicrobial,\textsuperscript{115} antioxidant,\textsuperscript{116} and anti-inflammatory\textsuperscript{117} activities.

Injection of 75 μg breviscapine (a flavonoid extracted from \textit{E. brevicaespus}) 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.\textsuperscript{117}

### 3.11 | \textit{Gastrodia elata}

\textit{G. elata} is a saprophytic perennial herb from the Orchidaceae family. The dried rhizome of \textit{G. elata} is used as a traditional Chinese medicine for remedy of neurological disorders such as Alzheimer, general paralysis, headache, convulsions, vertigo, stroke, and tetanus.\textsuperscript{118} The main components with neuropharmacological properties are 4-hydroxybenzaldehyde, gastrodin, vanillin, and vanillyl alcohol.\textsuperscript{119} It has been shown to have various pharmacological effects including antimicrobial,\textsuperscript{120} antimitogenic,\textsuperscript{121} antioxidative,\textsuperscript{122} and anti-inflammatory\textsuperscript{123} properties.

The effects of \textit{G. elata} aqueous extract on the CCI model of TBI in rat showed that \textit{G. elata} improved locomotor functions in the rotarod test and reduced the number of astrocytes in immunohistochemical staining and the expression of IL-6 and TNFα in the brain tissue.\textsuperscript{118}

### 3.12 | \textit{Malva sylvestris}

\textit{Malva sylvestris} (\textit{M. sylvestris}), or common mallow, belongs to the Malvaceae family. The main components of \textit{M. sylvestris} are polysaccharides malvin, flavonoids, scoropentin, courmarins, polyphenols, niacin, folic acid, tannins, and vitamins A, C, and E.\textsuperscript{124} \textit{M. sylvestris} is used as bacteriostatic, antinociceptive, anti-inflammatory, antioxidant, and anticholinesterase agent in Chinese medicine.\textsuperscript{124}

The preventive effect of \textit{M. sylvestris} methanolic extract orally on TBI-induced CCI model in rat showed improved cognitive functions in the 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 lipidperoxides (LPO), IL-1β, IL-6, and TNFα levels in the brain tissue.\textsuperscript{124}

### 3.13 | \textit{Panax ginseng}

\textit{P. ginseng} is a perennial herb from the Araliaceae family, native to Korea and China. Ginseng, the root of \textit{P. ginseng}, has been traditionally used as an herbal remedy.\textsuperscript{125} The main components of ginseng are ginseng oils, phytosterol, saponins, organic acids, nitrogenous substances, enzymes, vitamins, and minerals.\textsuperscript{126} It has been shown to have antimicrobial,\textsuperscript{127} antifungal,\textsuperscript{128} antioxidant,\textsuperscript{129} antiviral,\textsuperscript{130} anti-inflammatory and antifatigue,\textsuperscript{131} and anti-asthmatic activities.\textsuperscript{132}

Oral administration of ginsenoside Rb1, which is the main bioactive component in ginseng, significantly increased cell survival in the dentate gyrus and hippocampus, which could
be potentially related to its effects on memory and learning.\textsuperscript{133} In addition, ginsenoside Rg downregulated calpain I and caspase-3 and attenuated neuronal apoptosis induced by cerebral I/R injury.\textsuperscript{134}

Oral administration of \textit{P. ginseng} aqueous extract on WDIAI model of TBI in rat improved its neurological functions. In addition, \textit{P. ginseng} reduced the levels of MDA, nitrite, acetylcholinesterase (AChE), TNFα, and IL-6 and increased GSH, SOD, and CAT in hippocampus and cerebral cortex.\textsuperscript{19}

The major ingredient of \textit{P. ginseng}, ginseng total saponins (GTS), is shown to have neuroprotective effects against TBI. GTS when administered intraperitoneally significantly reduced neuronal loss in the 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.\textsuperscript{20}

In a similar study, assessment of the preventive effects of GTS on TBI-induced CCI model in rat showed that treatment with GTS after induction of TBI improved NSS score and reduced brain water content, neuronal loss in the hippocampus. This increased the activity of SOD; downregulated IL-1β, IL-6, and TNFα; and upregulated IL-10. This also inhibited the apoptotic cell death and expression of caspase-3, bax, and Bcl-2.\textsuperscript{21} Similarly, the effect of administration of GTS on the CI model of TBI rats was shown to have improved recovery of neurological functions, including learning and memory and reduced cell loss in the hippocampus.\textsuperscript{22}

In another study, GTS improved NSS score, increased SOD activity, and reduced brain water content, MDA level, and expression of IL-1β and TNFα.\textsuperscript{135} In addition, administration of GTS after induction of TBI improved neurological function and histological morphology of brain tissue in rats.\textsuperscript{23}

### 3.14 | Rheum tanguticum

\textit{Rheum tanguticum} (R. tanguticum), also known as rhubarb in Chinese, belongs to the Polygonaceae family. Traditionally, the roots and rhizomes of \textit{R. tanguticum} have been used as a poultice for their antispasmodic, antineoplastic, antibacterial, and antipyretic properties and also to reduce obesity, lipid, and blood pressure.\textsuperscript{136}

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 and increased SOD, CAT activities, GSH level, and GSH/GSSG ratio. It also decreased the levels of MDA and GSSG. Rhubarb also prevented the gp91phox subunit of NADPH oxidase activation-induced ROS production. Additionally, this inhibited ERK/MMP-9 pathway both in vivo and in vitro as well as downregulated GFAP in vitro.\textsuperscript{25,26} Oral administration of polysaccharide extracted from \textit{R. tanguticum} (RTP) for 5 days exhibited marked protective effects on oxidative stress and brain edema on the WDIAI model of TBI in rats by reduction of water content and MDA levels. This also resulted in the enhancement of SOD and Na+K+ATPase activity after injury.\textsuperscript{27}

### 3.15 | Salvia tomentosa

\textit{S. tomentosa} belongs to the Lamiaceae family. It has been used in traditional Chinese medicine to manage various conditions including stomatitis, glossitis, gingivitis, pharyngitis, flatulent dyspepsia, galactorrhea, and hyperhidrosis.\textsuperscript{137} The major components of the essential oil from \textit{S. tomentosa} include β-pinene, α-pinene, \textit{trans}-pinocarveol, myrtenol, caryophyllene oxide, and d-camphor.\textsuperscript{138} The reported effects of this herb include antioxidant,\textsuperscript{139} and antibacterial,\textsuperscript{140,141} activities.

