



Protective Effects of Plant-Derived Compounds Against Traumatic Brain Injury

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Abstract

Inflammation in the nervous system is one of the key features of many neurodegenerative diseases. It is increasingly being identified as a critical pathophysiological primitive mechanism associated with chronic neurodegenerative diseases following traumatic brain injury (TBI). Phytochemicals have a wide range of clinical properties due to their antioxidant and anti-inflammatory effects. Currently, there are few drugs available for the treatment of neurodegenerative diseases other than symptomatic relief. Numerous studies have shown that plant-derived compounds, in particular polyphenols, protect against various neurodegenerative diseases and are safe for consumption. Polyphenols exert protective effects on TBI via restoration of nuclear factor kappa B (NF- κ B), toll-like receptor-4 (TLR4), and Nod-like receptor family proteins (NLRPs) pathways. In addition, these phytochemicals and their derivatives upregulate the phosphatidylinositol-3-Kinase/Protein Kinase B (PI3K/AKT) and nuclear factor erythroid 2-related factor 2 (Nrf2) pathways, which have critical functions in modulating TBI symptoms. There is supporting evidence that medicinal plants and phytochemicals are protective in different TBI models, though future clinical trials are needed to clarify the precise mechanisms and functions of different polyphenolic compounds in TBI.

Keywords Traumatic brain injury (TBI) · Polyphenol · Neurodegenerative diseases · Neuroinflammation · Oxidative stress

Abbreviations

TBI Traumatic brain injury
WHO World Health Organization

BACE-1 β -Amyloid precursor protein–cleaving enzyme 1
NSAIDs Non-steroidal anti-inflammatory agents

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NF- κ B	Nuclear factor-kappa β	ERK1/2	Extracellular signal-regulated kinase 1/2
AD	Alzheimer's disease	PI3K-AKT	Phosphatidylinositol-3-kinase and protein kinase B
PD	Parkinson's disease	PGC1 α	Peroxisome proliferator-activated receptor-gamma coactivator
RNS	Reactive nitrogen species	DMSO	Dimethyl sulfoxide
ROS	Reactive oxygen species	Nrf2	Nuclear factor-erythroid factor 2-related factor 2
BBB	Blood-brain barrier	AMPK	AMP-activated protein kinase
RSV	Resveratrol	I κ B α	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
PQQ	Pyroloquinoline quinone	NSCs	Neural stem cells
GSK-3 β	Glycogen synthase kinase 3 beta	EGCG	Epigallocatechin gallate
NF- κ B	Nuclear factor kappa B	TGF- β	Transforming growth factor- β
TLR4	Toll-like receptor 4	NF-K β	Nuclear factor kappa-light-chain-enhancer of activated B cells
IL-1 β	Interleukin-1 β	GFAP	Glial fibrillary acidic protein
NLRP3	NLR family pyrin domain containing 3	iNOS	Inducible nitric oxide synthase
TNF- α	Tumor necrosis factor- α	CCI	Controlled cortical impact
iNOS	Inducible nitric oxide synthase	AICAR	5-Aminoimidazole-4-carboxamide ribonucleotide
MDA	Malondialdehyde	CMC	Sodium carboxymethylcellulose
8-oHdG	8-Hydroxy-2'-deoxyguanosine	ECs	Endothelial cells
SOD	Superoxide dismutase	Nrf2/HO-1	Nuclear factor erythroid 2-related factor 2/heme oxygenase 1
GSH	Glutathione	Nrf2	Nuclear factor erythroid 2 related factor 2
CAT	Catalase	HO-1	Heme oxygenase-1
Nrf2/HO-1	Nuclear factor erythroid 2 related factor 2/heme oxygenase 1	PI3K/AKT	Phosphatidylinositol 3-kinase/protein kinase B
Nrf2	Nuclear factor erythroid 2 related factor 2	Bax	BCL2-associated X
HO-1	Heme oxygenase-1	Bcl-2	B-cell lymphoma 2
PI3K/AKT	Phosphatidylinositol 3-kinase/protein kinase B	ERK 1/2	Extracellular signal-regulated kinase
Bax	BCL2-associated X	PPAR- γ	Peroxisome proliferator-activated receptor- γ
Bcl-2	B-cell lymphoma 2	PGC-1 α	PPAR- γ coactivator-1 α
ERK 1/2	Extracellular signal-regulated kinase	MMP	Mitochondrial membrane potential
PPAR- γ	Peroxisome proliferator-activated receptor- γ	EGCG	Epigallocatechin-3-gallate
PGC-1 α	PPAR- γ coactivator-1 α	IKK α/β	I kappa B kinase alpha/beta
MMP	Mitochondrial membrane potential	TGF-1 β	Transforming growth factor beta 1
EGCG	Epigallocatechin-3-gallate	PAMPs	Pathogen-associated molecular patterns
IKK α/β	I kappa B kinase alpha/beta	LPS	Lipopolysaccharide
TGF-1 β	Transforming growth factor beta 1	Myd88	Myeloid differentiation factor 88
PAMPs	Pathogen-associated molecular patterns	TRAF6	TNF receptor-associated factor 6
LPS	Lipopolysaccharide	TRIF	TIR domain-containing adaptor-inducing interferons
Myd88	Myeloid differentiation factor 88	NQO1	Nicotinamide adenine dinucleotide phosphate: quinone oxidoreductase-1
TRAF6	TNF receptor-associated factor 6	GSH-Px	Glutathione peroxidase
TRIF	TIR domain-containing adaptor-inducing interferons	ARE	Antioxidant response element
NQO1	Nicotinamide adenine dinucleotide phosphate: quinone oxidoreductase-1	CNS	Central nervous system
GSH-Px	Glutathione peroxidase	SD	Sprague Dawley
ARE	Antioxidant response element	WS	Wistar
CNS	Central nervous system	SOD	Superoxide dismutase
SD	Sprague Dawley	CAT	Catalase
WS	Wistar	MDA	Malondialdehyde
SOD	Superoxide dismutase	EPO	Erythropoietin
CAT	Catalase		
MDA	Malondialdehyde		
EPO	Erythropoietin		

Introduction

There is a growing public health concern associated with traumatic brain injuries (TBIs) in people under 45 years of age. TBI is predicted to become the third most common cause of death worldwide by 2020, according to the World Health Organization (WHO) [1]. It is estimated that patients who survive severe TBI are permanently disabled in terms of neurological and psychological functioning and suffer a heavy financial burden. According to Wittchen et al., the costs associated with TBI exceed €33 billion annually in Europe alone, making TBI a key research area on many national agendas [2]. Despite advances in prevention and early resuscitation techniques, long-term neurological morbidity and overall neurological recovery remain major health challenges. To the best of our knowledge, there are currently no approved treatments for TBI that have been approved by any of the regulatory agencies in order to prove their effectiveness [3]. TBI is complex and heterogeneous, and conventional methods of diagnosing and treating it have proved inadequate. As a consequence, alternative methods for developing TBI therapies should be explored [4].

Medicinal plants and their bioactive ingredients, in particular polyphenols, have been implicated in various biological activities, including, but not limited to, immunomodulation, anti-inflammatory, cardiovascular protection, antioxidant, and anticancer potential [5–7]. It is well known that plants produce polyphenols in the form of glycoside esters and free aglycones. The polyphenol family contains more than 8000 structural variants [8]. Fruits and vegetables contain polyphenols, bioactive compounds responsible for their color, flavor, and health benefits. Based on their chemical structures, they can be divided into several different classes: flavonoids such as flavonols, flavones, isoflavones, neoflavonoids, anthocyanidins, chalcones, and proanthocyanidins, phenolic acids, stilbenoids and phenolic amides [9]. Multiple aromatic rings are attached to hydroxyl ligands to form these molecules, which are predominantly plant metabolites. They can be classified according to their chemical structures [10]. Antioxidants derived from polyphenolic compounds are mainly phenolic compounds derived from plants. Some of these compounds may exist as ester derivatives (e.g., epigallocatechin gallate) or ether derivatives (e.g., ferulic acid) [11]. A polyphenolic compound can be divided into two categories based on the type of phenolic compound it belongs to. In addition, these flavonoids have also been found in pharmaceutical preparations. Among those are epigallocatechin gallate, epigallocatechin, catechins, fisetin, luteolin, and quercetin, which are often used as ingredients in pharmaceutical preparations [12]. There is an active ingredient in Quercetin which inhibits the activity of BACE-1, which is a cleaving enzyme of the amyloid precursor protein [13]. In neurodegenerative diseases like

Parkinson's disease (PD), traumatic brain injury (TBI), and Alzheimer's disease (AD), flavonoids and NSAIDs modulate the nuclear factor-kappa β (NF- κ B) signaling pathway [14]. By scavenging free radicals, polyphenols protect against chronic diseases characterized by the involvement of free radicals in their pathogenesis. Some plant species, such as black soybeans, contain polyphenolic phytochemicals that are effective in maintaining human health, particularly in preventing cancer, neurological disorders, cardiovascular disease, and diabetes. However, their effect on the progression of TBI is controversial, perhaps because of the irreversible brain damage following TBI [15]. A review of various *in vitro* and *in vivo* studies on the therapeutic benefits of plant-derived phytochemicals, with curcumin as an example, in TBI has been presented in this review (Fig. 1).

Pathogenesis of TBI

There has been a rapid increase in TBIs and they are considered a highly complex condition. Accidents involving motor vehicles, abuse, and concussions are among the leading causes of TBI. According to research, there are three levels of severity associated with this disease, mild, moderate, and severe. During recovery, there is sometimes a debilitating and transient neurological disorder. While injuries to other parts of the body contribute significantly to brain damage in severe cases such as polytrauma, injuries to the brain can cause even more significant damage [16].

