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A Novel Approach to the Management of Traumatic Brain Injury

Prof. (Dr.) Mrunal K Shirsat[1], Sandhya Suresh[2], Kajal Khan[3], Geeta Rawat[4], Muhammed Amanat[5], Pratik Prakash Terse[6], Prem Shankar Tyagi[7]*

[1] Professor/Principal, SBSPMs B-Pharmacy College Ambejogai District-Beed-431517
[2] Assistant Professor, Venkateshwar institute of Pharmacy
[3] Assistant Professor, Truba Institute of Pharmacy, Bhopal, 462033
[4a] Assistant Professor, Shree Guru Govind Tricentary University, Gurugram &
[4b] Sharda University, Greater Noida
[5] Central University of Punjab, Ghudda, Bathind-151401
[6] Assistant Professor, Shree Pushpasen Sawant college of Pharmacy, On Mumbai Goa Hwy, Post Digas, Tal. Kudal, District Sindhudurg, Rumadgaon, Maharashtra 416521
[7] Assistant Professor, Vishveshwarya Group of Institutions, Dadri, Gautam Buddh Nagar, Uttar Pradesh 203207

Corresponding Author Details:
Prem Shankar Tyagi
Vishveshwarya Group of Institutions, Dadri, Gautam Buddh Nagar, Uttar Pradesh 203207
Email: premtyagi44@gmail.com

Abstract: The purpose of the current paper is to examine several phytochemicals, or natural substances derived from plants, that have been studied in experimental animal models of TBI. By using search engines including ISI Web of Knowledge, Pub Med, Medline, Scopus, and Google Scholar to browse online literature resources, researchers were able to find studies, editorials, and reviews on the impact of medicinal plants on TBI and their potential processes. Preliminary studies suggest bioactive compounds may be employed as a possible TBI therapy. These substances often have minimal toxicity and few interactions with other medications. Additionally, a range of organic compounds have the capacity to focus on a range of secondary harm components. Certain phytonutrients could be therapeutically effective in preventing important steps in the secondary harm cascade. Studies using naturally occurring phytochemicals in TBI research should be regarded with care since not all studies have used the same degree of scientific integrity.

Keywords: Traumatic Brain Injury, Epidemiology of TBI, Medicinal Plants for TBI

Introduction

"A disruption in brain function or other signs of brain disease produced by an external force" is explicated as traumatic brain injury (TBI) (Menon et al., 2010). The Centres for Disease Control and Prevention describe a traumatic brain injury (TBI) as a disturbance in brain functioning caused by blunt or penetrating trauma (Ricker & Arenth, 2006). The number of new cases of TBI is estimated to be 50 million instances globally; as a result, over half of the world's population will have a TBI at some point in their lives (CDC, 2002). It is the leading cause of mortality and disability in those under the age of 40 in the United Kingdom (Azouvi

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et al., 2017). Furthermore, low- and middle-income nations have considerably greater rates of sickness and mortality (CDC Injury Center, n.d.). India's population is 13 billion people. In India, there are little accurate data on TBI epidemiology, and there is no governmental trauma registry. In India, the National Crime Records Bureau recorded 413457 unintentional fatalities in 2015, which is likely an underestimate of the true number. Between 2004 and 2015, there was a 49 percent rise in accident-related mortality, despite a 164% increase in population. According to the Towards Improved Trauma Care Outcomes (TITCO) trauma registry of Indian urban university hospitals (Roy N, BARC Hospital, Mumbai, India, intimate communication), approximately 50% of trauma deaths are likely to be related to TBI (Roy N, BARC Hospital, Mumbai, India, personal communication). TBI disables almost a million individuals in India each year, with road traffic accidents accounting for 60 percent to 70 percent of all TBIs (Burton, 2016; Das, 2012).