The effect of luteolin, which is a flavone, isolated from the aromatic flowering plant of \textit{S. tomentosa} on the CCI model of TBI in mice showed that it significantly reduced levels of TNFα and IL-1β in blood and brain tissue of mice.\textsuperscript{28}

### 3.16 | Nigella sativa

\textit{N. sativa} is a grassy plant from the Ranunculaceae family, which grows in cold and temperate climates. The seeds of \textit{N. sativa} contain thymoquinone (TQ) and monoterpene including p-cymene, a-pinene,\textsuperscript{141} nigellidine,\textsuperscript{142} nigellimine,\textsuperscript{143} and a saponin.\textsuperscript{144} The seeds have different pharmacological effects including anti-asthmatic, antidiyspnea,\textsuperscript{145} antinociceptive, antidepressant, anti-hypertensive,\textsuperscript{146} anti-inflammatory, immunomodulatory,\textsuperscript{147} anticonvulsant,\textsuperscript{148} anxiolytic,\textsuperscript{149} and antinociceptive effects.\textsuperscript{150}

It has been shown that \textit{N. sativa} improved neurological functions and reduced the infarct volume in middle cerebral artery-occluded rats.\textsuperscript{151} Treatment with thymoquinone orally for 1 week after the induction TBI by WDIAI model in mice reduced lactate dehydrogenase (LDH) activity and plasma copeptin level in the brain tissue.\textsuperscript{29}

### 3.17 | Dracaena cochinchinensis

\textit{D. cochinchinensis} belongs to the Asparagaceae family and is widely cultivated in different provinces of China. The main components of \textit{D. cochinchinensis} are flavonoids, terpenes, steroids, saponins, and phenols.\textsuperscript{152} Resina Draconis (RD), which is a resin obtained from \textit{D. cochinchinensis}, is a popular traditional Chinese medicine widely used for the management of various conditions including cerebral arterial thrombosis, ischemic heart disease,\textsuperscript{153} and trauma and allergic dermatitis.\textsuperscript{154,155} Several therapeutic effects of RD have been described including its
antitumor,156 antidiabetes,157 analgesic, anti-inflammatory,119 and immunomodulatory158 activities.

Administration of RD aqueous extract intraperitoneally for 5 days after the induction TBI by WDIAI model in rat reduced the serum levels of MDA, IL-1β, TNFα, and IL-6. It also reduced the amount of neuronal cell apoptosis in brain tissue as well as increased the serum SOD activity.159

3.18 | Polygonum cuspidatum

P. cuspidatum also known as Hu Zhang in Chinese belongs to the Polygonaceae family. It has been used as a traditional Chinese medicine for the management of inflammatory conditions, infections, jaundice, skin burns, and hyperlipidemia.30 The reported therapeutic effects include anti-inflammatory,160 analgesic, antibacterial, antiviral analgesic,161 immunomodulatory,162 and anticancer163 activities. The major compounds of P. cuspidatum are polydatin, resveratrol, torachryson-8-O-glucoside, and emodin.164

The effect of oral administration of emodin after the induction TBI by WDIAI model in rat significantly ameliorated brain edema after TBI, improved 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-9.165 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.31

3.19 | Rosmarinus officinalis

R. officinalis, known as rosemary, belongs to the Lamiaceae family. It has been shown to have different therapeutic effects including antibacterial (Huhtanen),166 antinociceptive, anti-inflammatory (Takaki et al.),167 antioxidant (Inatani et al.),168 and vascular smooth muscle relaxant properties (Aquels).169 The main constituents of the essential oil of R. officinalis are gamma-terpinene, p-cymene, linalool, eucalyptol, thymol, alpha-pinene, and beta-pinene.32

The neuroprotective effects of R. officinalis in the transient model of focal cerebral ischemia have shown to be related to its ability to decrease subcortical and cortical infarct volumes, NSS, cerebral edema, and BBB permeability.170 Oral administration of R. officinalis after induction of TBI by LFP model reduced the latency to find platform and increased time spent in target quadrants in Morris water maze (MWM). Additionally, it reduced neuronal degeneration and GFAP-positive cells. It also reduced the levels of TNFα, IL-1β, and IL-6 in hippocampus and increased activity of glutathione peroxidase (GPx), SOD, and CAT.171

3.20 | Centella asiatica

C. asiatica is a perennial plant belonging to the Umbelliferae family.33 The main components of C. asiatica are saponins, brahminoside, glycosides, isothankuniside and hankuniside, sterols, and flavonoids.172 This plant has been shown to have several pharmacological effects including anti-inflammatory,173 wound healing,174 sedative, anxiolytic,175 antidepressant,176 anticonvulsant,177 and antioxidant178 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.179 It has also been shown that after the induction TBI by WDIAI model in rat, administration of C. asiatica hydroethanolic extract intraperitoneally increased the activation of Krox-20, the expression of neuregulin-1 (NRG-1), and the distribution of phospholipids and improved neurological functions.180

3.21 | Curcuma longa

Curcumin is known as the golden spice, belongs to the family of Zingiberaceae. It is applied in Ayurvedic medicine for the treatment of inflammatory diseases for a long time. This plant and its bioactive polyphenols, curcuminoids, have been shown to exert several therapeutic actions including anti-asthmatic,34 antioxidant,181–183 immunomodulatory,35 hepatoprotective,36,37 antitumor,38,40,41 and anti-inflammatory39,184,185 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, and increased BDNF levels, as well as protected synaptic proteins and mitochondria.186–189 Treatment with curcumin intraperitoneally 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 tests.32 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 functions in the rotarod and open-field tests in the CCI-induced TBI in mice.190 In a similar study, assessing the preventive effect of curcumin after the induction TBI by WDIAI model in mice showed that curcumin reduced TNFα, MCP-1, IL-1β, IL-6, and RANTES (regulated upon activation, normal T cells expressed and secreted), TLR4 expression, and neuronal and apoptotic cell death. It also reduced microglial activation and improved NSS.191
3.22 | Curcuma zedoaria

Curcuma zedoaria, known as zedoary and white turmeric, belongs to the Zingiberaceae family. The main ingredients of the essential oil of C. zedoaria are curzerenone, germacrene, curdione, 1,8-cineole, cumene, α-phellandrene, β-turmerone, β-elemene, 1,8-cineole, and zingiberene. Different therapeutic effects include antisecretory ulcer, anti-inflammatory, antinociceptive, antioxidant, and anticancer properties.