There are several injuries that can result from TBI, including primary and secondary injuries. Besides lacerations and contusions, primary injuries can result in hemorrhages and ruptures. In addition to the primary injury caused by the traumatic event itself, the secondary injuries that develop as a result of inflammation, oxidative stress, and glutamate toxicity have been shown to play a significant role in determining the outcome of a traumatic brain injury. Edema and cell death occur in the brain due to calcium imbalance and oxidative stress after a post-TBI injury [17]. Often, secondary injury is observed within a few hours to a few days of the initial injury due to a cascade of events. After the primary injury mechanism is triggered, a second wave of pathological changes, commonly known as secondary injury mechanisms, is initiated, including metabolic changes, neuronal inflammation, vascular complications, cell death of glia and neurons, axonal damage, and mitochondrial dysfunction. Damaged mitochondria produce large amounts of oxygen near the site of injury. Autophagy destroys these mitochondria for relative neuronal protection and reduces oxidative stress [18, 19]. In neurons that have been damaged by cell death proteins such as those associated with mitochondrial apoptosis are triggered when mitochondrial membranes are damaged and permeability increases. Autophagy is one of

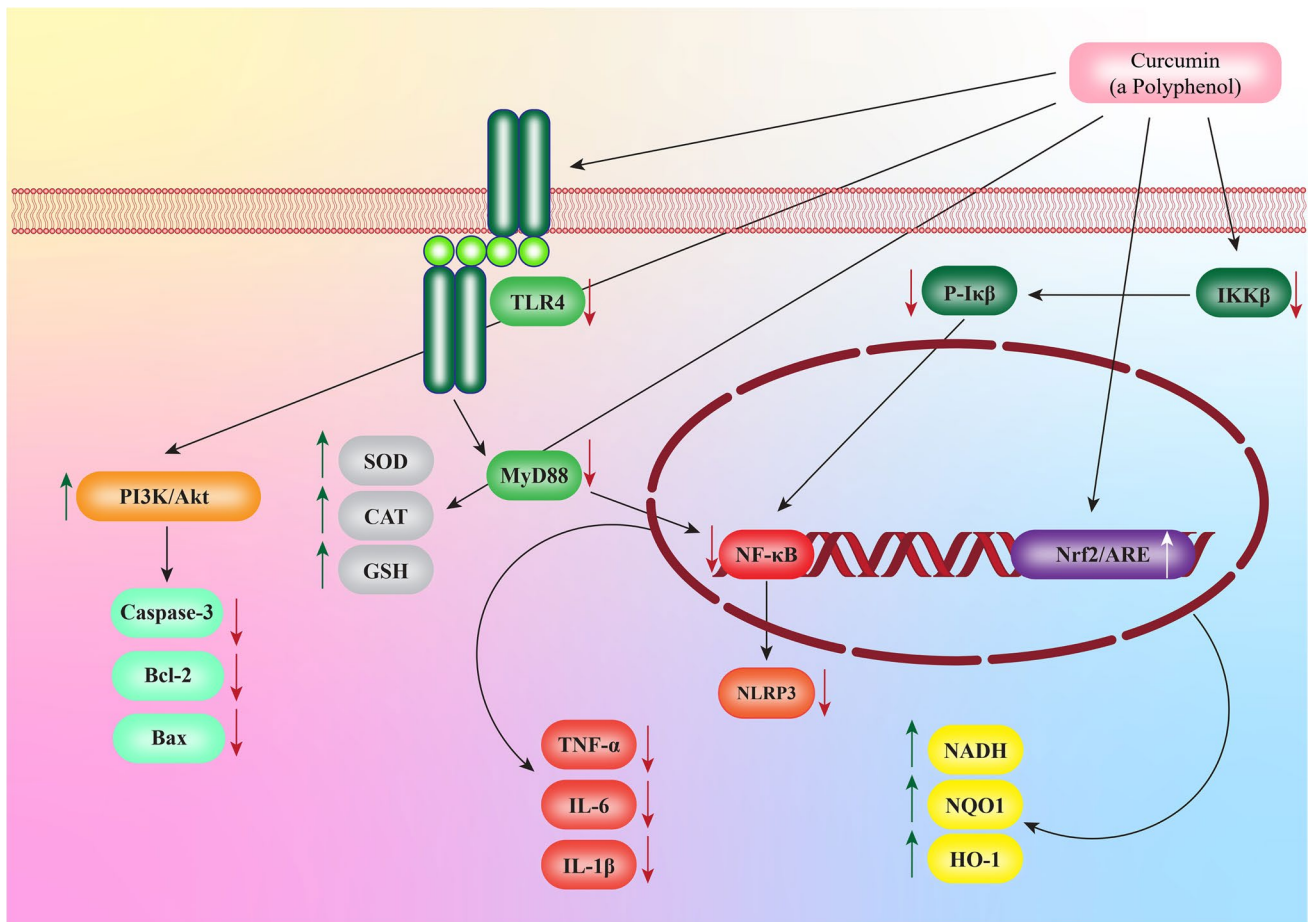


Fig. 1 Therapeutic advantages of curcumin, a polyphenol, against traumatic brain injury through interaction with different inflammatory signaling pathways and their effects on levels of cytokines and related biomarkers

the processes in the starvation response that is regulated by the organ and is responsible for the destruction and recycling of cellular components, as well as participating in organ circulation and controlling bioenergetics in the body [20]. Furthermore, autophagy prevents mitochondrial apoptosis or neuroinflammation, in addition to its neuroprotective effects. Furthermore, it is also important to note that excessive autophagy can also contribute to the generation of neuronal death when there are ischemic or hypoxic conditions, although its inhibition does the opposite.

Some signaling pathways such as phosphatidylinositol 3-kinase/ protein kinase B (PI3K/AKT), are involved in apoptosis, and induction of this pathway can suppress it post-TBI [21]. The secondary injury that results from TBI is characterized by an array of inflammatory responses. The Toll-like Receptors (TLRs) in the human immune system are located on the surface of the cells and are responsible for activating the immune system by releasing endogenous ligands and recognizing a wide range of pathogen-associated molecular patterns (PAMPs), including lipopolysaccharides (LPS) flagellin, and single-stranded and double-stranded

viral RNA. Multiple aspects of CNS homeostasis are affected by these patterns, which release enzymes and cytokines that trigger an inflammatory cascade [22]. There is increasing evidence that TLR4 plays a critical role in the initiation of inflammatory responses after trauma. TLRs activate two distinct pathways leading to the activation of transcription factors that regulate the expression of pro-inflammatory cytokine genes. Myeloid differentiation factor 88 (Myd88) activates the TNF receptor-associated factor 6 (TRAF6), producing pro-inflammatory cytokines. There is an interaction between adapter-inducing interferons (TRIF) that contain TIR domains, which are activated in a pathway independent of Myd88, and induce nuclear factor kappa B (NF-κB) to produce inflammatory mediators [23, 24].

The NF-κB family consists of five proteins, including NF-κB1 (p50), NF-κB2 (p52), p65, RELB, and c-REL. Both endogenous and exogenous ligands activate NF-κB and, when activated, is found in neurons and glia under various inflammatory conditions. In addition to the canonical pathway, a non-canonical pathway activates NF-κB [25]. The NF-κB pathway is also involved in a wide range of

immune responses and various cellular progressions such as apoptosis and proliferation. As a result of TBI, activation of NF- κ B releases several inflammatory agents that lead to secondary brain damage [26]. A recent study has shown that TBI exacerbates oxidative stress by producing free radicals [27]. There is increasing evidence that oxidative stress plays an important role in secondary damage in relation to primary damage. The nuclear factor erythroid 2 related factor 2 (Nrf2) is involved in a variety of functions within cells and accumulates in their cytoplasm under normal conditions [28]. In addition to regulating genes involved in oxidative stress, Nrf2 acts as a transcription factor. As a result of this component of Nrf2, antioxidant enzymes such as malondialdehyde (MDA), heme oxygenase-1 (HO1), superoxide dismutase (SOD), quinone oxidoreductase-1 (NQO1), and glutathione peroxidase (GSH-Px) are activated [29]. This enzyme acts by directly regulating the levels of reactive oxygen species (ROS), meaning that it can directly react with free radicals without harming the cells' vital function. The antioxidant response element (ARE) found in the gene promoter allows Nrf2 to promote the expression of antioxidant genes. The Nrf2/ARE signaling pathway modulates several pathological processes, including oxidative stress [29, 30].

Effect of Different Phytochemicals and Polyphenols on TBI Through Inflammatory Signaling Pathways

Polyphenols exert antioxidant activity through various mechanisms, some of which are multi-step mechanisms [31]. However, free radical scavenging is widely recognized as one mechanism by which polyphenols exert their antioxidant effects. The extended conjugation of the unpaired electron is another key property of polyphenolic antioxidant radicals that contributes to their increased stability. By quenching the reactive nitrogen species (RNS) and reactive oxygen species (ROS) produced by free radicals as they pass through a polyphenolic compound, polyphenolic compounds manifest their antioxidant benefits [32].

As a result of free radical oxidation, ROS, RNS, and other compounds are produced. The ROS and RNS commonly observed in free radical-induced oxidative damage include nitric oxide (\cdot NO), hydroxyl radicals (\cdot OH), superoxide radicals (O_2^-), and peroxyxynitrite anion ($O=NOO^-$). Fenton reactions catalyzed by metal ions (e.g., Fe^{2+} and Cu^+) generate ROS and RNS. When ROS and RNS are subjected to high levels of oxidative stress, they are highly reactive and have short half-lives, which, in conjunction with an imbalance between their production and destruction, can cause a significant amount of protein modifications as well as other reaction products to accumulate at the site of inflammation as a result of ROS and RNS-derived proteins. Inflammatory

conditions such as cancer, atherosclerosis, AD, and traumatic brain injury may arise as a result of an excessive accumulation of ROS and RNS-derived reaction products [33–35]. In addition to polyphenols, citrus flavanones, including hesperetin, hesperidin, and neohesperidin, can cross the blood–brain barrier (BBB). BBB permeability varies between polyphenols. In addition, animal studies has shown that blueberry consumption induces anthocyanin accumulation in the cortex and cerebellum of animal models (rats and pigs) [36]. Furthermore, the valerolactones undergo further metabolism resulting in the formation of phenolics and polyphenols, such as (hydroxyaryl)propanoic acid, (hydroxyaryl)cinmmic acid, (hydroxyaryl)valeric acid, hydroxybenzoic acid, and (hydroxyaryl)acetic acid derivatives. Secondary polyphenolic metabolites have a relatively higher degree of bioavailability and are more permeable to the BBB than flavonoids or dietary flavonoids and may inhibit neuroinflammation. As a result, polyphenols can be used therapeutically in a wide range of neurodegenerative diseases as well as TBI (Table 1 and 2) [37, 38].

