Recent Trends in Pharmaceutical Technology & Industries
Volume 7, Print Issue 1 - 2025, Pg. No. 31-42
Peer Reviewed Journal

Review Article

Ancient Remedies for Modern Challenges: Traditional Therapies in Traumatic Brain Injury Management

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How to cite this article:
Kumar D, Arora C, Sharma S, Vashisht M, Tanwar R. Ancient Remedies for Modern Challenges: Traditional Therapies in Traumatic Brain Injury Management. *Rec Trends Pharm Tech Indl* 2025 7(1): 31-42.

Date of Submission: 2025-03-08
Date of Acceptance: 2025-04-11

A B S T R A C T

Traumatic brain injury is a global health concern due to its impact on disease and mortality. It is costly to manage because of prevention, diagnosis, and treatment challenges. At this time, no treatment can undo the effects of a severe brain injury. There aren't currently any big clinical successes with new preventative treatments for serious traumatic brain injuries. The article highlights TBI's definition, causes, and global prevalence by age and gender. Diagnosis involves imaging, lab tests, and physical exams, while treatments include drugs, surgery, and complementary therapies like herbal medicine. It also covers synthetic drugs, recent advances like stem cells and neuroprotective strategies, and the limitations of animal models. Depending on the type of severe brain injury, treatment could either focus on fixing the problems that cause the secondary brain injury or on making the signs of the injury better. However, in many cases, the treatment should be complicated and include several different medical procedures and types of therapy.

Keywords: Traumatic Brain Injury, Brain, Trauma, Therapy, Herbal Medicine

Introduction

Traumatic brain injury (TBI) occurs when a force is exerted on the head or body, causing neuropathological damage and dysfunction. The Clinical Practice Guideline for the Management of Concussion/mTBI (version 1.0, April 2009) issued by the US Department of Veterans Affairs and the Department of Defense defines TBI as.

A structurally induced injury or physiological disruption of brain function caused by an external force, characterized by the new onset or symptoms of at least one clinical sign immediately following the event: any duration of loss or diminished level of consciousness (LOC), any memory loss for events immediately preceding or following the injury (post-traumatic amnesia [PTA]), any alteration in mental state at the time of the injury (confusion, disorientation, slowed cognition, etc.), neurological deficits (weakness, loss of balance, changes in vision, praxis, paresis/plegia, sensory loss, aphasia, etc.) that may be transient or persistent, or an intracranial lesion. (VA DoD, 2009).[1, 2]

The type of TBI may be assessed by many metrics. Four national organizations and one university medical center have issued varying definitions for mTBI: the CDC, the Department of Veterans Affairs and Department of Defense (VA/DoD), the American College of Rehabilitation Medicine

(ACRM),[3-7] the Eastern Association for the Surgery of Trauma (EAST), and the University of Arizona's Brain Injury Guidelines (BIG).[8]

TBI encompasses two types of injuries: primary, characterized by mechanical damage to brain tissue due to external forces, and secondary, involving pathophysiological processes that include oxidative stress, inflammation, apoptosis, and other complications that exacerbate brain deterioration.[3, 4] The establishment of several animal models for the examination of brain damage facilitates the development of therapies and improves overall results.[5, 6]

Clinical evaluation is used to measure trauma severity in the Glasgow Coma Scale (GCS) score and LOC or PTA duration. Clinical severity is widely used to predict prognosis, although its correlation with outcome is unclear. Physical, emotional, behavioral, and cognitive effects of all grades of TBI may permanently impair an individual's ability to do everyday tasks and return to employment.[7, 8]

The GCS is used to grade TBI as mild, moderate, or severe (Table 1).[9] An estimated 75–85% of patients with a GCS score of 13 to 15 are classified as having mild (mTBI). The main benefits of the GCS are its simplicity and utility as a standardized assessment that can be used to compare results across a group of patients of various severities of TBI.[10] Mild (TBI) encompasses concussion, sub-concussion, and some blast injuries related to improvised explosive devices. Sports include boxing, American football, rugby, soccer, cheerleading, ice hockey, and wrestling.[11-12]

In mild traumatic brain damage (GCS 9–13), the patient exhibits lethargy or stupor, but in severe TBI (GCS 3–8), the patient is comatose, and incapable of eye-opening or command following. Individuals with severe traumatic brain damage are at elevated risk for secondary brain injury, which encompasses hypotension, hypoxemia, and cerebral edema. In the lower GCS score ranges[3–9], mostly linked to severe traumatic brain injury, there exists a clear linear correlation with adverse outcomes, including significant neurological impairment, vegetative state, and mortality. Increased age, especially beyond 60 years, correlates with a heightened chance of adverse outcomes.[13]

The severity of TBI may be classified based on the length of LOC and PTA, which are found to correlate more effectively with patient outcomes than the GCS. MTBI is characterized by LOC lasting less than one hour and PTA for less than 24 hours; moderate TBI is indicated by LOC between one and 24 hours or PTA lasting 1 to 7 days; severe TBI is defined by LOC beyond 24 hours or PTA extending beyond one week.[14]