The effect of curdione after the induction middle cerebral artery occlusion surgery by cerebral I/R model in rat showed that curdione reduced the NSS and infarct size. It also improved cognitive function and neuronal morphologic damage. In addition, it decreased MDA content and improved cognitive function and neuronal morphologic damage. In addition, it decreased MDA content and improved cognitive function and neuronal morphologic damage. In addition, it decreased MDA content and improved cognitive function and neuronal morphologic damage.

3.23 | Salvia miltiorrhiza

Salvia miltiorrhiza (S. miltiorrhiza), 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. The chemical composition of S. miltiorrhiza are tanshinone I, tanshinone IIA, salvianolic acid (or salvianolic acid B), and dihydrotanshinone.

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

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. In folk medicine, S. khuzistanica is used as an analgesic and antiseptic. Several therapeutic effects for saffron including antidiarrhea and antispasmodic, anti-inflammatory, antinociceptive, and antioxidant properties have been described.

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

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

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.

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 that R. drynariae significantly reduced the level of CD8 T cells without affecting the levels of IL-2 and CD4 cells. 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, and improved cognitive function and NSS. In addition, in the CCI model of TBI in rats, blood monocyte numbers, IL-10, and the percentage of blood CD3 and CD4 T lymphocytes increased. This also inhibited macrophage and microglial activation.

4 | MOLECULAR MECHANISMS UNDERLYING THE NEUROPROTECTIVE EFFECTS ON TBI

It was shown that the therapeutic effects of medicinal plants on TBI are mainly mediated by anti-inflammatory, antioxidant, 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. 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. Protective effect of allicin on TBI is potentially associated with its antioxidative and anti-inflammatory properties through the Akt/eNOS pathway. 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.

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

Crocin has also shown to inhibit the production of pro-inflammatory cytokines and suppress notch signaling activation. In a CCI model of TBI, it was shown that DCXF aqueous extract improved the proliferation of NSCs and reduced BBB damage as well as brain edema. This also alleviated the neuronal loss and improvement in neurological functions including learning, memory, and motor abilities mainly through inhibition of inflammation process. 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 Ca²⁺, overload, excitatory amino acid toxicity, inflammatory suppression, regulation of brain blood vessel activity, and suppression of IL-6 expression. The protective effect of *G. elata* on TBI could be associated with the reduction of pro-inflammatory cytokines, inflammation, and astrocytes’ accumulation. Treatment with *M. sylvestris* prevented neurodegeneration after TBI by reducing astrocitosis, pro-inflammatory cytokines, and oxidative stress in the brain tissue.

The potential therapeutic effects of *P. ginseng* could be due to inhibition of inflammatory mediators, reactive oxygen species (ROS) production, and microglial activation. Ginsenosides have been shown to protect neurons from ischemic damage and rescue hippocampal neurons from ischemic damage by free radicals’ scavenging.

**FIGURE 1** Summary of neuroprotective mechanisms of medicinal plants against traumatic brain injury
administration after TBI has been shown to reduce secondary injuries by reducing oxidative and nitritative stress as well as attenuating the expression of pro-inflammatory cytokines and apoptotic cell death.21 The protective effect of GTS on neurobehavioral disorders after TBI was related to regulating the expression of nerve growth-related factors and improving neural stem/progenitor cells' proliferation.22 The underlying mechanisms of GTS on TBI induced and modified Feeney's method could be potentially mediated through various mechanisms including reducing MDA level, expression of TNFα and IL-1β, generation of reactive oxygen species (ROS), and elevating the activity of SOD and inflammatory reactions.135 R. tanguticum has been shown to have neuroprotective effects on TBI by inhibiting oxidative stress.25–27

The potential mechanism for protective effects of luteolin could be due to the inhibition of the release of inflammatory cytokines.28 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.29

Another study demonstrated the antioxidant and anti-inflammatory effects of RD aqueous extract through its effects on SOD, MDA, IL-1β, TNFα, and IL-6 levels in TBI rat.159 It has been shown that emodin attenuated brain edema and BBB disruption after TBI and mediated via inhibition of HIF-1α/AQP1s and HIF-1α/MMP-9 pathways.165 The protective effect of resveratrol was shown to have a protective effect on TBI by upregulation of postsynaptic density protein 95, synaptophysin, and by suppressing neuronal autophagy.31

R. officinalis has shown to improve cognitive deficits in TBI by inhibiting inflammation and oxidative stress.171 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.180 The proposed mechanism of curcumin on TBI includes inhibition of pro-inflammatory cytokines, oxidative stress, and TLR4 and NF-κB pathways.42,186–191 β-elemene had a protective effect on TBI that is most likely mediated via reduction of caspase-3 enzyme activity and expression of TLR4 and inflammatory cytokines.46 The neuroprotective effect of SalB against TBI was associated with its anti-inflammatory activities.198 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.206,207 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.202 The neuroprotective effect of baicalin in TBI-induced brain injury could be potentially mediated via inhibition of pro-inflammatory cytokines.204

5 | CONCLUSIONS

This review discussed the growing evidence on the protective effects and molecular mechanisms of medicinal plants and their constituents on TBI (Figure 1). 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 outcomes 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.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