Epidemiology of TBI

Trauma is the leading cause of morbidity and mortality in people aged 1 to 45, with traumatic brain injury (TBI) making up the majority of these deaths, which reach more than 50,000 in the United States each year (CDC Injury Center, n.d.; Langlois et al., 2006; Stocchetti & Maas, 2014). Based on the Glasgow Coma Scale (GCS) score, TBI can be clinically classified as mild, moderate, or severe, with permanent impairment rates of 10%, 60%, and 100%, respectively, and overall mortality rates of 20% to 30% (CDC Injury Center, n.d.; Crandall et al., 2014). Brazinova et al. showed substantial variation in crude TBI prevalence estimates (47.3–849 per 100,000 population per year), mean age at injury (range: 26.7–44.5 years), and gender ratio among nations and regions, while all studies indicated higher male occurrences (range: 55–80%)(Brazinova et al., 2021). Accidents, falls, assaults, and sports-related injuries are the most common causes of TBI. After a car collision, TBI is most common in young adult males (ages 15–25). Young babies and the elderly, in particular following falls, have two distinct peak occurrences (TIRET et al., 1990). TBI's evolving epidemiological trend was recently described by Roozenbeek et al. (Roozenbeek et al., 2013). They stated that the corresponding figure of TBI patients is rising, and that falls (which primarily affect the elderly) had surpassed traffic accidents as the major cause of TBI. Additionally, poorer socioeconomic level, pre-existing psychological illnesses, and/or drug misuse have all been linked to an increased risk of TBI (Nordström et al., 2013).

Traumatic brain injury (TBI) classification

TBI classification follows clinical severity and is assessed primarily using the Glasgow Coma Scale (G Teasdale, 1974; Menon DK, 2015; Teasdale, 2014). The Glasgow Coma Scale (range 3–15) consists of the sum of 3 component scores (eye, verbal, and motor scales) and offers a rapid assessment of brain injury severity (Table 1). A score of 13–15, 9–12, and ≤8 classify mild (mTBI), moderate, and severe TBI, respectively (Bodanapally, 2015; Teasdale, 2014). In addition to the Glasgow Coma Scale, TBI is evaluated by various imaging modalities to determine the severity of structural damage in the brain. TBI can be classified into primary and secondary injuries (N Besenski, 2002; Najem, 2018; Wayne S Kubal, 2012).

Table 1: Classification of Traumatic Brain Injury according to GCS (Glasgow Coma Scale)

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	GCS[a] (First 24 h)	Loss of Consciousness	Alteration of Consciousness	Imaging	PTA
Mild	13–15	0–30 min	Up to 24 h	Normal	0–1 d
Moderate	9–12	>30 min and <24 h	>24 h	Normal or abnormal	>1 d and <7 d
Severe	3–8	>24 h	>24 h	Normal or abnormal	>7 d

Pathophysiology of TBI

BBB disruption caused by brain ischemia, inflammation, and redox imbalances characterises the clinical signs of TBI (Greve & Zink, 2009). The BBB is disrupted in the early stages of trauma, as is diminished or altered blood flow, as well as neuronal and glial injury (Greve & Zink, 2009; Parmeet Kaur, 2018). Secondary injury follows the primary injury and manifests itself hours, days, or months later, involving oxidative stress, altered calcium homeostasis, inflammation, and axonal damage, eventually leading to cellular degeneration, disrupted neural circuits, and impaired synaptic transmission and plasticity (Greve & Zink, 2009). post-traumatic headache, sadness, personality changes, anxiety, anger, and deficiencies in inattentiveness, cognition, sensory processing, and communication are all behavioural manifestations of these changes (Chan & Woldeamanuel, 2020; Greve & Zink, 2009; Larsen et al., 2019). (Fig. 1-2) Traumatic brain injury may result in neuropathic pain, a chronic, debilitating illness (Kunal U. Shah, Nandkishor Mule, 2010).