Cause

Globally, annual brain injury rates remain among the most frequent causes of mortality & disability. Injury to that brain can be classified as traumatic or nontraumatic in origin. While non-traumatic brain injuries result from an attack such as a stroke or infection, traumatic brain injuries are a result of pressures such as falls or auto accidents. It is characterized that both kinds have a negative influence on a person's health & well-being.[15] Cerebral damage in surgery may lead to numerous afflictions which may range from the physical, and thought process as well as even behavioral to physical disabilities that may either be short-term or permanent and therefore hinder an individual from functioning suitably. Due to the diversity of patients, the nature of TBI, and the signs and symptoms of TBI, prevention, estimation, and therapeutic practices remain challenging yet imperative.[16]

Table 1.Standard Glasgow Coma Scale score

Eye-opening	Best verbal response	Best motor response
4: spontaneous	5: oriented	6: obeys commands
3: to speech	4: confused	5: localizes
2: to pain	3: inappropriate words	4: withdraws
1: none		3: abnormal flexion
	2: incomprehensible sounds	2: Extension
		1: none
	1: none	
Total Gcs Score: 3–15		

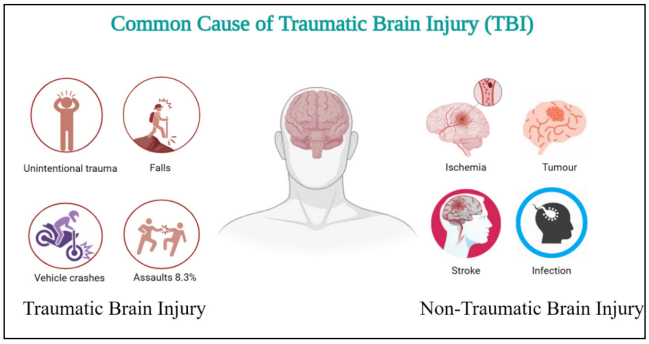

Figure 1.Common causes of Brain Injuries: - Sports, Falls Motor Vehicle Accidents, Stroke Chemo, Virus, Aneurysm, Co Poisoning.[16]

Pathophysiology

TBI is a complicated process involving the temporary/ permanent problems of neurological functions as a result of an external force. It involves two main types of injury: Primary and secondary. The first involved is the initial contact of the impact that nips the brain's tissue in the blink of an eye. The secondary injury occurs in the next minutes to days and depends on molecular, chemical, and inflammatory changes which inflict more damage to

the brain. Some of these include the actions that release chemicals in the brain that may cause raising in calcium levels and consequent stimulation of enzymes and free radicals that have destructive effects on the brain cells. Inflammation is also involved, offsetting the number and complexity and damaging the blood-brain barrier further. Over the R & D process, it was found that recovery from TBI entails the brain recategorizing itself at various strata. The main contents of the brain include brain parenchyma, CSG, and blood.[17] Focal and diffuse types of brain injuries may occur at the same time affecting the same patient. Direct and indirect consequences both can lead to focal injury; the latter is caused by the acceleration-deceleration force. Cerebral spinal fluid protects the brain, however, a direct blow to the head mesmerizes the brain to strike the skull's opposing side; this is called secondary impact. Cerebral contusion with direct damage to the frontal and temporal lobes was seen to present with disinhibition, impulse control disorders, and executive dysfunction.[18]

Focal Injury

Focal brain injuries can occur in various kinds of manners and are not necessarily expressed similarly in every human being. Some of the complications that stem from the above injuries include subdural hematoma, subarachnoid, epidural, and intraventricular hemorrhage which are distinct from some other brain complications. Because these injuries are severe, prompt care is needed.[23]

Epidemiology

TBI remains to be an enormous issue that impacts millions of people every year all over the globe. According to the CDC, between the years 2001 and 2010, there was a rise in TBI in terms of the sizes of emergency room visits, hospitalizations, and deaths.[17] According to the CDC, 2. Indeed, TBI-related ED visits in the US totaled 53 million in 2014. The non-fatal and fatal hospitalizations due to both adult and pediatric TBI in the United States were approximately 288,000 and 56,800, respectively. Having a look at the frequency of TBI-related ED visits by age, it emerges that people 75 years and above are most affected with a rate of 1682 / 100,000 people. Thus, young children between the ages of 0 to 4 years (1618. 6 / per 100,000 people) and adolescents and young adults between the range of 15-24 years (1010. 1 per 100,000 people) were the next age groups in terms of the incidence rate.[19]