Curcumin

The recent findings on curcumin demonstrate its remarkable versatility as a molecule that interacts with a variety of molecular targets [39–48]. There are curcumin compounds in the rhizomes of the turmeric plant (*Curcuma longa*), a plant belonging to the Zingiberaceae family. As an antioxidant, anti-infection, anti-inflammatory, and anti-tumor compound, curcumin has been approved by the United States Food and Drug Administration as a safe compound [49]. Various CNS disease models have been shown to be susceptible to curcumin's anti-inflammatory properties, including intracerebral hemorrhage, global brain ischemia, and neurodegeneration, all of which are associated with the inflammation of the CNS. Similarly, curcumin exerts neuroprotective effects in mammals when it crosses the blood–brain barrier. An experiment in mice modeling spinal and bulbar muscular atrophy revealed that 5-hydroxy-1,7-bis (3,4-dimethoxyphenyl)-1,4,6-heptatrien-3-one inhibited the aggregation of pathogenic androgen receptors. Curcumin is suspected to possess neuroprotective properties, but few studies have explored this possibility [49]. Curcumin has been shown to reduce cerebral edema, enhance membrane and energy homeostasis, and influence synaptic plasticity following TBI in a few studies. However, curcumin does not appear to have any immunomodulatory properties on inflammatory reactions.

Curcumin has been shown by numerous studies to be effective in reducing inflammation [50, 51]. A lot of research has shown that curcumin suppresses the activation of NF- κ B by inhibiting the phosphorylation and degradation of I κ B; as a result, curcumin reduces the inflammation caused by

Table 1 In vivo interventions

Study design	Disease	Intervention		Number of animals		Treatment duration	Results	Ref
		Case	Control	Case	Control			
Male SD rats	TBI	Cur (10 mg/kg, i.p.)	Vehicle	n = 5	n = 5	5 weeks	1) ↓ Levels of NLRP3, IL-1 β , IL-6, IL-18, TNF- α	[52]
		Cur (20 mg/kg, i.p.); Cur (30 mg/kg, i.p.); Cur (50 mg/kg, i.p.);					2) ↑ BDNF/TtkB and PI3K/Akt signaling	
Male SD rats	FPI-induced TBI	FPI+Cur derivatives (500 ppm, oral); Cur derivatives (500 ppm, oral); FPI-regular diet	Regular diet/Sham	n = 6-8	n = 6-8	1 week	1) ↓ SOD, Sirtuin 2 2) ↓ BDNF 3) ↓ CREB 4) ↓ Synapsin I	[54]
Wild type and Nrf2-knockout C57BL/6 mice	TBI (weight-drop impact)	TBI+Cur (500 mg/kg/day, i.p.); TBI+vehicle (DMSO equal volume, i.p.);	No treatment	n = 6-8	n = 6-8	1 day	1) ↑ Nrf2 expression & Activation 2) ↓ Ipsilateral cortex injury 3) ↓ Neutrophil infiltration 4) ↓ Microglia activation	[55]
Male SD rats	LFP-induced TBI	TBI+Cur (50 mg/kg, s.c.); TBI+SAHA (50 mg/kg, i.p.);	Vehicle (50 mg/kg, i.p.)	n = 6	n = 6	2 weeks	1) ↓ HAT 2) ↓ Mechanical sensitization	[56]
Male ICR mice	TBI	TBI TBI+Vehicle (equal volume of 10% DMSO, i.p.); TBI+Cur (50 mg/kg, i.p.); TBI+Cur (100 mg/kg, i.p.);	No treatment	n = 6	n = 6	3 days	1) ↑ Nrf2 expression & activation 2) ↓ Bcl-2 3) ↓ Caspase-3 4) ↑ HO-1, NQO1, and NAD(P)H 5) ↑ GPx and SOD 6) ↓ MDA	[57]
Male SD rats	FPI-induced TBI	FPI+Cur derivatives (500 ppm, oral); Cur derivatives (500 ppm, oral); FPI-regular diet;	Regular diet+Sham	n = 6	n = 6	4 weeks	1) ↓ BDNF 2) ↓ CREB 3) ↓ Synapsin I	[58]
Male Wistar rats	Subventricular zone surgery-induced TBI	TBI+Cur (100 mg/kg, i.p.); TBI+Cur+PM (100 mg/kg, i.p.); TBI+Cur+NS/PCs (100 mg/kg, i.p.); TBI+Cur+PM+NS/PCs (100 mg/kg, i.p.);	DMSO	n = 6	n = 6	4 weeks	Cur+PM+NS/PCs can also: 1) ↓ Lesion size, astrogliosis, macrophage, and microglial reaction 2) ↓ GFAP 3) ↓ Iba1 and CD68	[59]

Table 1 (continued)

Study design	Disease	Intervention		Number of animals		Treatment duration	Results	Ref
		Case	Control	Case	Control			
Male SD rats	TBI (weight-drop impact)	Sham;	Vehicle	<i>n</i> = 12	<i>n</i> = 12	1 week	1) ↑ Nrf2 expression & activation 2) ↓ Bcl-2 3) ↓ Bax 4) ↓ Caspase-3 5) ↑ HO-1, NQO1, and NAD(P)H 6) ↑ GPx and SOD 7) ↓ MDA	[60]
		TBI+ THC (10 mg/kg, i.p.); TBI+ THC (25 mg/kg, i.p.); TBI+ THC (50 mg/kg, i.p.);	(saline containing 1% DMSO)					
Male SD rats	FPI-induced TBI	FPI+ Cur (500 ppm, oral); FPI+ DHA + Cur (1.2%, 500 ppm, oral); FPI+ regular diet; FPI+ DHA diet (1.2%, oral);	Regular diet + Sham	<i>n</i> = 6	<i>n</i> = 6	2 weeks	FPI-DHA-Cur can also; 1) ↓ BDNF and its receptor p-trkB 2) ↓ Stress oxidative damage 3) ↓ Plasticity markers	[61]
		TBI; TBI+ vehicle (saline containing 1% DMSO, i.p.); TBI+ THC (25 mg/kg/day, i.p.); TBI+ THC (50 mg/kg/day, i.p.); Quercetin (50 mg/kg, i.p.) (0.5, 12, and 24 h after TBI)	No treatment	<i>n</i> = 6	<i>n</i> = 6	3 days	1) ↓ Brain edema 2) ↓ Apoptosis and neuron cell death 3) ↑ Neurobehavioral function 4) ↑ p-AKT 5) ↑ activation of PI3K/AKT	[63]
SD rats	TBI	Quercetin (50 mg/kg, i.p.) (0.5, 12, and 24 h after TBI)	-	<i>n</i> = 10	<i>n</i> = 10	3 days	1) cortical Nrf2/HO-1 pathway activation 2) improvement in neuroinflammation and oxidative stress	[88]
Female SD rats	TBI (weight-drop injury)	Quercetin (30 mg/kg, i.p.) (0, 24, 48, and 72 h post TBI)	Saline	<i>n</i> = 15	<i>n</i> = 15	4 weeks	1) ↑ cognitive function 2) ↓ oxidative stress 3) ↑ GSH-Px, SOD, and CAT activity	[90]
Male WS rats	TBI (weight-drop impact)	1) Quercetin (50 mg/kg, i.v.) 2) Mannitol (1 mg/kg, i.v.)	-	<i>n</i> = 10	<i>n</i> = 10	4 h	1) ↓ MDA levels 2) ↓ EPO Serum levels by mannitol 3) quercetin would be used as an alternative treatment	[89]

Table 1 (continued)

Study design	Disease	Intervention		Number of animals		Treatment duration	Results	Ref
		Case	Control	Case	Control			
Male SD rats	TBI (weight-drop impact)	1) Quercetin (50 mg/kg, i.p.) (0.5, 12 h, and 24 h after TBI) 2) Quercetin (50 mg/kg, i.p.) (0.5, 12 h, and 24 h after TBI) + LY294002 10 μ L (50 mM in 25% dimethyl sulfoxide in PBS (injection into the left ventricle))	-	n = 25	n = 25	9 days	1) improvement in neurological impairment and cognitive function 2) \downarrow neuronal autophagy and apoptosis via PI3K/Akt activation	[91]
Male SD rats	TBI (weight-drop impact)	Quercetin (50 mg/kg, i.p.) (0.5, 12, and 24 h after TBI)	-	n = 25	n = 25	5 days	1) inhibition of ERK1/2 and PI3K/Akt activation 2) improvement in brain edema and motor functions	[92]
Male ICR mice	TBI (weight-drop impact)	Quercetin (50 mg/kg, i.p.) (30 min after TBI)	DMSO + 0.9% saline	n = 24	n = 24	24 h	1) \uparrow PGC-1 α 2) \downarrow cytochrome c, MDA, and SOD levels	[93]
Male ICR mice	TBI (weight-drop impact)	Quercetin (50 mg/kg, i.p.) (30 min after TBI)	DMSO + 0.9% saline	n = 30	n = 30	24 h	1) \uparrow expression and activity of antioxidant enzymes 2) Nrf2 pathway activation	[94]
Male ICR mice	TBI (weight-drop impact)	Quercetin (50 mg/kg, i.p.) (30 min after TBI)	Vehicle (DMSO + 0.9% saline)	n = 24	n = 24	24 h	1) \uparrow PGC-1 α expression 2) \uparrow mitochondrial function 3) \downarrow cytochrome c, MDA, and SOD	[112]
WS rats	TBI (weight-drop impact)	Quercetin (10 mg/kg/ day, i.p.)	-	n = 10	n = 10	7 days	1) \downarrow oxidative-nitrosative stress 2) \downarrow peroxynitrite concentration 3) \downarrow iNOS activity	[113]
Male SD rats	TBI (CCI)	Catechin (1, 5, 10, 20, 30 mg/kg/ day, o.g.)	0.5% DMSO (1 mg/kg/day, o.g.)	n = 10	n = 10	28 days	1) \downarrow tight junction disruption 2) \downarrow JBBB disruption 3) neuroprotective	[96]
Male C57BL/6 mice	TBI (CCI)	1) EGCG (0.2%, w/v) in drinking water immediately after TBI 2) AICAR (500 mg/kg, i.p.) (5 min and 24 after TBI) 3) Metformin (250 mg/kg, i.p.) (5 min and 24 after TBI)	Normal drinking water	n = 16	n = 16	18 days	1) \uparrow AMPK pathway 2) preventing locomotor and cognitive damage 3) \downarrow phosphorylation of IKK α/β and I κ B α	[97]

Table 1 (continued)