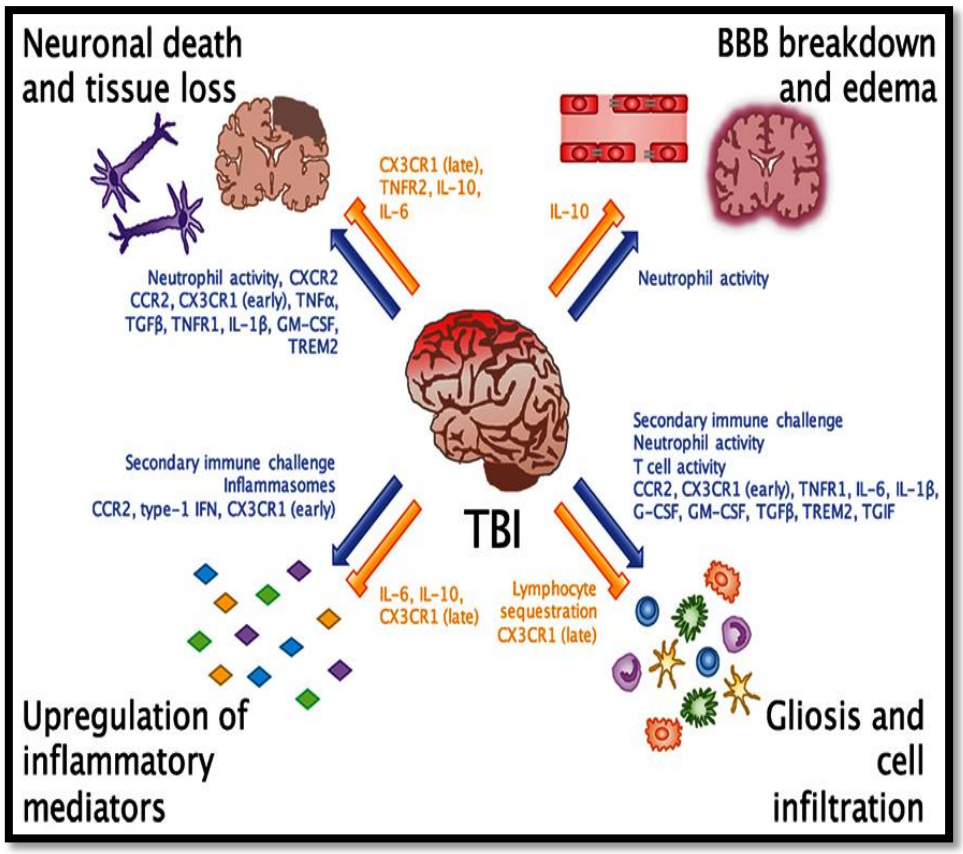

Fig.1 Traumatic Brain Injury

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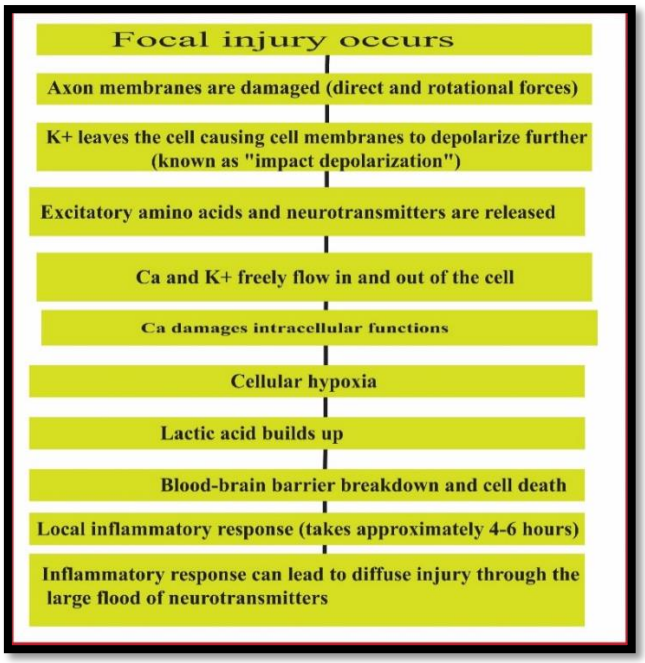