REFERENCES

1. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: A brief overview. J Head Trauma Rehabil. 2006;21:375–378.
2. Masel BE, DeWitt DS. Traumatic brain injury: A disease process, not an event. J Neurotrauma. 2010;27:1529–1540.
3. Andriessen TM, Jacobs B, Vos PE. Clinical characteristics and pathophysiological mechanisms of focal and diffuse traumatic brain injury. J Cell Mol Med. 2010;14:2381–2392.
4. Keshavarzi Z, Hadad MK, Zahedi MJ, Bahrami A. The effects of female sex steroids on gastric secretory responses of rat following traumatic brain injury. Iran J Basic Med Sci. 2011;14:231–239.
5. 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. Iran J Basic Med Sci. 2012;15:1102.
6. Keshavarzi Z, Khaksari M. The effects of female sexual steroids on gastric function and barrier resistance of gastrointestinal tract following traumatic brain injury. J Pharm Bioallied Sci. 2015;7:75.
7. Xiong Y, Mahmood A, Chopp M. Animal models of traumatic brain injury. Nat Rev Neurosci. 2013;14:128.
8. Baez-Jurado E, Vega GG, Aliev G, et al. Blockade of Neuroglobin reduces protection of conditioned medium from human mesenchymal stem cells in human astrocyte model (T98G) under a scratch assay. Mol Neurobiol. 2018;55:2285–2300.
9. Li Z, Wang Y, Zeng G, et al. Increased miR-155 and heme oxygenase-1 expression is involved in the protective effects of formononetin in traumatic brain injury in rats. Am J Transl Res. 2017;9:5653.
10. Kumar A, Kennedy-Boone D, Weisz HA, et al. Neuroprotective effects of Aframomum melegueta extract after experimental traumatic brain injury. Nat Prod Chem Res. 2015;3:167.
11. Gugliandolo E, D’Amico R, Cordaro M, et al. Neuroprotective effect of Artesunate in experimental model of traumatic brain injury. Front Neurol. 2018;9:590.

12. Wang Y, Zhang C, Peng W, et al. Hydroxysafflor yellow a exerts antioxidative effects in a rat model of traumatic brain injury. Mol Med Rep. 2016;14:3690–3696.

13. Yulug B, Kilic E, Altunay S, et al. Cinnamon polyphenol extract exerts neuroprotective activity in traumatic brain injury through modulation of Nrf2 and cytokine expression. CNS Neurol Disord Drug Targets. 2018;17:439–447.

14. He Y, Qu S, Wang J, et al. Neuroprotective effects of osthole pretreatment against traumatic brain injury in rats. Brain Res. 2012;1433:127–136.

15. Wang K, Zhang L, Rao W, et al. Neuroprotective effects of crocin against traumatic brain injury in mice: Involvement of notch signaling pathway. Neurosci Lett. 2015;591:53–58.

16. Liu Z-K, Ng C-F, Shiu H-T, et al. Treatment with ginseng total saponins improves the neurorestoration of rat after traumatic brain injury. J Ethnopharmacol. 2018;217:11–22.

17. 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 Regen Res. 2017;12:90.

18. Ng C-F, Ko C-H, Koon C-M, et al. The aqueous extract of rhizome of Gastrodia elata Blume attenuates locomotor defect and inflammation after traumatic brain injury in rats. J Ethnopharmacol. 2016;185:87–95.

19. Kumar A, Rinwa P, Dhar H. Microglial inhibitory effect of ginseng ameliorates cognitive deficits and neuroinflammation following traumatic head injury in rats. Inflammopharmacology. 2014;22:155–167.

20. Ji YC, Kim YB, Park SW, et al. Neuroprotective effect of ginseng total saponins in experimental traumatic brain injury. J Korean Med Sci. 2005;20:291–296.

21. 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. J Neurosci Res. 2012;90:1424–1436.

22. Hu B-Y, Liu X-I, Qiang R, et al. Treatment with ginseng total saponins improves the neurorestoration of rat after traumatic brain injury. J Ethnopharmacol. 2014;155:1243–1255.

23. Zou Q, Xiong L, Yang Z, Lv F, Yang L, Miao X. Expression levels of HMGA2 and CD9 and its clinicopathological significances in the benign and malignant lesions of the gallbladder. World J Surg Oncol. 2012;10:92.

24. Wang Y, Fan X, Tang T, 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. Sci Rep. 2016;6:37098.

25. Xu X, Lv H, Xia Z, et al. Rhein exhibits antioxidative effects similar to rhubarb in a rat model of traumatic brain injury. BMC Complement Altern Med. 2017;17:140.

26. Wang Z, Liu L, Mei Q-B, et al. Protective effect of rheum tanguticum polysaccharides (RTP) on traumatic brain injury in rats. Zhongguo Zhong Yao Za Zhi. 2003;28:974–976.

27. Sawmiller D, Li S, Shahaduzzaman M, et al. Luteolin reduces Alzheimer’s disease pathologies induced by traumatic brain injury. Int J Mol Sci. 2014;15:895–904.

28. Mohamed AAG. Potential therapeutic effect of amloidipine and thymoquinone alone or in combination on traumatic brain injury in mice. CU Theses: 2017. http://erepository.cu.edu.eg/index.php/cutheses/article/view/7131/6992

29. Hu W-H, Chan G-K-L, Lou J-S, et al. The extract of Polygony Cuspidati Rhizoma et radix suppresses the vascular endothelial growth factor-induced angiogenesis. Phytomedicine. 2018;42:135–143.

30. Feng Y, Cui Y, Gao JL, et al. Neuroprotective effects of resveratrol against traumatic brain injury in rats: Involvement of synaptic proteins and neuronal autophagy. Mol Med Rep. 2016;13:5248–5254.

31. Özcan MM, Chalchat J-C. Chemical composition and antifungal activity of rosemary (Rosmarinus officinalis L.) oil from Turkey. Int J Food Sci Nutr. 2008;59:691–698.

32. Gohil KJ, Patel JA, Gajjar AK. Pharmacological review on Cen- testa asiatica: A potential herbal cure-all. Indian J Pharm Sci. 2010;72:546.

33. Shakeri F, Roshan NM, Kaveh M, Eftekhar N, Boskabady MH. Curcumin affects tracheal responsiveness and lung pathology in asthmatic rats. Pharmacol Rep. 2018;70:981–987.

34. Abdollahi E, Montazzi AA, Johnston TP, Sahebkar A. Therapeu- tic effects of curcumin in inflammatory and immune-mediated diseases: A nature-made jack-of-all-trades? J Cell Physiol. 2018;233:830–848.

35. Panahi Y, Kianpour P, Mohtashami R, Jafari R, Simental- Mendia LE, Sahebkar A. Curcumin lowers serum lipids and uric acid in subjects with nonalcoholic fatty liver disease: A randomized controlled trial. J Cardiovasc Pharmacol. 2016;68:223–229.