Study design	Disease	Intervention		Number of animals		Treatment duration	Results	Ref
		Case	Control	Case	Control			
Male WS rats	TBI	EGCG (0.1% w/v) in drinking water	Normal drinking water	n=27	n=27	7 days	1) ↓ O ²⁻ and OH ⁻ 2) improvement in cerebral function 3) ↓ neuronal degeneration and apoptotic cell death	[98]
Male WS rats	TBI (CCI)	EGCG (0.1% w/v) in drinking water	Normal drinking water	n=18	n=18	7 days	1) protection of nestin-positive cells, including NSCs 2) ↓ free radical production's cell death of neuronal cells and NSCs	[99]
Male WS rats	TBI	1) EGCG (0.1% w/v) in drinking water pre-TBI 2) EGCG (0.1% w/v) in drinking water pre- and post-TBI 3) EGCG (0.1% w/v) in drinking water post-TBI	Normal drinking water	n=6	n=6	7 days	1) ↓ O ²⁻ and OH ⁻ 2) improvement in cognitive impairment 3) improvement in cerebral function	[114]
Male SD rats	TBI (CCI)	Honokiol (1.0 mg/kg/day, i.v.) (8,16 h after TBI)	(2.5% mixture of ethanol and cremophor EL in 5% dextrose)	n=24	n=24	21 days	1) neuroprotective 2) ↓ overactive cell cycle 3) ↓ cyclin D1, E2F1, and apoptosis in neurons	[107]
Male C57BL/6 mice	TBI (CCI)	Sesamin (30 mg/kg/day, i.p.)	vehicle	n=5	n=5	3 days	1) ↓ BBB disruption 2) ECs protection 3) anti-oxidative and anti-apoptotic effects on endothelial cells	[101]
Male SD rats	TBI	Magnolol (2 mg/kg, i.v.)	CMC (3 cc, i.v.)	n=8	n=8	3 days	1) ↓ oxidative brain injury, apoptosis, and neurologic deficits 2) free radical scavenging capability 3) ↑ TGF-β1 expression → antineuronal apoptosis	[103]
SD rats	TBI (weight-drop impact)	Honokiol (5 mg/kg/day, i.p.)	Isotonic saline solution (5 mg/kg, i.p.)	n=9	n=9	7 days	1) ↓ lipid peroxidation 3) improvement in the vascular wall 2) ↓ BBB disruption	[106]

Table 1 (continued)

Study design	Disease	Intervention		Number of animals		Treatment duration	Results	Ref
		Case	Control	Case	Control			
Male C57BL/6 mice	TBI (cold trauma model)	Cinnamon (10 mg/kg, i.p.) (0.5 h after TBI)	DMSO+0.9% saline (i.p.)	n=9	n=9	24 h	1) anti-inflammatory and antioxidant effects 2) balancing NF-κB, Nrf2, GFAP and inflammatory cytokines 3) neuroprotective	[110]
Male ICR mice	TBI (weight drop head trauma device)	Cinnamon (100 µg/mL, p.o.)	Normal Drinking water	n=13-21	n=10	35 days	1) ineffectiveness on anxiety levels and motor activity 2) improvement of cognitive function 3) ↓ memory loss	[115]
Male C57BL/6 mice	TBI (CCI)	Sodium benzoate (50 mg/kg/day, p.o.)	NaFO (50 mg/kg/day p.o.)	n=6	n=6	26 days	1) neuroprotective 2) ↓ iNOS expression 3) ↓ vascular damage and size cavity lesion	[111]
Male SD rats	TBI (CCI)	RVS (100 mg/kg/day, i.p.) (for 3 days)	Ethanol (2%, i.p.)	n=60	n=60	5 days	1) ↓ TLR4/NF-κB signaling pathway 2) ↓ brain edema 3) ↑ motor and cognitive function recovery 4) ↓ neuronal autophagy	[75]
Male SD rats	TBI (0310 Impactor)	RVS (100 mg/kg)	Vehicle	n=3	n=3	48 h	1) ↓ GSK-3 β-mediated autophagy and apoptosis 2) ROS/GSK-3 β/mitochondria pathway is the cause of cell death	[74]
Male SD rats	TBI (CCI)	1) RVS (10, 50 mg/kg, i.p.)	Vehicle	n=10	n=10	21 days	1) ↓ contusion volume 2) vulnerable neurons protection in CA1 and CA3 regions preservation of hippocamp 3) beneficial motor and cognitive effects	[76]
WS rats	TBI	RVS (100 mg/kg, i.p.) single dose	Saline, including 2% ethanol	n=7	n=7	17 days	1) ↓ anxiety 2) ↑ cortex/hippocampus-dependent memory 3) improvement in cognitive impairment	[83]

Table 1 (continued)

Study design	Disease	Intervention		Number of animals		Treatment duration	Results	Ref
		Case	Control	Case	Control			
Male C57/Bl6 mice	TBI (CCI)	RVS (100 mg/kg, s.c.) (5 min and 12 h after TBI)	Vehicle (corn oil)	n = 10	n = 10	3 days	1) ↓ neuroinflammation 2) ↓ IL-6 and IL-12	[82]
	TBI (FFW)	RVS (50, 100 mg/kg/day, i.p.)	-	n = 7	n = 7	8 days	1) ↑ GSH-Px and SOD 2) ↓ MDA and 8-OHdG accumulation	[81]
SD rats	TBI	1) RSV (0.2% v/v, p.o.) 2) p38 inhibitor SB203580 (1 mg/kg/day, i.p.)	-	-	-	7 days	1) ↓ cognitive deficits, brain apoptosis, and ROS generation 2) ↑ p38/Nrf2/HO1 signaling pathway	[80]
	TBI (free-falling impact)	1) RVS (100 mg/kg, i.p.) (0.5 h before TBI) 2) Sirtinol (10 mg/kg, i.p.) (0.5 h before TBI)	Saline (2% ethanol content)	n = 30	n = 6	48 h	1) ↓ ROS production and NLRP3 activation 2) Anti-inflammatory effects 3) ↑ SIRT1	[79]
SD rats	mild TBI	1) RVS (50 mg/L) in drinking water 2) 3S supplement (100 g prebiotic, 300 g DHA, and 600 g of standard diet)	95% ethanol (1 mL) added to drinking water	n = 32	n = 14	14 days	1) improvement in neural repair 2) improvement in behavioral deficits 3) ↓ Aqp4, Gfap, Igf1, NFL, and SIRT1 expression	[78]
	TBI (weight-drop impact)	RSV (100 mg/kg/day, i.p.) (up to 5 days)	ethanol (2%)	n = 60	n = 60	5 days	1) ↓ brain edema and neuronal autophagy 2) ↑ cognitive functional recovery 3) ↑ synaptic proteins	[77]

Table 2 In vitro interventions

Study design	Disease	Intervention		Number of cells		Treatment duration	Results	Ref
		Case	Control	Case	Control			
Cortical astrocytes	TBI (OGD)	RSV (5, 10, and 25 μ M)	Saline	-	-	24 h	1) \downarrow ERK1/2, and p38MAPK 2) enhancement of ammonia, ischemia, and cell swelling	[73]
CGNs	TBI	RSV (5 and 10 μ M)	PQQ (1 μ M)	380000	380000	4 days	1) \uparrow number of viable CGNs 2) \uparrow survival of CGNs in the K ⁺ /FCS deprivation model	[72]
TLR4-/- male C57BL/6 mice	LPS-induced TBI	Cur (0.5, 1, 2, 5 and 10 μ M)	DMSO	300,000	-	3 days	1) \uparrow TLR4, MyD88, and NF- κ B 2) \downarrow Neuronal apoptosis by \downarrow caspase-3 3) \downarrow Inflammatory mediator release (IL-1 β , IL-6, TNF- α , MCP-1 and RANTES)	[53]

NF- κ B. The effects of curcumin have been shown to be not only reduced post-TBI neuroinflammation, but also decreased levels of inflammatory mediators that are produced following a TBI [52]. The anti-inflammatory effects of curcumin were demonstrated in an in vitro study using 100 mg/kg of curcumin [53]. According to the report, curcumin was able to reduce the amounts of damage after TBI induction and apoptosis, particularly in the cortical cell model derived from embryonic 15-day pregnant mice, resulting in reduced damage. One study in rats with TBI administered 30 and 50 mg/kg of curcumin daily for 35 days reduced levels of NLRP3, IL-1 β , IL-6, IL-18, and TNF- α [52]. Additionally, PI3K/AKT signaling pathways were activated, whereas the BDNF/TrkB signaling pathway was downregulated. There was a conclusion reached by researchers that if you want to receive the maximum benefits from curcumin, 30 mg per kilogram is the most effective dose. There was a reduction in neuroinflammation and subsequent complications of TBI when curcumin was administered. In another FPI (Fluid percussion injury) rat model, animals received 500 ppm of synthetic curcumin, which penetrated the blood–brain barrier, exhibited improved cognitive and locomotor functioning, as well as decreased SOD, Sirtuin 2, BDNF, and CREB levels [54]. Furthermore, curcumin (at 500 mg/kg/day) decreased injury in the ipsilateral cortex as a result of its ability to enhance neutrophil infiltration (weight drop model-TBI). Furthermore, curcumin reduced apoptosis in cells and increased antioxidant activity [55], suggesting potential neuroprotective effects. The pain levels decreased when curcumin (50 mg/kg) was administered to surgically induced TBI rats [56]. However, the compound did not

improve mechanical deficits. However, the compound did not improve mechanical deficits.

Curcumin has been found to inhibit non-selective histone acetyltransferases, suggesting potential benefits through histone acetylation. In a rat model of TBI induced by FPI, curcumin (100 mg/kg) exerted neuroprotective properties by activating the Nrf2 pathway. HO-1, NQO1, GSH-Px, and SOD activity were enhanced, and caspase-3 activity was decreased, while Bcl-2 levels increased, suppressing apoptosis [57]. BDNF, synapsin I, and CREB levels were reduced in animal models following TBI after curcumin treatment (500 ppm) [58]. A combination of curcumin (100 mg/kg) neural stem/progenitor cells and PuraMatrix decreased the size of the lesion cells and their apoptosis. In addition, bromodeoxyuridine, GFAP (Glial fibrillary acidic protein), Doublecortin microtubule-associated protein 2, oligodendrocyte transcription factor, Iba1, and CD68 levels were reduced [59]. According to another study, tetrahydrocurcumin (THC), a primary reduced metabolite of curcumin, when administered at a dose of 500 mcg in a rat model of TBI, reduced neuronal damage associated with the injury. The activities of Nrf2, SOD, and GSH-Px were increased while Bcl-2, Bax, and caspase-3 were reduced by THC [60]. When given oral doses of 100 mg/kg of curcumin per day, oxidative damage was decreased, and omega-3 fatty acid DHA levels and 4-HNE (an indicator of membrane lipid peroxidation) increased [61]. Curcumin supplements may have neuroprotective effects after brain injury and may increase the activity of docosahexaenoic acid and fatty acid-transport protein. According to Sharma et al.'s study published in 2010, curcumin reduced iPLA2, 4-HNE, and STX-3, which improved learning progress and

relieved complications associated with TBI [62]. The PI3K/AKT pathway was activated by THC in animal models of TBI according to Gao et al. in 2016. A combination of THC and PI3K/AKT, administered for 72 h, promotes neuroprotection and suppresses apoptosis [63].