Fig.2 Pathophysiology of traumatic brain injury Focal

Pharmacologic-and non-pharmacologic therapies for TBI

The primary objective of one aspect of therapeutic management following brain trauma aims to control or decrease the development of secondary injury cascades (SIC). Such efforts would lead to the possible rescue of adjacent areas (penumbra) and enhance a positive outcome (Scheff & Ansari, 2017a). This control process is complicated by the fact that other pathophysiological facets of TBI, such as enhanced cerebral perfusion pressure (CPP), intracranial pressor (ICP), and subarachnoid haemorrhage (SAH), play a role in exacerbating SIC. These factors are directly associated with the disruption of the blood-brain barrier (BBB), (Bayir et al., 2003; Werner & Engelhard, 2007) providing an uncontrolled exchange of ions and molecules between the brain and bloodstream and access into the cerebrospinal fluid (CSF) (Reiber & Peter, 2001; Stahel et al., 2001). Several neuroprotective approaches that have been used for TBI clinical trials or animal models include Calcium channel blockers, Osmotherapy, Erythropoietin (EPO), Hypothermia and DC. Increased intracellular calcium is a very important element in the cascade of cellular damage after TBI. Using 2 types of calcium channel blockers (L-type and N-type) to neutralize intracellular calcium has shown benefits in preventing TBI-induced cellular death (Kostron et al., 1984; Langham et al., 2003; Vergouwen et al., 2006; Y Xiong et al., 2009). The neuroprotective effect of nimodipine was reported in 1984 (Kostron et al., 1984) based on the regulation in brain perfusion and prevention of further neuronal damage. However, a systematic review contradicted those results and revealed that the mortality and morbidity displayed no significant difference between placebo and nimodipine treatment in TBI patients (Vergouwen et al., 2006). Ziconotide (SNX-111) is an N-type calcium channel blocker. It has been shown that administration of ziconotide during the period of 15 min to 6 h after TBI improves mitochondrial function in patients 41; however, significant side effects such as hypotension were also observed. SNX-185 was reported to show neuroprotective effects when directly injected to hippocampal CA2 and CA3, 24 h after TBI (Y Xiong et al., 2009). Amantadine is

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a dopamine agonist used for Parkinson's disease. Amantadine can distribute in frontal lobes and acts as an N-methyl-D-Aspartate (NMDA) receptor antagonist. Many studies have demonstrated that amantadine in dose of 100–400 mg/d may increase the arousal and improve cognitive function when given within 12 wk after the TBI (Marklund & Hillered, 2011; Sawyer et al., 2008). Several studies have demonstrated that Erythropoietin (EPO) shows anti-excitotoxic, antioxidant, anti-edematous, and anti-inflammatory effects in TBI (Bramlett et al., n.d.; Cerami et al., 2001; Peng et al., 2014; Ponce et al., 2013). Brain injury causes upregulation of EpoR expression (Hasselblatt et al., 2006). In 1945, Fay reported the possible benefits of hypothermia on severe cerebral trauma (FAY & T, 1943). Since then, many studies have shown that hypothermia improves outcomes in animal models of TBI (Clifton et al., 2016; Fujita et al., 2012; Gu et al., 2015; J. H. Lee et al., 2014; MULLAN et al., 1961; Tisherman et al., 1991). Temperature management in the brain is very important after a cerebral injury (Dietrich & Bramlett, 2016; W D Dietrich, n.d.). Deep hypothermia (below 30^0C) appears to show no benefits for TBI while mild to moderate hypothermia (32 to 35^0C) displays neuroprotective effects (Badjatia, 2013; KH Polderman, 2008). Recent studies have shown that therapeutic hypothermia significantly alters genomic transcripts and microRNA responses and regulates protein synthesis and translation in rat models of TBI (Feng et al., 2010; Knight & Willis, 2015; Truettner et al., 2011). DC is a neurosurgical procedure, which allows a swelling brain to expand without being compressed. DC has been used to reduce ICP in conditions of brain tumour, stroke, and severe TBI (Bohman & Schuster, 2013). DC as a treatment of TBI was originally reported by Emil Theodor Kocher (Plesnila, 2007). However, due to the controversial findings in both clinical and experimental studies, DC is recommended as a third-tier therapy for the treatment of elevated ICP by most national and international guidelines (Plesnila, 2007; Sahuquillo & Dennis, 2019).