36. Panahi Y, Kianpour P, Mohtashami R, Jafari R, Simental- Mendia LE, Sahebkar A. Efficacy and safety of Phytosomal Curcumin in non-alcoholic fatty liver disease: A randomized controlled trial. Drug Res. 2017;67:244–251.

37. Iranshahi M, Sahebkar A, Takasaki M, Konoshima T, Tokuda H. Cancer chemopreventive activity of the prenylated coumarin, umbelliprenin, in vivo. Eur J Cancer Prev. 2009;18:412–415.

38. Sahebkar A, Cicero AFG, Simental-Mendia LE, Aggarwal BB, Gupta SC. Curcumin downregulates human tumor necrosis factor-α levels: A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res. 2016;107:234–242.

39. Montazi AA, Shahabipour F, Khatibi S, Johnston TP, Pirro M, Sahebkar A. Curcumin as a MicroRNA regulator in cancer: A review. Rev Physiol Biochem Pharmacol. 2016;171:1–38.

40. Montazi AA, Sahebkar A. Difluorinated curcumin: A promising curcumin analogue with improved anti-tumor activity and pharmacokinetic profile. Curr Pharm Des. 2016;22:4386–4397.

41. 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. Pharmacol Biochem Behav. 2013;110:238–244.

42. Sefidkon F, Ahmad S. Essential oil of Satureja khuzistanica Jamzad. J Essential Oil Res. 2000;12:427–428.

43. Vosough-Ghanbari S, Rahimi R, Kharabaf S, et al. Effects of Satureja khuzistanica on serum glucose, lipids and markers of oxidative stress in patients with type 2 diabetes mellitus: A
double-blind randomized controlled trial. Evid Based Complement Alternat Med. 2010;7:465–470.
45. 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 Biosci. 2013;3:42–48.
46. Meng X, Li N, Zhang Y, et al. Beneficial effect of β-elemene alone and in combination with hyperbaric oxygen in traumatic brain injury by inflammatory pathway. Transl Neurosci. 2018;9:33–37.
47. Wang B-Q. Salvia miltiorrhiza: Chemical and pharmacological review of a medicinal plant. J Med Plant Res. 2010;4:2813–2820.
48. Al-Amier H, Eyles SJ, Craker L. Evaluation of extraction methods for isolation and detection of Formononetin in black cohosh (Actaea racemosa L.). J Medicinally Active Plants. 2012;1:6–12.
49. Rathore R, Rahal A, Mandil R, et al. Comparative anti-inflammatory activity of Cimicifuga racemosa and Mimosa pudica. Asian J Anim Vet Adv. 2002;9:65–71.
50. Szymczak G, Wójciak–Kosior M, Sowa I, Zapala K, Bogucka-Kocka A. Comparison of phenolic content and antioxidant activity of Actaea racemosa L. and Actaea cordifolia DC. Nat Prod Res. 2015;29:1149–1152.
51. Winterhoff H, Spengler B, Christofoel V, Butterweck V, Löhnig A. Cimicifuga extract BNO 1055: Reduction of hot flushes and hints on antidepressant activity. Maturitas. 2003;44:S51–S58.
52. Smith MJ, Germolec DR, Frawley RP, White KL Jr. Immuno-modulatory effects of black cohosh (Actaea racemosa) extract in female B6C3F1/N mice. Toxicology. 2013;308:146–157.
53. Kokwaro J. Medicinal plants of East Africa. Nairobi, Korea: East
54. Okoli C, Akah P, Nwafor S, Ihemelandu U, Amadife C. Anti-inflammatory activity of seed extracts of Aframomum melegueta in rats. Int J Pharmacognosy. 1995;33:311–316.
55. 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 Sci. 2011;3:154–158.
56. Schafer G, Kaschula CH. The immunomodulation and anti-inflammatory effects of garlic organosulfur compounds in cancer chemoprevention. Anti-Cancer Agents Med Chem. 2014;14:233–240.
57. Rahman M, Fazlic V, Saad N. Antioxidant properties of raw garlic (Allium sativum) extract. Int Food Res J. 2012;19:589–591.
58. Chen W, Qi J, Feng F, et al. Neuroprotective effect of allicin against traumatic brain injury via Akt/endothelial nitric oxide synthase pathway-mediated anti-inflammatory and anti-oxidative activities. Neurochem Int. 2014;68:28–37.
59. Efferth T. Seminars in cancer biology. Amsterdam, the Netherlands: Elsevier, 2017.
60. Chevallier A. The encyclopedia of medicinal plants. London: Dorling Kindersley, 1996.
61. Stuart G (1984) Chinese Materia Medica. Taipei. Southern Materials Centre. A translation of an ancient Chinese herbal.
62. Kim W-S, Choi WJ, Lee S, et al. Anti-inflammatory, antioxidant and anti-nociceptive activity of Artemisia annua L.: A promising aromatic and medicinal. J Ethnopharmacol. 2007;109:501–506.
63. Umukoro S, Ashorobi R. Further evaluation of the anti-inflammatory activity of Aframomum melegueta seed extract and its possible mechanism of action. Niger J Health Clin Sci. 2005;4:35–39.
64. Yamasaki T, Li L, Lau BH. Garlic compounds protect vascular endothelial cells from hydrogen peroxide-induced oxidant injury. Phytother Res. 1994;8:408–412.
65. Jayanthi M, Jyoti M. Experimental animal studies on analgesic and anti-nociceptive activity of Allium sativum (garlic) powder. Indian J Res Rep Med Sci. 2012;2:1–6.
66. Noori S, Naderi G-A, Hassan ZM, Habibi Z, Bathaie SZ. Chemical composition and antioxidant activities of essential oil alone and in combination with hyperbaric oxygen in traumatic brain injury by inflammatory pathway. Transl Neurosci. 2018;9:33–37.
67. Wang B-Q. Salvia miltiorrhiza: Chemical and pharmacological review of a medicinal plant. J Med Plant Res. 2010;4:2813–2820.
68. Al-Amier H, Eyles SJ, Craker L. Evaluation of extraction methods for isolation and detection of Formononetin in black cohosh (Actaea racemosa L.). J Medicinally Active Plants. 2012;1:6–12.
69. Rathore R, Rahal A, Mandil R, et al. Comparative anti-inflammatory activity of Cimicifuga racemosa and Mimosa pudica. Asian J Anim Vet Adv. 2002;9:65–71.
70. Szymczak G, Wójciak–Kosior M, Sowa I, Zapala K, Bogucka-Kocka A. Comparison of phenolic content and antioxidant activity of Actaea racemosa L. and Actaea cordifolia DC. Nat Prod Res. 2015;29:1149–1152.