Resveratrol

Resveratrol is a stilbenoid polyphenol with anti-apoptotic, anti-inflammatory, neuroprotective, antidepressant, and antioxidant properties [64–67] despite some controversies on its clinical efficacy [68–71]. It is found in *Polygonum cuspidatum* and other natural sources such as grapes, cranberries, plums, peanuts, and mulberries [64]. Shanani et al. conducted in-vitro research on cerebellar granule neuron cultures. It was shown that resveratrol (RSV) at a dose of 5 μM tended to have wound healing effects, but it was not remarkable. However, it was reported that RSV in combination with pyrroloquinoline quinone (PQQ) did not have synergistic effects on the wound healing process. It was also shown that RSV at doses of 5 and 10 μM could increase the number of cerebellar granular neurons but did not result in a significant increase in neurite length. Furthermore, both RSV and PQQ alone were shown to increase cerebellar granule neuron viability in a fetal calf serum (K + /FCS) model [72]. Taherian et al. settled down a study to investigate the effects of RSV on astrocyte swelling following ammonia exposure, ischemia, and trauma in an in vitro model. It was shown that RSV at the doses of 10 and 25 μM could reduce ammonia-induced astrocyte swelling before or after treatment. In addition, Taherian and colleagues showed that RSV (25 μM) could also reduce astrocyte swelling following trauma as a pre-treatment. In addition, it was observed that 25 μM of this chemical could reduce astrocyte swelling following ischemia as a pre- or post-treatment [73].

In another in vitro study, Len and colleagues showed that RSV could increase neuronal cell survival and simultaneously decrease ROS deposition and mitochondrial damage via downregulation of the glycogen synthase kinase 3 Beta (GSK-3 β) pathway [74]. Feng et al. showed that RSV at a dose of 100 mg/kg reduces autophagy in brain cells after TBI occurrence in a rat model. RSV decreased brain edema and neuronal injury while increasing learning and memory performance. It was also observed that RSV decreases LC3-positive NeuN cells, which represent the level of autophagy in neuronal cells. In addition, RSV was shown to exert its beneficial neuroprotective effects via downregulation of NF- κB and TLR4 pathways suppression [75]. Singleton et al. conducted a research to evaluate the effects of RSV on the TBI rat model post-injury. RSV at 100 mg/kg was found to improve motor function and memory ability. The compound reduced neuronal loss (CA1 and CA3) and attenuated behavioral impairment [76]. In 2016, an in vivo study

conducted by Feng et al. investigated the neuroprotective effects of RSV. RSV (100 mg/kg) increased synaptic activity and decreased neuronal autophagy, which reduces Beclin 1 and LC3II proteins. RSV also attenuated the brain edema measured by the Morris water maze test and improved neurological impairment and cognition after TBI [77]. In another study, RSV in an adjunctive regimen improves neurological function and reduces the long-term adverse effects of TBI. In a rat model, RSV improves behavioral functions assessed by the beam walk, open field, and elevated plus maze tests in a rat model [78]. According to Zou et al., RSV was found to have neuroprotective effects on TBI after traumatic brain injury. There is evidence to suggest that RSV reduces ROS and inflammation-related cytokines such as interleukin-1 β (IL-1 β), and IL-18. NLRP3 inflammasome and Sirtuin 1 (SIRT1) activation are affected by RSV, which alleviates brain edema and improves mental function [79].

In 2018, Shi et al. demonstrated that RSV could increase cognitive function, which was assessed by the Morris water. Although it was suggested that RSV administration upregulates the Nrf2, and HO-1 expressions. RSV reduced ROS production and neuronal apoptosis. Furthermore, RSV was shown to exert its beneficial effects via activation of the p38 pathway activation [80]. RSV at the doses of 50 mg/kg and 100 mg/kg reduced neurodegeneration and apoptosis. SOD and glutathione levels increased inversely following RSV administration, while MDA and 8-hydroxy-2'-deoxyguanosine (8-oHdG) levels were decreased [81]. In another in vivo study, RSV at 100 mg/kg suppressed inflammation after TBI by decreasing microglial activation and reducing IL-6 and IL-12 [82]. Sonmez et al. showed that RSV at 100 mg/kg reduced neuronal apoptosis and anxiety after TBI, while improving memory and behavioral function [83].

Quercetin

There are a variety of pharmacological benefits associated with quercetin (QUE), a natural bioflavonoid found in a wide range of plant species [84–86]. QUE is readily absorbed from the gastrointestinal tract and excreted in the urine via the kidneys. QUE has beneficial effects including antioxidant activity, 5-HT, anti-inflammatory effects, antidepressant properties, and reduction of HPA activation [87]. In Song et al.'s study, QUE at 5, 20, and 50 mg/kg significantly reduced microglia inflammation, inflammatory and inflammatory biomarkers, such as TNF- α , inducible nitric oxide synthase (iNOS), IL-1 β , and IL-6. In addition, MDA levels were decreased by QUE as well as catalase (CAT), SOD, and GSH levels were increased by QUE. Additionally, this compound upregulated the Nrf2/HO-1 pathway, which is implicated in its beneficial effects. Additionally, QUE decreased Iba-1 protein levels and brain water levels [88].

Similar results were obtained after the use of QUE (50 mg/kg intravenously). QUE decreased MDA levels with concomitant increases in serum GSH and CAT levels [89]. Another study showed that QUE improved cognitive function after TBI injury. QUE at a dose of 30 mg/kg decreased the IL-6, TNF- α , and IL-1 β levels, which led to a reduction in neuroinflammation. QUE also increased the expression of SOD, CAT, GSH, and IL-10 [90]. Similarly, in 2016, Du et al. demonstrated that QUE improves cognitive behavior after TBI via upregulation of the PI3K/AKT pathway. It was elucidated that 50 mg/kg QUE decreased LC-3 positive cells and neuronal apoptosis, probably by reducing caspase-3 and BCL2-associated X (Bax) and inversely increased B-cell lymphoma 2 (Bcl-2) and P-Akt expression [91].

In another in vivo study, QUE at the dose of 50 mg/kg reduced the brain water and cerebral edema. QUE improved motor function and neuronal activity, reducing neuronal apoptosis via activation of the Akt pathway and attenuating the extracellular signal-regulated kinase (ERK 1/2) signaling pathway [92]. In a similar study, QUE attenuated brain edema and neuronal apoptosis via regulation of peroxisome proliferator-activated receptor- γ (PPAR- γ) coactivator-1 α (PGC-1 α). QUE at 50 mg/kg regulated SOD and MDA levels, reduced oxidative stress, and downregulated caspase-3 expression [93]. According to Li et al., QUE at 50 mg/kg decreased the levels of MDA in rats and increased the levels of SOD. TBI was alleviated, and mitochondrial membrane potential (MMP) increased due to Nrf2 upregulation. [94].

Catechin

The group of flavonoids found in tea is largely responsible for producing catechins (flavan-3-ol). Among the compounds that can contribute to breast cancer prevention and treatment include (-)-epigallocatechin-3-gallate (EGCG), (-)-epicatechin-3-gallate, and (-)-epigallocatechin. Unfermented green tea is one of the best sources of catechins. There are a variety of types and origins of green tea leaves that have different antioxidant properties. Wine, berries, coffee, and tea also contain catechins naturally. Including catechin-containing products in the diet is recommended because catechins have many health-promoting properties. The most important properties of the catechins are their antioxidant, anti-inflammatory and chemopreventive effects [95]. Jiang et al. conducted important research on the neuroprotective effects of catechin on a TBI rat model. Catechin reduces neuronal damage while improving motor function and cognition. Catechin at 20 mg/kg attenuated brain edema and inflammation, reducing inflammatory cytokines such as IL-1 β , iNOS, and IL-6 while increasing the arginase 1 levels (an inflammatory marker). Moreover, the chemical was also beneficial to maintaining the integrity

of the blood–brain barrier (BBB) and reducing the loss of some tight junction proteins, such as occludin and zonula occludens protein-1 [96].

In another study in 2020, EGCG showed beneficial effects in improving neurological deficits after TBI in a rat model. EGCG increased learning and memory after administration. It has been claimed that EGCG reduces the expression of I kappa B kinase alpha/beta (IKK α/β), and NF- κ B, reducing inflammatory cytokines and oxidative stress [97]. In 2011, Itoh et al. demonstrated that EGCG ameliorated neuronal dysfunction and regulated serum MDA levels in a rat model. The compound also reduced apoptosis and oxidative stress while increasing neuronal survival. Furthermore, the single-stranded DNA-positive cells were alleviated after consumption of EGCG (0.1% w/v) [98]. In another study by Itoh and colleagues, EGCG (0.1% w/v) reduced peroxidation levels and increased the amount of nestin-positive in the injured area after TBI [99].

Lignans

Lignans are a class of natural antioxidant polyphenols found in whole grains, nuts, beans, seeds, and vegetables. Several neuropathological conditions and neurodegenerative diseases, such as PD and AD, are being studied using plant metabolites as potential therapeutics. Some lignans have been shown to have significant anti-inflammatory, neuroprotective, antioxidant, and immunomodulatory properties [100]. Liu et al. in 2017 investigated the effects of sesamin on TBI in a rat model. Sesamin, a lignan, reduced neuronal loss and apoptosis while reducing oxidative stress. However, it was shown that sesamin at 30 mg/kg could reduce brain edema as assessed by brain water content. Sesamin was also shown to reduce the loss of tight junction proteins such as occludin. Finally, sesamin was shown to exert its beneficial effects by reducing the activation of ERK, p-38, and caspase-3 [101].