Animal models used for TBI

Various aspects of human TBI have been studied in a variety of animal models over the decades to have a better understanding of the pathophysiology and potential treatments. These models of TBI include cortical impact injury (CCI), fluid percussion injury (FPI), blast injury and weight drop–impact acceleration injury (Ye Xiong et al., 2013). Some models are discussed in table 2.

Table 2: Animal models for TBI

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

Herbalism and TBI: role of Medicinal plants

It is now recognized that there are at least two different phases following any type of traumatic brain injury (TBI). The first is the primary injury resulting from the mechanical

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trauma itself. This could be the direct bruising of the tissue inside the cranial vault or the shearing of axons as the brain is forced to very quickly shift position. These types of changes can only be prevented by pre-injury circumvention (Johnson et al., 2013). What is now clear is the fact that after mechanical trauma, multiple secondary injury cascades (SIC) are initiated. If left unchecked, these cascades contribute to additional TBI-associated pathology resulting in numerous neurological problems. Disruption of the BBB is generally viewed as a negative consequence of trauma, however, it allows greater access to possible therapeutic agents (especially natural compounds of large molecular size), which could aid the recovery process (Scheff & Ansari, 2017a).

Various traditional supplements and herbal medicine therapies for TBI have been developed recently. These include both crude extracts and isolated compounds from plants and has shown to have neuroprotective effects due to their antioxidant and anti-inflammatory action on nerve function. Research has begun to investigate the possibility of using natural compounds as a therapeutic intervention following TBI. These compounds normally have very low toxicity and have reduced interactions with other pharmaceuticals. In addition, many natural compounds have the potential to target numerous different components of secondary injury (Scheff & Ansari, 2017b).

Lee b et al., (2019) conducted a systematic review protocol that describes the methods that will be used to evaluate the efficacy and safety of herbal medicine in treating traumatic brain injury.

Li, et al. (2018 & 2017) improved NSS score, increased cortical, neuronal numbers and IL-10 Decreased IL-6 and TNF-α of Black Cohosh (Formononetin), family-A. racemose at the dose of 10 and 30 mg/kg in WDIAI (Li, 2018; Li et al., 2017).

Aswathi Kumar et al., (2015) reduced neuronal injury and microglial activation of Guinea pepper (Seed, Aqueous Ethanolic Extract), family-A. melegueta at the dose of 10, 100, 250, 500 and 1000 mg/kg in FPI (Aswathi Kumar et al., 2015).

Keshavarzi et al., (2019) reduced contusion volume, water content, Bcl-2/Bax ratio, MDA, protein carbonyl, TNF-α and IL-1β Increased CAT, SOD, GST, IL-10, TGF-β1, Akt and Enos Inhibited the activation of caspase-3 and PARP Reduced of Garlic (Allicin), family - A. sativum at the dose of 1,10 and 50 mg/kg in CCI (Keshavarzi et al., 2019).

Gugliandolo et al., (2018) reduced tissue damage and inflammation, expression of Il-1β, TNFα, iNOS, BDNF, VEGF, GDNF, and inflammasome components (NLRP3, ASC, and caspase-1) of Sweet Wormwood (Atesunate), family- A. annua at the dose of 30 mg/kg in CCI (Gugliandolo et al., 2018).

Yang Wang et al., (2016) increased the SOD, CAT, GSH, and GSH/GSSG ratio Decreased MDA and GSSG of Safflower (HSYA), family- C. tinctorius at the dose of 10 and 30 mg/kg in CCI (Yang Wang et al., 2016).