71. Winterhoff H, Spengler B, Christofoel V, Butterweck V, Löhnig A. Cimicifuga extract BNO 1055: Reduction of hot flushes and hints on antidepressant activity. Maturitas. 2003;44:S51–S58.
72. Smith MJ, Germolec DR, Frawley RP, White KL Jr. Immuno-modulatory effects of black cohosh (Actaea racemosa) extract in female B6C3F1/N mice. Toxicology. 2013;308:146–157.
73. Kokwaro J. Medicinal plants of East Africa. Nairobi, Korea: East African Literature Bureau, 1976 243251.
74. Okoli C, Akah P, Nwafor I, Ihemelandu U, Amadife C. Anti-inflammatory activity of seed extracts of Aframomum melegueta. J Herbs Spices Med Plants. 2007;13:11–21.
75. Galal AM. Antimicrobial activity of 6-paradol and related compounds. Int J Pharmcognosy. 1996;34:64–69.
76. Rafaatullah S, Galal A, Al-Yahya M, Al-Said M. Gastric and duodenal analnicl and cytoprotective effects of Aframomum melegueta in rats. Int J Pharmcognosy. 1995;33:311–316.
77. Onoja SO, Omegh VN, Ezeja MI, Chukwu MN. Evaluation of the in vitro and in vivo antioxidant potentials of Aframomum melegueta methanolic seed extract. J Trop Med. 2014;2014;159343.
78. Gbolade AA. Inventory of antiabetic plants in selected districts of Lagos state, Nigeria. J Ethnopharmacol. 2009;121:135–139.
79. Ikegbumam M, Ukamaka M, Emmanuel O. Evaluation of the antifungal activity of aqueous and alcoholic extracts of six spices. Am J Plant Sci. 2016;7:118.
80. Lawal B, Adenigbe A, Essiet G, Essien A. Hypotensive and antihypertensive effects of Aframomum melegueta in humans. Int J Pharm. 2007;3:311–318.
81. Umukoro S, Ashorobi RB. Further studies on the antinociceptive action of aqueous seed extract of Aframomum melegueta. J Ethnopharmacol. 2007;109:501–504.
82. Ilic NM, Dey M, Poulev AA, Logendra S, Kuhn PE, Raskin I. Anti-inflammatory activity of grains of paradise (Aframomum melegueta Schum) extract. J Agric Food Chem. 2014;62:10452–10457.
82. Masterjohn C. The anti-inflammatory properties of safflower oil and coconut oil may be mediated by their respective concentrations of vitamin E. J Am Coll Cardiol. 2007;49:1825–1826.
83. 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;16:694–702.
84. Hiramatsu M, Takahashi T, Komatsu M, Kido T, Kasahara Y. Antioxidant and neuroprotective activities of Mogami-benibana (safflower, Carthamus tinctorius Linne). Neurochem Res. 2009;34:795–805.
85. Loo WT, Cheung MN, Chow LW. The inhibitory effect of a herbal formula comprising ginseng and Carthamus tinctorius on breast cancer. Life Sci. 2004;76:191–200.
86. Ren R, Shi C, Cao J, et al. Neuroprotective effects of a standardized flavonoid extract of safflower against neurotoxin-induced cellular and animal models of Parkinson's disease. Sci Rep. 2016;6:22135.
87. 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;203:139–143.
88. Fu P-K, Pan T-L, Yang C-Y, Jeng K-C, Tang N-Y, Hsieh C-L. Carthamus tinctorius Amerelates brain injury followed by cerebral ischemia-reperfusion in rats by antioxidant and anti-inflammatory mechanisms. Iranian J Basic Med Sci. 2016;19:1368.
89. Chericoni S, Prieto JM, Iacopini P, Cioni P, Morelli I. In vitro activity of the essential oil of Cinnamomum zeylanicum and eugenol in potoxynitrile-induced oxidative processes. J Agric Food Chem. 2005;53:4762–4765.
90. Ranasinghe P, Pigera S, Premakumara GS, Galappaththy P, Cisowski W, Mazol I, Glowniak K, Czuczwar SJ. Osthole suppresses seizures in the mouse maximal electroshock seizure model. Eur J Pharmacol. 2009;607:107–109.
91. 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. Eur J Pharmacol. 2010;636:96–101.
92. Zimecki M, Artym J, Cisowski W, Mazol I, Wlodarczyk M, Gniś M. Immunomodulatory and anti-inflammatory activity of selected osthole derivatives. Zeitschrift für Naturforschung C. 2009;64:361–368.
93. 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. J Chromatogr A. 1995;699:107–118.
94. Rios J, Recio M, Giner R, Manez S. An update review of saffron and its active constituents. Phytother Res. 1996;10:189–193.
95. Boskabady MH, Farkhondeh T. Antiinflammatory, antioxidant, and immunomodulatory effects of Crocus sativus L. and its main constituents. Phytother Res. 2016;30:1072–1094.
96. Hosseinzadeh H, Noraei NB. Anxiolytic and hypnotic effect of Crocus sativus aqueous extract and its constituents, crocin and safranal, in mice. Phytother Res. 2009;23:768–774.
97. Sadeghnia H, Cortez M, Liu D, Hosseinzadeh H, Sneed OC. Antiabesence effects of safranal in acute experimental seizure models: EEG and autoradiography. J Pharm Pharmac. 2008;11:1–14.
98. Geromichalos GD, Lamari FN, Papandreou MA, et al. Saffron as a source of novel acetylcholinesterase inhibitors: Molecular docking and in vitro enzymatic studies. J Agric Food Chem. 2012;60:6131–6138.
99. 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. J Stroke Cerebrovasc Dis. 2014;23:106–113.
100. Liu Z-K, Ng C-F, Shiu H-T, et al. A traditional Chinese formula composed of Chuaxiong Rhizoma and Gastrodiae Rhizoma (Da Chuaxiong Formula) suppresses inflammatory response in LPS-induced RAW 264.7 cells through inhibition of NF-kB pathway. J Ethnopharmacol. 2017;196:20–28.
101. Wang L, Zhang J, Hong Y, Feng Y, Chen M, Wang Y. Phytochemical and pharmacological review of Da Chuaxiong Formula: A famous herb pair composed of chuaxiong rhizoma and gastrodiae rhizoma for headache. Evid Based Complement Alternat Med. 2013;2013:425369.
102. Li X, Song K, Yang J, Yi T. Isolation and characterization of 11 new microsatellite loci in Erigeron brevisscapus (Asteraceae),
an important Chinese traditional herb. Int J Mol Sci. 2011;12:7265–7270.