Magnolol

Magnolia officinalis is well known for its root and bark, which contains magnolol, a phenolic compound. Chinese and Japanese medicine have traditionally used this herb to treat a variety of ailments without causing significant toxicity. In addition, magnolol inhibits lipid peroxidation in rat heart mitochondria 1000 times more effectively than tocopherol and 50,000 times better than glutathione [102]. After TBI, magolol (2 mg/kg intravenously) decreased the presence of TBI markers like glycerol and 2,3-dihydroxybenzoic acid, decreased the size of the infarct, and reduced neuronal apoptosis by promoting proteins such as transforming growth factor-beta 1 (TGF- β 1) in neurons [103].

Honokiol

Several species of Magnolia plants contain an abundant amount of lignan called honokiol. This substance has been used traditionally in medicine for centuries. Magnolias are widely distributed worldwide, with most species found in East and Southeast Asia [104]. Honokiol has been identified as a compound with multiple therapeutic functions, including anticancer, antimicrobial, anti-inflammatory, antithrombotic, antidepressant, and neuroprotective effects due to its BBB-crossing properties [105]. Honokiol ameliorated TBI injury in a rat model by reducing inflammation and improving endothelial cell damage. This phytochemical induced vascular endothelial growth factor expression and reduced pyramidal neuron apoptosis [106]. In another study by Wang et al. in 2014, honokiol (0.5 or 2 mg/kg) showed improved motor, sensory and cognitive functions after TBI in a rat model. The compound reduced neuronal apoptosis and lesion size and decreased cell cycle proteins such as cyclin D1, cyclin-dependent kinase 4, retinoblastoma protein, and E2 promoter binding factor 1 [107].

Cinnamon

As well as being an essential ingredient of cooking, cinnamon (*Cinnamomum cassia*) is also used in traditional medicine to treat gastritis, dyspepsia, inflammatory conditions, and circulatory issues. Various pharmacological properties of cinnamon include anti-inflammatory, anti-diabetic, antimicrobial, and anti-tumor properties [108, 109]. Yulug et al. in 2018 investigated the beneficial effects of cinnamon on TBI in a rat model. Cinnamon (10 mg/kg) reduced lesion size and neuronal apoptosis and may improve neuronal survival. This compound exerts its therapeutic effects by suppressing the expression of IL-1, IL-6, and NF- κ B expression. Cinnamon regulated the expression of various factors such as MDA, CAT, SOD, and GSH. Cinnamon reduced brain edema, as assessed by brain water content [110]. In another in vivo study, Cinnamon was shown to reduce iNOS expression in an animal model after TBI. This compound reduced the activation of microglia and astrocytes. And vascular damage and lessen the size of the lesion while improving memory and motor ability [111].

Conclusion and Future Perspectives

Traumatic Brain Injury (TBI) stands as a significant public health concern, constituting a leading cause of disability, particularly affecting individuals under 45 years old.

TBI encompasses primary and secondary injuries, often accompanied by systemic symptoms. Secondary injury arises from a complex cascade of oxidative and apoptotic events following head trauma, underscoring the critical role of oxidative stress in TBI's injury pathways and potential therapeutic implications. While several studies, such as the one by Zahedi et al., suggest promising effects of curcuminoids, developing effective therapeutic strategies necessitates rigorous preclinical studies and clinical trials. The heterogeneous nature of TBI underscores the need for comprehensive research addressing translational barriers. Several phytochemicals, including QUE, RSV, cinnamon, honokiol, and magnolol, have demonstrated the capacity to modulate signaling pathways crucial in attenuating neuroinflammation associated with TBI. For instance, they have shown inhibitory effects on pathways like TLR4, NF- κ B, and NLRP-3 while generally upregulating Nrf2 and PI3K/AKT signaling pathways. These phytochemicals also exhibit modulation of various inflammatory and pro-inflammatory cytokines (e.g., IL-13, IL-1 β , IL-6, IL-18, IL-15, TNF- α), collectively underscoring their neuroprotective potential in TBI. However, despite these promising findings, the absence of robust clinical trials poses a significant gap. It is imperative to design clinical trials that assess the appropriate dosage, safety, bioavailability, pharmacokinetics, duration of use, sustained improvement, and potential side effects of phytochemicals, in particular polyphenols, in patients suffering from TBI. Furthermore, elucidating the specific signaling pathways, molecules, and genetic components involved in the therapeutic effects of phytochemicals in TBI models remains an essential avenue for research to better understand their mechanisms of action.

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Declarations

Ethics Approval N/A.

Consent to Participate N/A.

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References

- Murray CJ, Lopez AD (1997) Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 349(9064):1498–1504
- Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B et al (2011) The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 21(9):655–679
- Taylor CA, Bell JM, Breiding MJ, Xu L (2017) Traumatic brain injury-related emergency department visits, hospitalizations, and deaths - United States, 2007 and 2013. *MMWR Surveill Summ* 66(9):1–16
- Miller GF, Kegler SR, Stone DM (2020) Traumatic brain injury-related deaths from firearm suicide: United States, 2008–2017. *Am J Public Health* 110(6):897–899
- Khanal LN, Sharma KR, Pokharel YR, Kalauni SK (2022) Phytochemical analysis and in vitro antioxidant and antibacterial activity of different solvent extracts of *Beilschmiedia roxburghiana* Nees Stem Barks. *Sci World J* 2022:6717012
- Ahmadi A, Jamialahmadi T, Sahebkar A (2022) Polyphenols and atherosclerosis: a critical review of clinical effects on LDL oxidation. *Pharmacol Res* 184:106414
- Hosseini SA, Zahedipour F, Sathyapalan T, Jamialahmadi T, Sahebkar A (2021) Pulmonary fibrosis: therapeutic and mechanistic insights into the role of phytochemicals. *BioFactors* 47(3):250–269
- Ganesan K, Xu B (2017) A critical review on polyphenols and health benefits of black soybeans. *Nutrients* 9(5):455. <https://doi.org/10.3390/nu9050455>
- Mottaghipisheh J, Doustimotlagh AH, Irajie C, Tanideh N, Barzegar A, Irajie A (2022) The promising therapeutic and preventive properties of anthocyanidins/anthocyanins on prostate cancer. *Cells* 11(7):1070. <https://doi.org/10.3390/cells11071070>
- Si W, Zhang Y, Li X, Du Y, Xu Q (2021) Understanding the functional activity of polyphenols using omics-based approaches. *Nutrients* 13(11):3953. <https://doi.org/10.3390/nu13113953>
- de Andrade Teles RB, Diniz TC, Costa Pinto TC, de Oliveira Júnior RG, Gama ESM, de Lavor ÉM et al (2018) Flavonoids as therapeutic agents in Alzheimer's and Parkinson's diseases: a systematic review of preclinical evidences. *Oxid Med Cell Longev* 2018:7043213
- Jha NK, Jha SK, Kar R, Nand P, Swati K, Goswami VK (2019) Nuclear factor-kappa β as a therapeutic target for Alzheimer's disease. *J Neurochem* 150(2):113–137
- Scalbert A, Johnson IT, Saltmarsh M (2005) Polyphenols: antioxidants and beyond. *Am J Clin Nutr* 81(1 Suppl):215s–s217
- Obrenovich ME, Nair NG, Beyaz A, Aliev G, Reddy VP (2010) The role of polyphenolic antioxidants in health, disease, and aging. *Rejuvenation Res* 13(6):631–643
- Kempuraj D, Thangavel R, Kempuraj DD, Ahmed ME, Selvakumar GP, Raikwar SP et al (2021) Neuroprotective effects of flavone luteolin in neuroinflammation and neurotrauma. *BioFactors* 47(2):190–197
- Cornelius C, Crupi R, Calabrese V, Graziano A, Milone P, Pennisi G et al (2013) Traumatic brain injury: oxidative stress and neuroprotection. *Antioxid Redox Signal* 19(8):836–853
- Angeloni C, Prata C, Vieceli Dalla Sega F, Piperno R, Hrelia S (2015) Traumatic brain injury and NADPH oxidase: a deep relationship. *Oxid Med Cell Longev* 2015:370312. <https://doi.org/10.1155/2015/370312>
- Maiuri MC, Ciriollo A, Kroemer G (2010) Crosstalk between apoptosis and autophagy within the Beclin 1 interactome. *EMBO J* 29(3):515–516
- Gao Y, Zhuang Z, Gao S, Li X, Zhang Z, Ye Z et al (2017) Tetrahydrocurcumin reduces oxidative stress-induced apoptosis via the mitochondrial apoptotic pathway by modulating autophagy in rats after traumatic brain injury. *Am J Transl Res* 9(3):887
- Lucas K, Maes M (2013) Role of the toll like receptor (TLR) radical cycle in chronic inflammation: possible treatments targeting the TLR4 pathway. *Mol Neurobiol* 48(1):190–204
- Zhang L, Ding K, Wang H, Wu Y, Xu J (2016) Traumatic brain injury-induced neuronal apoptosis is reduced through modulation of PI3K and autophagy pathways in mouse by FTY720. *Cell Mol Neurobiol* 36(1):131–142
- Akira S, Takeda K (2004) Toll-like receptor signalling. *Nat Rev Immunol* 4(7):499–511
- Ahmad A, Crupi R, Campolo M, Genovese T, Esposito E, Cuzocrea S (2013) Absence of TLR4 reduces neurovascular unit and secondary inflammatory process after traumatic brain injury in mice. *PLoS ONE* 8(3):e57208
- Li G-Z, Zhang Y, Zhao J-B, Wu G-J, Su X-F, Hang C-H (2011) Expression of myeloid differentiation primary response protein 88 (Myd88) in the cerebral cortex after experimental traumatic brain injury in rats. *Brain Res* 1396:96–104
- Sun SC (2017) The non-canonical NF-kappaB pathway in immunity and inflammation. *Nat Rev Immunol* 17(9):545–558
- Chen C-C, Hung T-H, Wang Y-H, Lin C-W, Wang P-Y, Lee C-Y et al (2012) Wogonin improves histological and functional outcomes, and reduces activation of TLR4/NF- κ B signaling after experimental traumatic brain injury. *PLoS ONE* 7(1):e30294
- Bayır H, Kochanek PM, Kagan VE (2006) Oxidative stress in immature brain after traumatic brain injury. *Dev Neurosci* 28(4–5):420–431
- Zhang L, Wang H (2018) Targeting the NF-E2-related factor 2 pathway: a novel strategy for traumatic brain injury. *Mol Neurobiol* 55(2):1773–1785
- De Vries HE, Witte M, Hondius D, Rozemuller AJ, Drukarch B, Hoozemans J et al (2008) Nrf2-induced antioxidant protection: a promising target to counteract ROS-mediated damage in neurodegenerative disease? *Free Radical Biol Med* 45(10):1375–1383
- Itoh K, Tong KI, Yamamoto M (2004) Molecular mechanism activating Nrf2-Keap1 pathway in regulation of adaptive response to electrophiles. *Free Radical Biol Med* 36(10):1208–1213
- Poti F, Santi D, Spaggiari G, Zimetti F, Zanotti I (2019) Polyphenol health effects on cardiovascular and neurodegenerative disorders: a review and meta-analysis. *Int J Mol Sci* 20(2):351. <https://doi.org/10.3390/ijms20020351>
- Losada-Barreiro S, Bravo-Díaz C (2017) Free radicals and polyphenols: the redox chemistry of neurodegenerative diseases. *Eur J Med Chem* 133:379–402
- Li C, Li Y, Zhao Z, Lv Y, Gu B, Zhao L (2019) Aerobic exercise regulates synaptic transmission and reactive oxygen species production in the paraventricular nucleus of spontaneously hypertensive rats. *Brain Res* 1712:82–92