Yulug et al., (2018) reduced infarct and oedema formation suppressing the expression of NF-κB, IL-1, IL-6, GFAP, NCAM, and Nrf2 of Cinnamon Tree (Polyphenol E), family - C. zeylanicum at the dose of 10 mg/kg in CI (Yulug, 2018).

He et al., (2012) reduced neurological deficits, cerebral oedema, and hippocampal neuron loss Increased SOD, GSH MDA, Bcl-2/Bax, the expression of active caspase-3, and the number of apoptotic cells of Water hyssop **(**Osthole), family- C. monnieri at the dose of 10, 20, and 40 mg/kg in WDIAI (He, 2012).

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Wang K. et al., (2015) activated the notch signalling pathway Reduced microglial activation, cell apoptosis, and release of IL-1β and TNFα Improved NSS and brain oedema of Saffron **(**Crocin), family- C. sativus at the dose of 20 mg/kg in CCI (K. Wang et al., 2015).

Liu et al., (2018) improved behavioural tests Reduced BBB permeability, brain oedema, microglia and astrocyte activation, and neurons loss of Chinese traditional medicine **(**AE),family- DCXF (Da Chuanxiong Formula) at the dose of 520.6 and 2,603.0 mg/kg in CCI (Liu et al., 2018).

Jiang et al., (2017) improved NSS score Reduced expression of IL-6 in the injured cortex and IL-6-positive cell number in injured brain tissue of Dengzhanxixin **(**Breviscapine), family- E. breviscapus at the dose of 75 μg in CCI (Jiang et al., 2017).

Ng et al., (2016) improved locomotor functions Reduced the number of astrocytes and the expression of IL-6 and TNFα of Traditional Chinese medicine (AE), family- G. elata at the dose of 505 and 1,515 mg/kg (Ng et al., 2016).

Anil Kumar et al., (2014) & *Ji et al.,* (2005) and *Hu et al.,* (2014) reduced neuronal loss in the hippocampal regions of CA1, CA2, and CA3, contusion volume, and percentage of contusion Improved neurological deficits of Ginseng (AE & GTS),family- P. ginseng at the dose of 50, 100, and 200 mg/kg & 100 and 200 mg/kg in WDIAI & CCI (Hu et al., 2014; Ji, 2005; Anil Kumar, 2014).

Qin et al., (2017) improved cognitive function in MVM test Reduced neuronal loss, GFAP-positive cells, ROS production, and levels of LPO, IL-1β, IL-6, and TNFα Increased SOD level of Mallow, family- M. sylvestris at the dose of 250 and 500 mg/kg in CCI (Qin et al., 2017).

Wang Y. et al., (2016); Xia et al., (2017) & Keshavarzi et al., (2019) ameliorated BBB damage and brain oedema Increased SOD, CAT, GSH, and GSH/GSSG ratio Decreased the MDA and GSSG levels & reduced water content and MDA levels Increased SOD and Na+K+ATPase activity of Chinese rhubarb (AE) & (Polysaccharide), family -R. tanguticum at the dose of 3, 6, and 12 mg/kg & 100, 200, and 400 mg/kg in CCI & WDIAI (Keshavarzi et al., 2019; Y Wang et al., 2016; Xia et al., 2017).

Sawmiller et al., (2014) reduced levels of TNFα and IL-1β in blood and brain tissue of **Yellow** bauhinia **(**Luteolin),family- S. tomentosa at the dose of 20 mg/kg in CCI (Sawmiller et al., 2014).

Asmaa A. et al. (2017) reduced activity of LDH and plasma copeptin level in brain tissue of Black caraway (TQ), family- N. Sativa at the dose of 10 mg/kg in WDIAI (Asmaa Ahmed, 2017).

Zhang & Dai (2016) reduced serum levels of MDA, IL-1β, TNFα, and IL-6, and the amount of neuronal cell apoptosis in brain tissue Increased serum SOD activity of Siam Rosewood (AE), family - D. cochinchinenesis at the dose of 40 and 80 mg/kg in WDIAI (Zhang & Dai, 2016).