Symptoms

Ever since the symptoms of a traumatic brain injury are very diverse, they affect cognitive and behavioral, sensory, and physical functions. While some of these symptoms may vary, some of the more physical symptoms may be; Headaches, increased sensitivity to light or loud noises, nausea, fatigue, dizziness, and problems with sight or hearing among others. Examples of cognitive symptoms include; forgetfulness, inability to concentrate, reduced rate of thinking, and confusion.[20] Further on the usual physical disorders are behavioral, and emotional issues like anger, anxiety, sadness, mood changes, and irregular sleeping patterns. Some of the sensory disturbances may be hearing and may be followed by alterations in the known taste, smell, or touch. Precisely, there are cases where difficulty in receiving, interpreting, or producing verbal information could be evident, as depicted by the following: In some cases, tuberoid infectious diseases can cause seizures or even unconsciousness.[21]

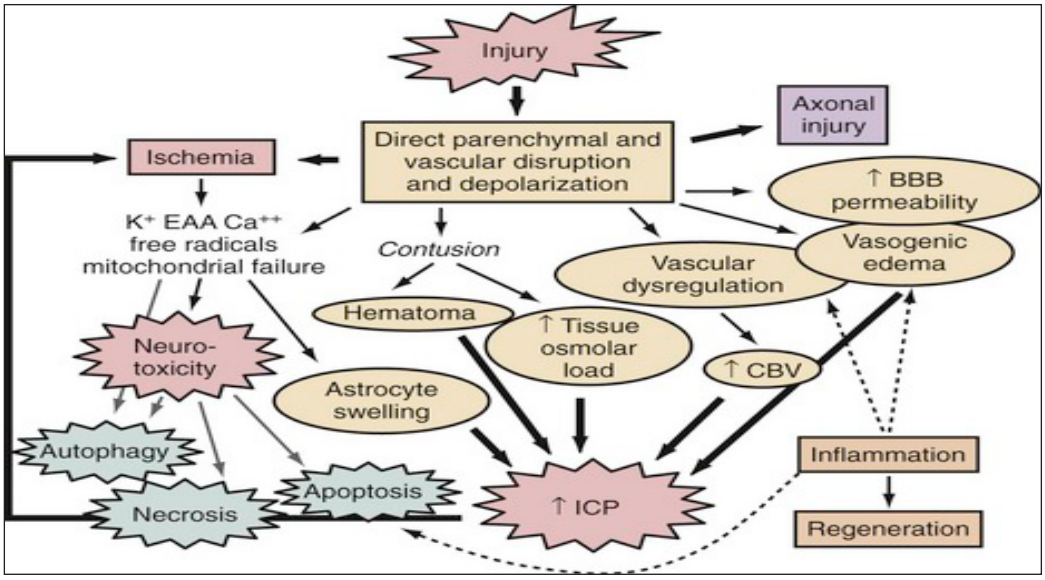

Figure 2.Categories of biochemical, cellular, and molecular mechanisms involved in the evolution of secondary damage after ischemic or traumatic brain injury. Three major categories of secondary mechanisms include: 1) Ischemia, excitotoxicity, energy failure, and cell death cascades; 2) Cerebral Swelling; and 3) Axonal Injury 4) A fourth category, inflammation, and regeneration, influences each of these cascades.[18]

Table 2.Different types of TBI symptoms[21]

Symptoms				
Mild traumatic brain injury Physical symptoms:	**Moderate to severe traumatic brain injuries Physical symptoms:**	**Children's symptoms**	**Cognitive or mental symptoms:**	**Cognitive, behavioral, or mental symptoms:**
Headache	Loss of consciousness from several minutes to hours	Change in eating or nursing habits	Profound confusion	Loss of consciousness for an only small period
Nausea or vomiting	Persistent headache or headache that worsens	Unusual or easy irritability	Agitation, combativeness, or other unusual behavior	No loss of consciousness, but a state of being dazed, confused, or disoriented
Fatigue or drowsiness	Repeated vomiting or nausea	Persistent crying and inability to be consoled	Slurred speech	Memory or concentration problems
Problems with speech	Convulsions or seizures	Change in ability to pay attention	Coma and other disorders of consciousness	Mood changes or mood swings
Dizziness or loss of balance	Dilation of one or both pupils of the eyes	Change in sleep habits		Feeling depressed or anxious
Sensory symptoms:	Clear fluids draining from the nose or ears	Seizures		Difficulty sleeping
blurred vision, ringing in the ears, a bad taste in the mouth, or changes in the ability to smell	Inability to awaken from sleep	Sad or depressed mood		Sleeping more than usual
	Weakness or numbness in fingers and toes	Drowsiness		
Sensitivity to light or sound	Loss of coordination	Loss of interest in favorite toys or activities		

Diagnosis of TBI

TBI demands the use of imaging tests, physical assessment, and a patient's history as a patient. Using the GCS, TBI severity is evaluated based on the patient's level of awareness. If one wants to visualize anything inside the brain and even look for any morphological abnormalities or bleeding, imaging procedures that are CT or MRI could be done.[22]

Glasgow Coma Scale

The 15-point Glasgow Outcomes Scale is applied by medical professionals to assess the severity of the first brain injury using eye and limb movements, the patient's capacity for following instructions, and coherent speech.[23]