114. Zahoor A, Hussain H, Khan A, Ahmed I, Ahmad VU, Krohn K. Chemical constituents from Erigeron bonariensis L. and their chemotaxonomic importance. Rec Nat Prod. 2012;6:376.

115. Liu H, Yang X, Ding J, Feng Y, Xu H. Antibacterial and antifungal activity of Erigeron brevicaesp. Fitoterapia. 2003;74:387–389.

116. Wang M, Xie C, Cai R-L, Li X-H, Luo X-Z, Qi Y. Studies on antioxidant activities of brevicaesp in the cell-free system. Am J Chin Med. 2008;36:1199–1207.

117. Zhang Z, Luo P, Li J, et al. Comparison of the antiinflammatory activities of three medicinal plants known as “meiduoluomi” in Tibetan folk medicine. Yakugaku Zasshi. 2008;128:805–810.

118. Zhang Z, Luo P, Li J, et al. Comparison of the antiinflammatory activities of three medicinal plants known as “meiduoluomi” in Tibetan folk medicine. Yakugaku Zasshi. 2008;128:805–810.

119. Kim B-W, Koppula S, Kim J-W, et al. Modulation of LPS-antioxidant activities of brevicaesp in the cell-free system. J Ethnopharmacol. 2012;139:549–561.

120. Duan R, Zhou H, Yang Y, et al. Antimicrobial meroterpenoids from the endophytic fungus Penicillium sp. T2-8 associated with Gastrodia elata Blume and its components. Evid Based Complement Alternat Med. 2015;2015:1–14.

121. Chen X, Cao D, Zhou L, et al. Structure of a polysaccharide from Gastrodia elata Bl., and oligosaccharides prepared thereof with chemotaxonomic importance. Rec Nat Prod. 2012;6:376.

122. Hsieh C-L, Chen C-L, Tang N-Y, et al. Gastrodia elata Bl mediates the suppression of nNOS and microglia activation to protect against neuronal damage in kainic acid-treated rats. Am J Chin Med. 2005;33:599–611.

123. Hwang SM, Lee YJ, Kang DG, Lee HS. Anti-inflammatory effect of Gastrodia elata Blume and its components. Evid Based Complement Alternat Med. 2015;2015:1–14.

124. Kim B-W, Koppula S, Kim J-W, et al. Modulation of LPS-stimulated neuroinflammation in BV-2 microglia by Gastrodia elata: 4-hydroxybenzyl alcohol is the bioactive candidate. J Ethnopharmacol. 2012;139:549–557.

125. Duan R, Zhou H, Yang Y, et al. Antimicrobial meroterpenoids from the endophytic fungus Penicillium sp. T2-8 associated with Gastrodia elata. Phytochem Lett. 2016;18:197–201.

126. Chen X, Cao D, Zhou L, et al. Structure of a polysaccharide from Gastrodia elata Bl., and oligosaccharides prepared thereof with anti-pancreatic cancer cell growth activities. Carbohydr Polym. 2011;86:1300–1305.

127. Hsieh C-L, Chen C-L, Tang N-Y, et al. Gastrodia elata BL mediates the suppression of nNOS and microglia activation to protect against neuronal damage in kainic acid-treated rats. Am J Chin Med. 2005;33:599–611.

128. Hwang SM, Lee YJ, Kang DG, Lee HS. Anti-inflammatory effect of Gastrodia elata rhizome in human umbilical vein endothelial cells. Am J Chin Med. 2009;37:395–406.

129. Paul D. A review on biological activities of common mallow (Malva sylvestris L.). Innovare J Life Sci. 2016;4:1–5.

130. Coon JT, Ernst E. Panax ginseng. Drug Saf. 2002;25:323–344.

131. Hou JP. The chemical constituents of ginseng plants. Am J Chin Med. 1977;5:123–145.

132. Kachur K, Suntres ZE. The antimicrobial properties of ginseng and ginseng extracts. Expert Rev Anti Infect Ther. 2016;14:81–94.

133. Sung WS, Lee DG. In vitro candidacidal action of Korean red ginseng saponins against Candida albicans. Biol Pharm Bull. 2008;31:139–142.

134. Kim H-G, Yoo S-R, Park H-J, et al. Antibacterial effects of Panax ginseng CA Meyer in healthy subjects: A randomized, placebo-controlled clinical trial. Food Chem Toxicol. 2011;49:2229–2235.

135. 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 calcivirus as surrogates for human norovirus. J Ginseng Res. 2011;35:429.

136. Hong M, Lee YH, Kim S, et al. Anti-inflammatory and anti-fatigue effect of Korean Red Ginseng in patients with non-alcoholic fatty liver disease. J Ginseng Res. 2016;40:203–210.

137. 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. J Ginseng Res. 2013;37:167.
Dracaena cochinchinensis, a plant source of the ethnomedicine “Dragon's blood.” Molecules. 2014;19:10650–10669.

153. Xin N, Li Y-J, Li Y, et al. Dragon's blood extract has antithrombotic properties, affecting platelet aggregation functions and anticoagulation activities. J Ethnopharmacol. 2011;135:510–514.

154. Zheng Q, Chen J, Zhang Y, Yang C. The chemical constituents and pharmaceutical activities of Dragon's blood, a famous traditional medicinal herb. Nat Prod Res Dev. 2005;17:84–95.