34. Perron NR, Brumaghim JL (2009) A review of the antioxidant mechanisms of polyphenol compounds related to iron binding. *Cell Biochem Biophys* 53(2):75–100
35. Pourzand C, Albieri-Borges A, Raczek NN (2022) Shedding a new light on skin aging, iron- and redox-homeostasis and emerging natural antioxidants. *Antioxidants (Basel)* 11(3):471. <https://doi.org/10.3390/antiox11030471>
36. Andres-Lacueva C, Shukitt-Hale B, Galli RL, Jauregui O, Lamuela-Raventos RM, Joseph JA (2005) Anthocyanins in aged blueberry-fed rats are found centrally and may enhance memory. *Nutr Neurosci* 8(2):111–120
37. Croft KD (2016) Dietary polyphenols: antioxidants or not? *Arch Biochem Biophys* 595:120–124
38. Carregosa D, Carecho R, Figueira ICNS (2020) Low-molecular weight metabolites from polyphenols as effectors for attenuating neuroinflammation. *J Agric Food Chem* 68(7):1790–807
39. Cicero AFG, Sahebkar A, Fogacci F, Bove M, Giovannini M, Borghi C (2020) Effects of phytosomal curcumin on anthropometric parameters, insulin resistance, cortisolemia and non-alcoholic fatty liver disease indices: a double-blind, placebo-controlled clinical trial. *Eur J Nutr* 59(2):477–483
40. Iranshahi M, Sahebkar A, Takasaki M, Konoshima T, Tokuda H (2009) Cancer chemopreventive activity of the prenylated coumarin, umbelliprenin, in vivo. *Eur J Cancer Prev* 18(5):412–415
41. Keihanian F, Saeidinia A, Bagheri RK, Johnston TP, Sahebkar A (2018) Curcumin, hemostasis, thrombosis, and coagulation. *J Cell Physiol* 233(6):4497–4511
42. Marjaneh RM, Rahmani F, Hassanian SM, Rezaei N, Hashemzahi M, Bahrami A et al (2018) Phytosomal curcumin inhibits tumor growth in colitis-associated colorectal cancer. *J Cell Physiol* 233(10):6785–6798
43. Mohajeri M, Sahebkar A (2018) Protective effects of curcumin against doxorubicin-induced toxicity and resistance: a review. *Crit Rev Oncol Hematol* 122:30–51
44. Mokhtari-Zaer A, Marefati N, Atkin SL, Butler AE, Sahebkar A (2018) The protective role of curcumin in myocardial ischemia-reperfusion injury. *J Cell Physiol* 234(1):214–222
45. Momtazi AA, Sahebkar A (2016) Difluorinated curcumin: a promising curcumin analogue with improved anti-tumor activity and pharmacokinetic profile. *Curr Pharm Des* 22(28):4386–4397
46. Panahi Y, Fazlolahzadeh O, Atkin SL, Majeed M, Butler AE, Johnston TP et al (2019) Evidence of curcumin and curcumin analogue effects in skin diseases: a narrative review. *J Cell Physiol* 234(2):1165–1178
47. Panahi Y, Sahebkar A, Amiri M, Davoudi SM, Beiraghdar F, Hoseinnejad SL et al (2012) Improvement of sulphur mustard-induced chronic pruritus, quality of life and antioxidant status by curcumin: results of a randomised, double-blind, placebo-controlled trial. *Br J Nutr* 108(7):1272–1279
48. Sahebkar A (2014) Curcuminoids for the management of hypertriglyceridaemia. *Nat Rev Cardiol* 11(2):123. <https://doi.org/10.1038/nrcardio.2013.140-c1>
49. Khayatan D, Razavi SM, Arab ZN, Niknejad AH, Nouri K, Momtaz S et al (2022) Protective effects of curcumin against traumatic brain injury. *Biomed Pharmacother* 154:113621
50. Mohammadi A, Blesso CN, Barreto GE, Banach M, Majeed M, Sahebkar A (2019) Macrophage plasticity, polarization and function in response to curcumin, a diet-derived polyphenol, as an immunomodulatory agent. *J Nutr Biochem* 66:1–16
51. Ferguson JJA, Abbott KA, Garg ML (2021) Anti-inflammatory effects of oral supplementation with curcumin: a systematic review and meta-analysis of randomized controlled trials. *Nutr Rev* 79(9):1043–1066
52. Sun G, Miao Z, Ye Y, Zhao P, Fan L, Bao Z et al (2020) Curcumin alleviates neuroinflammation, enhances hippocampal neurogenesis, and improves spatial memory after traumatic brain injury. *Brain Res Bull* 162:84–93
53. Zhu HT, Bian C, Yuan JC, Chu WH, Xiang X, Chen F et al (2014) Curcumin attenuates acute inflammatory injury by inhibiting the TLR4/MyD88/NF- κ B signaling pathway in experimental traumatic brain injury. *J Neuroinflammation* 11:59
54. Wu A, Ying Z, Schubert D, Gomez-Pinilla F (2011) Brain and spinal cord interaction: a dietary curcumin derivative counteracts locomotor and cognitive deficits after brain trauma. *Neurorehabil Neural Repair* 25(4):332–342
55. Dong X (2018) Current Strategies for Brain Drug Delivery. *Theranostics* 8(6):1481–1493
56. Liang DY, Sahbaie P, Sun Y, Irvine KA, Shi X, Meidahl A et al (2017) TBI-induced nociceptive sensitization is regulated by histone acetylation. *IBRO Rep* 2:14–23
57. Dai W, Wang H, Fang J, Zhu Y, Zhou J, Wang X et al (2018) Curcumin provides neuroprotection in model of traumatic brain injury via the Nrf2-ARE signaling pathway. *Brain Res Bull* 140:65–71
58. Wu A, Ying Z, Gomez-Pinilla F (2006) Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition. *Exp Neurol* 197(2):309–317
59. Attari F, Ghadiri T, Hashemi M (2020) Combination of curcumin with autologous transplantation of adult neural stem/progenitor cells leads to more efficient repair of damaged cerebral tissue of rat. *Exp Physiol* 105(9):1610–1622
60. Wei G, Chen B, Lin Q, Li Y, Luo L, He H et al (2017) Tetrahydrocurcumin provides neuroprotection in experimental traumatic brain injury and the Nrf2 signaling pathway as a potential mechanism. *NeuroImmunoModulation* 24(6):348–355
61. Wu A, Ying Z, Gomez-Pinilla F (2014) Dietary strategy to repair plasma membrane after brain trauma: implications for plasticity and cognition. *Neurorehabil Neural Repair* 28(1):75–84
62. Sharma S, Ying Z, Gomez-Pinilla F (2010) A pyrazole curcumin derivative restores membrane homeostasis disrupted after brain trauma. *Exp Neurol* 226(1):191–199
63. Gao Y, Li J, Wu L, Zhou C, Wang Q, Li X et al (2016) Tetrahydrocurcumin provides neuroprotection in rats after traumatic brain injury: autophagy and the PI3K/AKT pathways as a potential mechanism. *J Surg Res* 206(1):67–76
64. Razavi SM, Khayatan D, Arab ZN, Momtaz S, Zare K, Jafari RM et al (2021) Licofelone, a potent COX/5-LOX inhibitor and a novel option for treatment of neurological disorders. *Prostaglandins Other Lipid Mediat* 157:106587
65. Mirhadi E, Roufogalis BD, Banach M, Barati M, Sahebkar A (2021) Resveratrol: mechanistic and therapeutic perspectives in pulmonary arterial hypertension. *Pharmacol Res* 163:105287
66. Omraninava M, Razi B, Aslani S, Imani D, Jamialahmadi T, Sahebkar A (2021) Effect of resveratrol on inflammatory cytokines: a meta-analysis of randomized controlled trials. *Eur J Pharmacol* 908:174380
67. Parsamanesh N, Asghari A, Sardari S, Tasbandi A, Jamialahmadi T, Xu S et al (2021) Resveratrol and endothelial function: a literature review. *Pharmacol Res* 170:105725
68. Sahebkar A (2013) Effects of resveratrol supplementation on plasma lipids: a systematic review and meta-analysis of randomized controlled trials. *Nutr Rev* 71(12):822–835
69. Sahebkar A, Serban C, Ursioniu S, Wong ND, Muntner P, Graham IM et al (2015) Lack of efficacy of resveratrol on C-reactive protein and selected cardiovascular risk factors - results from a systematic review and meta-analysis of randomized controlled trials. *Int J Cardiol* 189(1):47–55