Imaging tests

CT scan- When observing a TBI, this is among the first tests conducted in the emergency department. Several X-ray pictures are taken to create a computer tomography (CT) scan of the brain, as a method of diagnosis. An essential advantage of a CT scan is its capability to effectively determining the existence of fractures at the same time as signs of hemorrhage, hematomas, and contusions, as well as edemas of the brain tissue within a brief amount of time.[23, 24]

- **MRI:** Magnetic resonance imaging (MRI) is an X-ray that uses magnets and strong radio waves to provide the best picture of the brain. It is suggested that in case the patient's symptoms do not improve right after

the incident this test could be done once the patient's condition has settled down.[25]

- **Biochemical tests:** This test involves blood or lumbar puncture Csf to prove some details concerning how severe the brain injury is and the evidence of oxidative stress or inflammation. To assess brain damage, specific enzymes and markers like GFAP, NSE and S100B are frequently utilized.[26]
- **Inflammatory markers:** The TNF-α, CRP, and Interleukins (IL-6, IL-8), which are usually elevated in TBI and indicate inflammation.[27]
- **Oxidative stress indicators:** TBI can result in a rise in the formation of ROS and a decrease in antioxidants in the affected areas as indicated by the following; GPx, MDA, SOD, and catalase.[28]
- **Histopathological assessment:** Histopathological studies on the brain tissue that have been obtained through necropsy examination indicate a lot concerning the character & intensity of the brain damage such as the levels of inflammation, cell death, and tissue disruption.[29]

Intracranial pressure monitor

Pressure build-up within the skull as a result of brain tissue inflammation and swelling as a result of a TBI results in more injury to brain tissue. To monitor this pressure, physicians may insert a device into the head.[30]

Treatment of TBI

Decreased levels of oxidative stress, inflammation, and their markers are among the important objectives of the pathogenetic treatment complex in traumatic brain injury. The treatments that have been applied to human models include; treatments for hypothermia, neuroprotective drugs and antioxidants, anti-inflammatory drugs, hyperoxygen chambers, and oxygen. Antioxidants and anti-inflammatory drugs, gene therapy, behaviour modification, and stem cell therapy are some of the treatments employed in animal TBI models. Besides simple biochemical tests based on the determination of the level of ROS, MDA, GSH, and pro-inflammatory cytokines and histological examination of the samples to identify signs of damage and neurodegeneration, oxidative stress, and inflammation. The post-injury strategy of these approaches aims to enhance the recovery rate and reduce secondary damage after TBI.

Pharmacological and Non-pharmacological Treatment

TBI management is as a result treated by using non-drug intervention and drug intervention. The intended objectives of pharmacological treatment are quite often to decrease ICP and, thus, prevent issues. Phenytoin is used to help prevent seizures and is commonly observed in patients with TBI whereas mannitol can be utilized to lower the intracranial pressure. Corticosteroids, including dexamethasone, are effective for inflammatory conditions, however, their application is disputable because of potential side effects. Any other treatment process that is not medicated and is meant to fix skull fractures or even get rid of hematomas is classified under nonpharmacological treatment. Another approach to the treatment of TBI entails rehabilitation which involves speaking therapy for those individuals with communication difficulties as well as occupation therapy, physical therapy that enhances strength and movement of the affected parts of the body as well and cognitive therapy that helps to address some of the difficulties that the individual may face with memory and other cognitive aspects. The idea of using these approaches is to create a stable state of the patient's condition, avoid new injuries, and restore health and independence in activities.

- **Corticosteroids:** Corticosteroids have been used for a long time to treat inflammatory and immune-related diseases because they reduce inflammation and weaken the immune system. It is used in secondary brain edema and swelling raise intracranial pressure, which changes the brain's structure even more and lowers blood flow and oxygen levels in the brain.
- **Progesterone:** After corticosteroids failed to treat TBI, researchers looked into progesterone, a brain hormone, for early treatment. Animal studies showed that progesterone reduced brain swelling, cell loss, and behavior issues after TBI. However, large clinical trials (SYNAPSE and PROTECT III) involving many patients didn't show any significant benefits for survival or recovery, despite earlier smaller trials being promising. This ended the initial excitement around progesterone as a treatment for TBI.
- **Erythropoietin:** Erythropoietin (EPO), a protein that helps produce red blood cells, is naturally made by the kidneys in response to low oxygen. In animal studies, EPO has shown promise in protecting brain cells, reducing inflammation, and helping brain recovery after TBI.
- **Amantadine:** Dopamine agonist amantadine helps Parkinson's. Amantadine, an NMDA receptor antagonist, may be administered to the frontal lobes. Amantadine therapy may protect neurones from glutamate excitotoxicity after acute TBI by increasing striatal dopamine levels and inhibiting NMDA receptor activity. At 200–400 mg per day, amantadine increases arousal and cognition in TBI patients. Other studies found that amantadine accelerated functional recovery in severe TBI patients compared to placebo.
- **N-Acetylcysteine:** N-acetylcysteine (NAC) has been proven in many animal models to have an effective neuroprotective effect, minimizing the consequences of

secondary neuronal injury. Rat models have proven the beneficial antioxidant effects of NAC in the treatment of brain damage.