155. Choy C-S, Hu C-M, Chiu W-T, 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. J Ethnopharmacol. 2008;115:455–462.

156. He L, Liu Y, Shi J, Pei Q. Synthesis and antitumor activity of cholest-4α-methyl-7-en-3β-ol derivatives. Steroids. 2006;71:476–483.

157. Gu H-J, Lv J-C, Yong K-L, Chen X, Liu P-P, Zhang X-B. Anti-inflammatory and antinociceptive effects of Rosmarinus officinalis L. essential oil and their derivatives. J Ethnopharmacol. 1991 May-Jun; 33(1-2):57–62.

158. 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. Iran J Pharm Res. 2016;15:875.

159. Song H, Xu L, Zhang R, 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. Neurosci Lett. 2016;622:95–101.

160. Siddiqui B, Aslam H, Ali S, Khan S, Begum S. Chemical constituents of Centella asiatica. J Asian Nat Prod Res. 2007;9:407–414.

161. Park JH, Choi JY, Son DJ, et al. Anti-inflammatory effect of tetratricopeptide repeat domain of Centella asiatica in phthalic anhydride-induced allergic dermatitis animal model. Int J Mol Sci. 2017;18:738.

162. Parameshwaraiah S, Shivakumar H. Evaluation of topical formulations of aqueous extract of Centella asiatica on open wounds in rats. Indian J Exp Biol. 1998;36:569–572.

163. Kumar MV, Gupta Y. Effect of different extracts of Centella asiatica on cognition and markers of oxidative stress in rats. J Ethnopharmacol. 2002;79:253–260.

164. 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. 2003;26:870–873.

165. Hansen B. Centella asiatica (Indian pennywort), an effective therapeutically but a weak sensitizer. Contact Dermatitis. 1993;29:175–179.

166. Pittella F, Dutra RC, Junior DD, Lopes MT, Barbosa NR. Antioxidant and cytotoxic activities of Centella asiatica (L) Urb. Int J Mol Sci. 2009;10:3713–3721.

167. Thong-asu W, Tilokskulchai K, Chompoonong S, Tantisira MH. Effect of Centella asiatica on pathophysiology of mild chronic cerebral hypoperfusion in rats. Avicenna J Phytother. 2018;8:210.

168. Jazmi AF, Alfianya PF, Nurarifah SAH, Purmitasari EA, Vitania LA, Riawan W. Spade leaf extract Phytosome modulates Krox-20, Neuregulin-1, phospholipids, and cognitive function of traumatic brain injury model in rats. Indones J Cancer Chemoprev. 2015;6:105–110.

169. Sahebkar A, Serban MC, Ursoniu S, Banach M. Effect of curcuminoids on oxidative stress: A systematic review and meta-analysis of randomized controlled trials. J Funct Foods. 2015;18:898–909.

170. Panahi Y, Khalili N, Sahebi E, et al. Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: A randomized controlled trial. Inflammopharmacology. 2017;25:25–31.

171. Shakeri F, Soukhtanloo M, Boskabady MH. The effect of hydroethanolic extract of Curcuma longa rhizome and curcumin on total and differential WBC and serum oxidant, antioxidant biomarkers in rat model of asthma. Iranian J Basic Med Sci. 2017;20:155.

172. Abdollahi E, Momtazi AA, Johnston TP, Sahebkar A. Therapeutic effects of curcumin in inflammatory and immune-mediated diseases: A nature-made jack-of-all-trades? J Cell Physiol. 2018;233:830–848.

173. Karimian MS, Pirro M, Majeed M, Sahebkar A. Curcumin as a natural regulator of monococyte chemoattractant protein-1. Cyto-kine Growth Factor Rev. 2017;33:55–63.

174. Wu A, Ying Z, Gomez-Pinilla F. Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition. Exp Neurol. 2006;197:309–317.
187. 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;161:1037–1044.

188. Sharma S, Ying Z, Gomez-Pinilla F. A pyrazole curcumin derivative restores membrane homeostasis disrupted after brain trauma. Exp Neurol. 2010;226:191–199.

189. 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. Neurorehabil Neural Repair. 2011;25:332–342.

190. Laird MD, Sukumari-Ramesh S, Swift AE, Meiler SE, Zhu H-t, Bian C, Yuan J-c, et al. Curcumin attenuates acute inflammatory injury by inhibiting the TLR4/MyD88/NF-κB signaling pathway in experimental traumatic brain injury. J Neuroinflammation. 2014;11:59.

191. Gupta RP, Ali M, Eranna D, Setty RS. Evaluation of anti-ulcer effect of root of Curcuma zedoaria in rats. Indian J Tradit Know. 2003;2:375–377.

192. Ullah HA, Zaman S, Juhara F, et al. Evaluation of anti-nociceptive, in-vivo & in-vitro anti-inflammatory activity of ethanolic extract of Curcuma zedoaria rhizome. BMC Complement Altern Med. 2014;14:346.

193. 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. Int J PharmTech Res. 2015;8:88–94.

194. Li X-J, Liang L, Shi H-X, Sun X-P, Wang J, Zhang L-S. Neuroprotective effects of Rhizoma drynariae on interleukin-2 and T-lymphocyte levels in rats after severe head injury. J Ethnopharmacol. 2012;142:300–304.

195. Wang W-z, Pan Y-z, Wei J-h, 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. J Ethnopharmacol. 2012;142:300–304.

196. Wang W, Li H, Yu J, et al. Protective effects of Chinese herbal medicine rhizoma drynariae in rats after traumatic brain injury and identification of active compound. Mol Neurobiol. 2016;53:4809–4820.

197. Wang W, Li H, Yu J, et al. Protective effects of Chinese herbal medicine rhizoma drynariae in rats after traumatic brain injury and identification of active compound. Mol Neurobiol. 2016;53:4809–4820.

198. Wang W, Zhang W-b, Zhu J-h, Fu G-s, Zhou B-q. Breviscapine ameliorates cardiac dysfunction and regulates the myocardial Ca2+-cycling proteins in streptozotocin-induced diabetic rats. Acta Diabetol. 2010;47:209–218.

199. 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 Res Int. 2015;2015:680756.

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