Zeng et al., (2017) & FENG (2016) improved NSS Reduced BBB permeability and ameliorated brain oedema inhibited the expression of AQP-1, AQP-4 and AQP-9, HIF-1α, and MMP-9 & improved NSS Reduced escape latency, brain oedema, levels of the autophagic marker proteins, microtubule-associated protein light chain 3-II and Beclin1 in the hippocampus of Knotweed and Knotgrass **(**Emodin) & (Resveratrol), family-P. cuspidate at the dose of 10 mg/kg & 100 mg/kg in WDIAI (FENG, 2016; Zeng et al., 2017).

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Song et al., (2016) decreased latency to find platform, neuronal degeneration and GFAP-positive cells, ROS generation, levels of IL-1β, IL-6, and TNFα Increased time spent in target quadrant and activity of SOD, GPx, and CAT of Rosemary(AE),family- R. officinalis at the dose of 40, 80, and 160 mg/mL in LFP (Song et al., 2016).

Jazmi et al., (2017) increased the activation of Krox-20, the expression of NRG-1, and the distribution of phospholipids of Indian pennywort(AEE),family- C. asiatica at the dose of 90 mg/kg in WDIAI (Jazmi et al., 2017).

Sharma et al., (2009, 2010) & *Samini et al.,* (2013) improved cognitive function in MVM test Reduced oxidative stress Increased BDNF levels Protected synaptic proteins and mitochondria, reduced IL-1β, IL-6, TNFα, MCP-1 and RANTES, TLR4 expression, neuronal and apoptotic cell death, and microglial activation Improved NSS, reduced cerebral oedema, AQP4 expression, NF-κB activation, and IL-1β expression Improved neurological function & reduced cerebral damage and brain levels of MDA improved neurological functions are also shown of Turmeric **(**Curcumin),family- C. longa at the dose of 500 ppm, 50, 100, and 200 mg/kg, 75, 150, and 300 mg/kg & 50 and 100 mg/kg in FPI,WDIAI,CCI,WDIAI respectively (Samini et al., 2013; Sharma et al., 2009, 2010).

Meng et al., (2018) improved NSS Reduced TNFα, IL-1β, TUNEL positive cells, apoptosis index, and expression of TLR4 and caspase-3 Increased expression of IkB of Zedoary **(**β-Elemene), family- C. zedoaria at the dose of 100 mg/kg in WDIAI (Meng et al., 2018).

Wang et al., (2012) & *Wang W. et al.,* (2016) reduced the level of CD8 T cells No effect on IL-2 and CD4 levels & decreased brain lesion volume, IL-6 Improved NSS and cognitive function Increased IL-10, blood monocyte numbers and percentage of blood CD3 and CD4 T lymphocytes inhibited microglial/macrophage activation of Lucky bamboo (AE), family - D. Fortune at the dose of 45 ± 0.05 mL/ra & 20 mg/kg in WDIAI & CCI (W. Wang et al., 2012; Wenzhu Wang1 et al., 2016).

Chen et al., (2011) reduced brain water content, lesion volume, PMN, Iba-1, TNFα, and IL-1β Increased IL-10 and TGF-β1 Improved neurological function of Red sage, Chinese sage **(**SalB), family- S. miltiorrhiza at the dose of 25 mg/kg in CCI (Chen et al., 2011).

Abbasloo et al., (2016) 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 of Jamzad (EO), family- S. Khuzistanica at the dose of 50, 100, and 200 mg/kg in WDIAI (Abbasloo et al., 2016).

S-F Chen and *C-W Hsu* (2008) reduced the number of degenerating neurons, contusion volume, and mRNA and protein expression of TNFα, IL-1β, and IL-6 Improved neurological functions of Baikal skullcap **(**Baicalein), family- S. baicalensis at the dose of 30 mg/kg in CCI (S-F Chen, C-W Hsu, 2008).