- **Minocycline:** The neuroprotective properties of minocycline (MINO), a tetracycline antibiotic, have been proven both in isolation and conjunction with NAC. Rat models have shown that MINO is useful in treating neurological issues brought on by traumatic brain damage. In a cortically moderately induced paradigm, animals' memory and cognition were improved by combination therapy with MINO + NAC, which also repaired white matter via protecting oligodendrocytes.
- **Phenserine:** In the management of traumatic brain injury (TBI), phenserine action reduces neuroinflammation, promotes amyloid deposition, inhibits apoptosis, and alleviates several secondary damage processes.
- **Calcium Channel Blockers:** Nimodipine, an L-type calcium channel blocker, enhance the prognosis of patients experiencing spontaneous subarachnoid hemorrhages. A comprehensive analysis, however, did not discover a statistically significant difference in the rates of mortality and morbidity between TBI patients receiving nimodipine and placebo. It has been shown that giving mice the N-type calcium channel blocker ziconotide (SNX-111) between 15 minutes and 10 hours following traumatic brain injury (TBI) enhances mitochondrial activity. It has been shown that SNX-185, another N-type calcium channel blocker, is neuroprotective when given directly to rat hippocampus CA2 and CA3 24 hours after TBI. The efficacy and safety of calcium channel blockers in the treatment of traumatic brain injury need more clinical investigation.
- **Antioxidants:** Cyclosporin A, an immunosuppressant that effectively regulates mPTPs, shows neuroprotective effects in experimental TBI models. A modest randomized clinical study of cyclosporin A in traumatic brain injury surprisingly revealed no improvement in neurological outcomes or biochemical measures in individuals with severe traumatic brain injury.
- **Beta-Blockers:** Early beta-blocker therapy improves clinical outcomes and survival rates in traumatic brain injury, according to several retrospective and prospective observational studies. The major stroke's adrenergic storm may worsen subsequent brain injury by constricting blood vessels and causing ischaemia. Therefore, hyperadrenergic activity increases mortality risk by aggravating secondary brain injury and causing extracranial multiorgan dysfunction, notably in the cardiovascular, pulmonary, and inflammatory systems. Since catecholamine-induced vasoconstriction reduces cerebral perfusion and oxygen delivery, beta-blockers improve the cerebral environment. In isolated severe traumatic brain injury, immediate oral propranolol medication increases survival and function for up to six months. The above data support beta-blocker usage in controlled neuroeducation. A meta-analysis by Ding et al. found beta-blockers safe and effective after traumatic brain injury. Beta-blockers' usefulness and safety in treating traumatic brain injury need additional study.
- **Metformin:** Metformin, an antihyperglycemic agent, used in treatment of diabetes. In addition to its role in glucose regulation, metformin stimulates neurogenesis and exhibits significant anti-inflammatory properties. These properties position metformin as a noteworthy candidate for treating CNS injuries. Recent studies indicate that metformin exhibits neuroprotective effects in multiple models of central nervous system injury. Metformin markedly enhances cognitive function following controlled cortical injury in mice, evidenced by improved spatial learning and nest-building behaviors.
- **Cerebrolysin:** Several studies have proposed the use of the multimodal neuropeptide cerebrolysin in the treatment of TBI. Cerebrolysin regulates oxidative stress, microglial activation, inflammation, and blood-brain barrier dysfunction to reduce secondary damage. Cerebrolysin studies in inoperable severe traumatic brain injury patients is scarce. A recent meta-analysis found that intravenous cerebrolysin improved Glasgow Outcome Scale and modified Rankin Scale ratings in TBI patients. Inoperable severe TBI patients treated with cerebrolysin had better Glasgow Outcome Scale scores and shorter hospital stays than the control group.
- **Vitamin D:** Brain trauma patients often suffer from infectious consequences like pneumonia and sepsis. A high percentage of these individuals are vitamin D deficient. In TBI patients, vitamin D insufficiency may cause unconsciousness, delayed neurological recovery, and prolonged critical illness polyneuropathy. Thus, vitamin D medication may be essential for TBI patients. Arabi et al. found that vitamin D reduces TBI mortality and inflammation.
- **Anti-Alzheimer Drugs for Treatment of Symptoms and Neurological Protection:** The medications are critical in post-TBI management as well as neuroprotection. Analgesic medications such as acetaminophen or NSAIDs are commonly employed in cases of headaches and other pain that occurs along with TBI. Epilepsy following TBI can be prevented with phenytoin which is an anticonvulsant. While for stiffness and spasms, the use of muscle relaxants is useful, for increased mental activity the use of stimulants methylphenidate is useful. Two of the possible neuroprotective drugs include progesterone and erythropoietin; however,

they are yet to be effectively discovered. Essentially, these drugs enhance results and quality of life in TBI cases in combination with therapy.