70. Rafiee S, Mohammadi H, Ghavami A, Sadeghi E, Safari Z, Askari G (2021) Efficacy of resveratrol supplementation in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis of clinical trials. *Complement Ther Clin Pract* 42:101281
71. Visioli F (2014) The resveratrol fiasco. *Pharmacol Res* 90:87
72. Shanan N, GhasemiGharagoz A, Abdel-Kader R, Breitinger HG (2019) The effect of pyrroloquinoline quinone and resveratrol on the survival and regeneration of cerebellar granular neurons. *Neurosci Lett* 694:192–197
73. Taherian M, Norenberg MD, Panickar KS, Shamaladevi N, Ahmad A, Rahman P et al (2020) Additive effect of resveratrol on astrocyte swelling post-exposure to ammonia, ischemia and trauma in vitro. *Neurochem Res* 45(5):1156–1167
74. Lin CJ, Chen TH, Yang LY, Shih CM (2014) Resveratrol protects astrocytes against traumatic brain injury through inhibiting apoptotic and autophagic cell death. *Cell Death Dis* 5(3):e1147
75. Feng Y, Cui Y, Gao JL, Li MH, Li R, Jiang XH et al (2016) Resveratrol attenuates neuronal autophagy and inflammatory injury by inhibiting the TLR4/NF- κ B signaling pathway in experimental traumatic brain injury. *Int J Mol Med* 37(4):921–930
76. Singleton RH, Yan HQ, Fellows-Mayle W, Dixon CE (2010) Resveratrol attenuates behavioral impairments and reduces cortical and hippocampal loss in a rat controlled cortical impact model of traumatic brain injury. *J Neurotrauma* 27(6):1091–1099
77. Feng Y, Cui Y, Gao JL, Li R, Jiang XH, Tian YX et al (2016) Neuroprotective effects of resveratrol against traumatic brain injury in rats: involvement of synaptic proteins and neuronal autophagy. *Mol Med Rep* 13(6):5248–5254
78. Salberg S, Yamakawa G, Christensen J, Kolb B, Mychasiuk R (2017) Assessment of a nutritional supplement containing resveratrol, prebiotic fiber, and omega-3 fatty acids for the prevention and treatment of mild traumatic brain injury in rats. *Neuroscience* 365:146–157
79. Zou P, Liu X, Li G, Wang Y (2018) Resveratrol pretreatment attenuates traumatic brain injury in rats by suppressing NLRP3 inflammasome activation via SIRT1. *Mol Med Rep* 17(2):3212–3217
80. Shi Z, Qiu W, Xiao G, Cheng J, Zhang N (2018) Resveratrol attenuates cognitive deficits of traumatic brain injury by activating p38 signaling in the brain. *Med Sci Monit* 24:1097–1103
81. Atalay T, Gulsen I, Colcimen N, Alp HH, Sosuncu E, Alaca I et al (2017) Resveratrol treatment prevents hippocampal neurodegeneration in a rodent model of traumatic brain injury. *Turk Neurosurg* 27(6):924–930
82. Gatson JW, Liu MM, Abdelfattah K, Wigginton JG, Smith S, Wolf S et al (2013) Resveratrol decreases inflammation in the brain of mice with mild traumatic brain injury. *J Trauma Acute Care Surg* 74(2):470–4
83. Sönmez U, Sönmez A, Erbil G, Tekmen I, Baykara B (2007) Neuroprotective effects of resveratrol against traumatic brain injury in immature rats. *Neurosci Lett* 420(2):133–137
84. Iranshahi M, Sahebkar A, Hosseini ST, Takasaki M, Konoshima T, Tokuda H (2010) Cancer chemopreventive activity of diversin from *Ferula diversivittata* in vitro and in vivo. *Phytomedicine* 17(3–4):269–273
85. Zou H, Ye H, Kamaraj R, Zhang T, Zhang J, Pavak P (2021) A review on pharmacological activities and synergistic effect of quercetin with small molecule agents. *Phytomedicine* 92:153736
86. Wang G, Wang Y, Yao L, Gu W, Zhao S, Shen Z et al (2022) Pharmacological activity of quercetin: an updated review. *Evid Based Complement Alternat Med* 2022:3997190
87. Guan LP, Liu BY (2016) Antidepressant-like effects and mechanisms of flavonoids and related analogues. *Eur J Med Chem* 121:47–57
88. Song J, Du G, Wu H, Gao X, Yang Z, Liu B et al (2021) Protective effects of quercetin on traumatic brain injury induced inflammation and oxidative stress in cortex through activating Nrf2/HO-1 pathway. *Restor Neurol Neurosci* 39(1):73–84
89. Kalemci O, Aydin HE, Kizmazoglu C, Kaya I, Yilmaz H, Arda NM (2017) Effects of quercetin and mannitol on erythropoietin levels in rats following acute severe traumatic brain injury. *J Korean Neurosurg Soc* 60(3):355–361
90. Yang T, Kong B, Gu JW, Kuang YQ, Cheng L, Yang WT et al (2014) Anti-apoptotic and anti-oxidative roles of quercetin after traumatic brain injury. *Cell Mol Neurobiol* 34(6):797–804
91. Du G, Zhao Z, Chen Y, Li Z, Tian Y, Liu Z et al (2016) Quercetin attenuates neuronal autophagy and apoptosis in rat traumatic brain injury model via activation of PI3K/Akt signaling pathway. *Neurol Res* 38(11):1012–1019
92. Du G, Zhao Z, Chen Y, Li Z, Tian Y, Liu Z et al (2018) Quercetin protects rat cortical neurons against traumatic brain injury. *Mol Med Rep* 17(6):7859–7865
93. Li X, Wang H, Wen G, Li L, Gao Y, Zhuang Z et al (2018) Neuroprotection by quercetin via mitochondrial function adaptation in traumatic brain injury: PGC-1 α pathway as a potential mechanism. *J Cell Mol Med* 22(2):883–891
94. Li X, Wang H, Gao Y, Li L, Tang C, Wen G et al (2016) Protective effects of quercetin on mitochondrial biogenesis in experimental traumatic brain injury via the Nrf2 signaling pathway. *PLoS ONE* 11(10):e0164237
95. Musial C, Kuban-Jankowska A, Gorska-Ponikowska M (2020) Beneficial properties of green tea catechins. *Int J Mol Sci* 21(5):1744. <https://doi.org/10.3390/ijms21051744>
96. Jiang Z, Zhang J, Cai Y, Huang J, You L (2017) Catechin attenuates traumatic brain injury-induced blood-brain barrier damage and improves longer-term neurological outcomes in rats. *Exp Physiol* 102(10):1269–1277
97. Wu Y, Cui J (2020) (-)-Epigallocatechin-3-gallate provides neuroprotection via AMPK activation against traumatic brain injury in a mouse model. *Naunyn-Schmiedeberg Arch Pharmacol* 393(11):2209–2220
98. Itoh T, Imano M, Nishida S, Tsubaki M, Hashimoto S, Ito A et al (2011) (-)-Epigallocatechin-3-gallate protects against neuronal cell death and improves cerebral function after traumatic brain injury in rats. *Neuromolecular Med* 13(4):300–309
99. Itoh T, Imano M, Nishida S, Tsubaki M, Mizuguchi N, Hashimoto S et al (2012) (-)-Epigallocatechin-3-gallate increases the number of neural stem cells around the damaged area after rat traumatic brain injury. *J Neural Transm (Vienna)* 119(8):877–890
100. Giuliano C, Siani F, Mus L, Ghezzi C, Cerri S, Pacchetti B et al (2020) Neuroprotective effects of lignan 7-hydroxymatairesinol (HMR/lignan) in a rodent model of Parkinson's disease. *Nutrition* 69:110494
101. Liu YL, Xu ZM, Yang GY, Yang DX, Ding J, Chen H et al (2017) Sesamin alleviates blood-brain barrier disruption in mice with experimental traumatic brain injury. *Acta Pharmacol Sin* 38(11):1445–1455
102. Dong L, Zhou S, Yang X, Chen Q, He Y, Huang W (2013) Magnolol protects against oxidative stress-mediated neural cell damage by modulating mitochondrial dysfunction and PI3K/Akt signaling. *J Mol Neurosci* 50(3):469–481
103. Wang CC, Lin KC, Lin BS, Chio CC, Kuo JR (2013) Resuscitation from experimental traumatic brain injury by magnolol therapy. *J Surg Res* 184(2):1045–1052
104. Talarek S, Listos J, Barreca D, Tellone E, Sureda A, Nabavi SF et al (2017) Neuroprotective effects of honokiol: from chemistry to medicine. *BioFactors* 43(6):760–769
105. Li W, Wang S, Zhang H, Li B, Xu L, Li Y et al (2021) Honokiol restores microglial phagocytosis by reversing metabolic reprogramming. *J Alzheimers Dis* 82(4):1475–1485

106. Çetin A, Deveci E (2019) Expression of vascular endothelial growth factor and glial fibrillary acidic protein in a rat model of traumatic brain injury treated with honokiol: a biochemical and immunohistochemical study. *Folia Morphol (Warsz)* 78(4):684–694
107. Wang H, Liao Z, Sun X, Shi Q, Huo G, Xie Y et al (2014) Intravenous administration of Honokiol provides neuroprotection and improves functional recovery after traumatic brain injury through cell cycle inhibition. *Neuropharmacology* 86:9–21
108. Seibel R, Schneider RH, Gottlieb MG (2021) Effects of spices (saffron, rosemary, cinnamon, turmeric and ginger) in Alzheimer's disease. *Curr Alzheimer Res* 18(4):347–357
109. Sadeghi S, Davoodvandi A, Pourhanifeh MH, Sharifi N, ArefNezhad R, Sahebnaasagh R et al (2019) Anti-cancer effects of cinnamon: insights into its apoptosis effects. *Eur J Med Chem* 178:131–140
110. Yulug B, Kilic E, Altunay S, Ersavas C, Orhan C, Dalay A et al (2018) Cinnamon polyphenol extract exerts neuroprotective activity in traumatic brain injury in male mice. *CNS Neurol Disord Drug Targets* 17(6):439–447
111. Rangasamy SB, Raha S, Dasarathy S, Pahan K (2021) Sodium benzoate, a metabolite of cinnamon and a food additive, improves cognitive functions in mice after controlled cortical impact injury. *Int J Mol Sci* 23(1):192. <https://doi.org/10.3390/ijms23010192>
112. Li X, Wang H, Gao Y, Li L, Tang C, Wen G et al (2016) Quercetin induces mitochondrial biogenesis in experimental traumatic brain injury via the PGC-1 α signaling pathway. *Am J Transl Res* 8(8):3558–3566
113. Yavtushenko IV, Nazarenko SM, Katrushov OV, Kostenko VO (2020) Quercetin limits the progression of oxidative and nitrosative stress in the rats' tissues after experimental traumatic brain injury. *Wiad Lek* 73(10):2127–2132
114. Itoh T, Tabuchi M, Mizuguchi N, Imano M, Tsubaki M, Nishida S et al (2013) Neuroprotective effect of (-)-epigallocatechin-3-gallate in rats when administered pre- or post-traumatic brain injury. *J Neural Transm (Vienna)* 120(5):767–783
115. Qubty D, Rubovitch V, Benromano T, Ovadia M, Pick CG (2021) Orally administered cinnamon extract attenuates cognitive and neuronal deficits following traumatic brain injury. *J Mol Neurosci* 71(1):178–186

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