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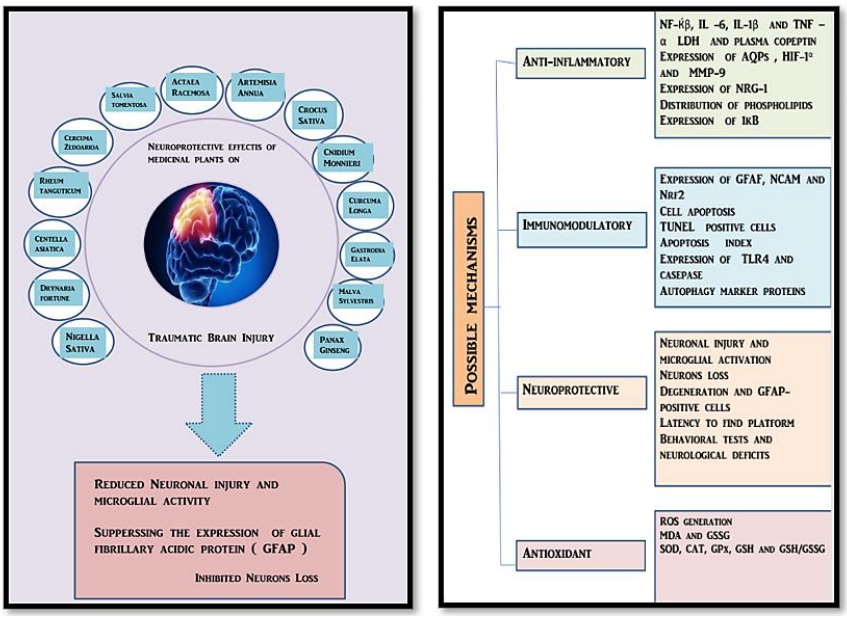

Fig.3: Medicinal Plants for management of Traumatic Brain Injury (TBI) and their possible mechanisms

The authors suggested that this study will provide the basic research foundation for the development of optimal protocols for HM for TBI and/or PCS and the development of new drugs for these conditions in the pharmaceutical industry (B. Lee et al., 2019).

Conclusion

Trauma-induced brain tissue damage includes falls, motor vehicle traffic injuries, being struck (by/against), abuse, and unknown/other causes. TBI affects 10 million people worldwide, straining the healthcare system. TBI survivors have a high mortality and morbidity rate and a significant economic burden, with some having long-term disabilities. TBI causes major motor, sensory, cognitive, and emotional issues. Moderate TBI symptoms include headaches, nausea/vomiting, dizziness, tinnitus, visual abnormalities, impaired proprioception, mood and memory changes, memory and concentration difficulties, tiredness, and sleep disturbances. TBI treatment emphasises neuroprotective approaches, particularly methods to identify and target systems involved in the intricate secondary-injury cascade. The findings shows that eurocentric neuroprotective medications have focused on neuronal-based damaging pathways. The literature supports endothelium, microglia, astroglia, oligodendroglia, and progenitor cell injury. Recent neuroprotection methods emphasise non-neuronal cell regrowth and optimal function while blocking neuronal cell death. PEA formulations and biologics are potential novel neuroprotective, neurorestorative, and anti-inflammatory therapeutics. Experts also recommend innovative neurotechnologies and neuro markers of brain injuries for accurate diagnosis and appropriate neuropsychological rehabilitation treatments like neurotherapy. Post-TBI neural therapies confront several challenges owing to the complexity and variety of brain damage. No TBI medication works clinically. Thus, the present study examined the growing body of data on medicinal plant protective characteristics, components, and TBI reversal mechanisms. TBI research has focused on natural compounds since they treat stroke and ischemia. TBI patients may have similar consequences, even though this study was mostly done in animals. This research shows that natural compounds may reduce neurodegeneration and improve functional results

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in TBI patients. However, further study is required to evaluate medicinal plant and extract therapeutic advantages and molecular mechanisms in TBI. **References**

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