- **Rehabilitation Therapies:** Among the many potential therapies used during the rehabilitation of TBI patients, they might be prescribed occupational therapy if they have lost some daily skills, speech therapy to overcome speech difficulties, cognitive therapy to address problems with memory and problem-solving, physical treatment for movement and muscle strength issues, and psychological treatment to address the behavioral changes about which the patient's loved ones reported to traumatology specialists. These therapies aim at enhancing the mental, emotional, and physical condition of the client in the process of healing.

Herbal Remedies

Medicines have been used from times immemorial when phytochemical substances, fruits, roots, stems, leaves, and other parts of the plant were employed for curing ailments. Over 6 decades evidence-based information is available on the utilization of medicinal herbs in which Sumerians are considered as pioneers. According to the same source, conventional medicine is used by about 90 percent of the population in Africa and more than 70 percent of the population in India. Morbidity data reveals that in over 90% of the Chinese hospitals traditional medicine accounts for 40% of the total healthcare services. The advantages of herbal medications are better acknowledged because they are obtained from nature, possess ethnomedical actions, are objectively cheaper, have minimum side effects, and are easier to administer. Higher plant species that are used in traditional medicine are only 10% of the total species and therapeutically active compounds are only 1%-5% of the total species there. Employing phytochemicals, and herbal therapy for TBI is aimed at increasing the course of the injury's healing period and decreasing the signs of brain injury. Some examples are Ginkgo biloba, Panax ginseng, Bacopa monnieri, Curcuma longa, Centella Asiatica, and Withania somnifera – that possess such chemicals which have neuroprotective, anti-inflammatory, and antioxidant properties. For the formulation of herbal remedies for TBI from traditional medicines, which optimally enhance cognitive function and promote faster recovery, it is a prerequisite to appreciate the various functions and modes of action of these phytoconstituents.

Herbs & their Active Compounds

Carthamus tinctorius L

Traditionally, thrombosis, irregular menstruation, spasms, and flatulence have been treated using Carthamus tinctorius L., a dried flower from the composite family. Research has mostly focused on the neuroprotective qualities of crocin in TBI , but it also contains several other active chemicals, such as safranal, isophorone, crocetin, and crocin. By raising the levels of NSS and GSH and lowering those of IFN-γ, TNF-α, MPO, and MDA, crocin administration improved anti-inflammatory and antioxidant responses in a controlled cortical impact (CCI)-induced TBI mouse model.

Panax notoginseng

Part of the Araliaceae family, Panax notoginseng, commonly referred to as sanqi, is well-known in China for its capacity to relieve blood stasis, increase blood circulation, and reduce pain. As a result, it has earned the moniker "the miraculous agent capable of stopping the blood. Active ingredients include ginsenoside, dencichine, flavones, and P. notoginseng saponins (PNS). According to research, ginsenoside protects TBI .(76) By decreasing the levels of p-p65, thromboplastin time (t-PA), prothrombin time (PT), activated partial thromboplastin time (APTT), and endothelin (ET) while raising CD61 and CD62, research proved that P. notoginseng treatment conferred neuroprotection in TBI. Furthermore, intraperitoneal PNS injection following TBI induction in a WDI rat model enhanced behavioral test results by upregulating the expression of Akt, mTOR, and phosphatidylinositol 3-kinase (P13K).

Rhubarb

According to research, rhubarb increases the amounts of glutamic acid (Glu) and aspartic acid (Asp), 5-hydroxytryptamine (5-HT), 5-hydroxy indole acetic acid (5-HIAA), and γ-aminobutyric acid (GABA) in rats that have suffered brain damage. Neurological advantages in traumatic brain injury (TBI) can be obtained from chemicals derived from R. palmatum, specifically Rhein and Emodin. Rhein is absorbed by brain tissues when given orally, and by blocking neuronal proptosis, it can protect mice from neurological damage after traumatic brain injury. Rhein furthermore dramatically lowers the amounts of GSDMD, NOD-like receptor protein 3 (NLRP3), TLR4, MyD88, NLRP3, IL-1β, IL-18, and IFN-γ while raising the amounts of p10, p20, and p45.(78) In vivo, emodin has neuroprotective benefits by upregulating intercellular adhesion molecule-1 (ICAM-1), S100B, IL-6, TNF-α, and NF-κB p65 while downregulating these same molecules.

Curcuma longa

Curcuma longa is used to treat immune system malfunction, malignancies, inflammation, and asthma. Its main ingredient, curcumin, has neuroprotective effects in traumatic brain damage (TBI)-stricken animals via the p38/MAPK signaling pathway. After TBI, oral curcumin administration significantly decreases the expression of p38/MAPK signaling components, including NF-κB and p-p38, lowers IL-1β, IL-6, and TNF-α levels, and increases

resistance to neurological impairment. Moreover, giving curcumin after traumatic brain injury (TBI) reduces the deterioration of spatial memory, encourages neurogenesis, and increases the expression of PI3K, AKT, tyrosine kinase receptor b (TrkB), and brain-derived neurotrophic factor (BDNF).

Gastrodia elata

The dried rhizome of the Orchidaceae species Gastrodia elata is widely used to treat neurological conditions like vertigo, headaches, strokes, and Alzheimer's disease. The treatment of G. elata aqueous extract showed neuroprotective properties, improved rotarod test performance, and decreased the number of astrocytes as well as levels of TNF and IL-6 in a rat model of traumatic brain injury (TBI). Among the active ingredients in G. elata are vanillin, 4-hydroxybenzaldehyde, and gastrodin; of these, gastrodin has been shown to have neuroprotective benefits against traumatic brain injury. Following the production of TBI in a rat model using controlled cortical impact (CCI), the treatment of gastrodin markedly inhibited pyroptosis and altered the nerve cells' anti-inflammatory response by lowering proinflammatory cytokines such as TNF-α, IL-1β, and IL-18 and by blocking the production of Gasdermin D (GSDMD), NLRP3, ASC, caspase-1, and caspase-11. The State Drug Administration of China has approved gastrodin tablets, a nonprescription medication derived from G. elata, for the treatment of migraine, headaches, and neurasthenia.

Ginkgo biloba

In the animal model of TBI brought on by CCI, ginkgo biloba, which is obtained as dried leaves from the Ginkgoaceae family, has been studied for potential effects. G. biloba extract taken orally after injury greatly decreased cerebral edema and increased neurological severity scores (NSS). To lessen oxidative stress and inflammation, it also decreased the expression levels of VEGF, p-AKT, phosphatidylinositol 3-kinase (PI3K), and MMP-9. An isolated G. biloba component called ginkgolide B also helps the brain TBI. (86) Oral administration of ginkgolide B in a rat model of weight-drop impact (WDI)-induced TBI significantly decreased the number of apoptotic nerve cells by increasing the level of X-linked inhibitor of apoptosis protein & decreasing Omi/Htr A2, procaspase-3, procaspase-9, and cleaved poly ADP-ribose polymerase levels.

Salvia miltiorrhiza

Salvia miltiorrhiza, Lamiaceae family is recognized for its dried roots and rhizome, which contain several therapeutic chemicals. Chinese clinical therapies frequently employ salvianolic acid A, which is derived from S. miltiorrhiza, as a standardized injection. Salvianolic acid A administered intraperitoneally after traumatic brain injury (TBI) has been shown to have neuroprotective effects by significantly reducing brain water content, improving neurological severity scores (NSS), improving spatial learning and memory functions, and lowering TNF and IL-1β levels. Research has demonstrated that Tanshinone IIA, a different chemical obtained from S. miltiorrhiza, greatly inhibits both apoptosis and oxidative stress. To achieve this, it lowers the levels of p47phox, CD11, AQP4, glial fibrillary acidic protein (GFAP), MDA, catalase (CAT), IL-1β, and TNF-α while raising the levels of glutathione peroxidase (GSH-PX) and superoxide dismutase (SOD).

Polygonum cuspidatum

Dried plant roots and stems from the Polygonaceae family, known as Polygonum cuspidatum, are used to treat infections, inflammatory diseases, jaundice, and hyperlipidemia. The substance P. cuspidatum contains, resveratrol, has been proven in rats with traumatic brain damage (TBI) to have neuroprotective benefits connected to the SIRT1/PGC-1 signaling pathway. Resveratrol administered post-TBI improves SIRT1/PGC-1 signaling, including elevated levels of SIRT1, PGC-1, and synaptophysin (SYN), and markedly lowers P-p38 MAPK expression. Edema is also reduced and resistance to cognitive impairment is increased by this treatment. Furthermore, by raising levels of P62, P-pI3K, P-Akt, and P-mTOR and lowering levels of LC3 II, Beclin-1, IL-1β, and TNF-α, resveratrol enhances cognitive function and lessens cerebral inflammation and fluid accumulation.

Alternative Approaches

Pharmacological Treatments

Other drugs could be used to treat TBI to reduce damage and enhance healing. For example, NSAIDs and corticosteroids are often prescribed for the reduction of brain inflammation following an injury. This type of drug helps to reduce brain tissue destruction after by diminishing inflammation after this. Neuroprotective agents like cyclosporine A are important in preventing further damage to brain cells and maintaining normal neurological function. In dealing with post-injury cellular damage in the brain tissues, antioxidants such as Vitamins E and C including stronger synthetic ones also help stop oxidative stress. Cognitive enhancers such as amantadine and methylphenidate may also be used to improve awakeners and cognitive performance among TBI patients.

Physical and Rehabilitative Treatments

TBIs are handled by using a mix of physical and rehabilitative therapies that seek to improve or restore cognitive as well as physical function. Physical therapy employs tailored exercises and activities to facilitate the mobility of patients and perform day-to-day tasks more effectively by improving their physical capabilities, strength, balance,

or coordination. Occupational therapy is used to achieve this goal by helping patients learn how to do basic daily chores again, enabling them to feel better about themselves and live independently. Speech and language therapy is also necessary to help patients regain their ability to speak and read words that have been lost due to injury. (104) Neurorehabilitation provides an all-around approach targeting physical cognition and emotional rehabilitation for a wholesome recovery process.

Technological and Surgical Interventions

Options for handling TBI cases are progressively increasing and are often essential due to the development of technological and surgical procedures. In a pressurized room or chamber, a patient receiving HBOT treatment can inhale a hundred percent purified oxygen thus supplying the brain tissues with considerable amounts of oxygen. This enhances the chance of finding oxygen to heal the affected areas and reduces on cases of swelling for total rewiring of the brain. Another type of treatment is called DBS which entails; the implantation of electrodes that have electrical signals being given to specific regions of the brain and is practiced mostly in severe cases. With this method, symptoms related to severe TBI can be alleviated and brain function can be influenced. A procedure that does not require surgical intervention is TMS, where the magnetic fields trigger the nerve cells in the brain to mitigate the condition of depression in addition to enhancing one's mental abilities. This approach would prove very useful in instances where an individual has a mood disorder or an intellectual disability due to a serious head injury. Unexpected head injuries also lead to breakages on the skull and penetrating injuries happen a craniotomy is often carried out when there are hematoma, traumatic brain swelling, or comminuted fractures in the skull. In patients with serious HI, surgery is essential because surgery is the only way to save life, stop further injury, or promote more recovery.

Experimental and Emerging Therapies

Some therapies are experimental or in the developmental stage and may be the answer to the healing and rehabilitation of TBI patients. Stem cell treatment is designed based on investigation for using stem cells to replace and repair the dysfunctional or damaged brain tissue in particular. Stem cell therapy is intended to enhance the treatment results of traumatic brain injury patients – maybe because it is used to restore or regenerate those brain cells that have been injured or lost. Now, speaking of the progressive approach to restoring that patient to normal life after TBI, gene therapy is another promising medicine that deals with how to change or repair genes. By doing so, the source of brain injury may be eradicated genetically and the inherent capacity to treat the ailment may furthermore be enhanced.

Advancements in Herbal Therapies

Research done on the efficacy of using herbs in the cure of TBI has demonstrated rather encouraging features with regard to management of the symptoms as well as the condition at large.

- **Ibogaine:** A team of scientists from Stanford Medicine has recently established that ibogaine, a psychoactive alkaloid obtained from the root of the African shrub, effectively reduces neuropsychiatric disturbances about TBI in veterans. Several enhancements in PTSD, depression, and anxiety signs, and better cognitive and function scores were reported from the study. With Ibogaine treatment that included Magnesium for cardiac safety one month post-treatment, they stated a percentage decrease in symptoms as follows; Post Traumatic Stress Disorder (PTSD) by 88% and anxiety by 81%.
- **Anti-inflammatory Macrophage Therapy:** The side effect of TBI is inflammation and a technique using anti-inflammatory macrophage therapy has been invented. This treatment utilizes the immunomodulating effects of macrophages to safeguard the blood-brain barrier and reduce additional brain damage like haemorrhagic strokes. This therapy is yet in its infancy, but it has the capability of reducing inflammation to a very large extent in the context of TBI.
- **Herbal Compounds and Neuroprotection:** The recent reviews have discussed the possible role of different herbal products form TBI management. Such compounds are designed to offer neuroprotection and act on the causes of the second brain insult. Some of the hopeful therapeutic herbs under consideration are based on traditional medicine, which mainly involves the reduction of inflammation, oxidative stress, & apoptosis in the brain tissues.
- **Curcumin:** Curcumin, extracted from turmeric, has indications toward the decrease of inflammation and oxidative stress in traumatic brain injury patients. Thus, it influences such pathways as NF-kB and Nrf2, known to be involved in regulating inflammation and antioxidant defense. Neuroprotective Effects: The literature review has revealed that curcumin has the potential to prevent/lessen neuronal loss and enhance learning/cognitive abilities after TBI. This gives the compound the possibility to act as a therapeutic because it is capable of passing the blood-brain barrier. Ginkgo Biloba: Increased Capsilarisation: Ginkgo biloba has the element that has the properties of dilating the blood vessels hence increasing Cerebral circulation and oxygen supply, which is vital for healing after TBI has taken place. Antioxidant and Anti-apoptotic Effects: The two chemical categories, flavonoids and

terpenoids present in Ginkgo biloba have been found to possess antioxidant ability that erased proven oxidant stress and apoptosis of cerebral cells. Bacopa Monnieri (Brahmi): Cognitive Enhancer: Bacopa monnieri is one of the oldest herbs used in Ayurvedic tradition and indeed possesses significant effects on the cognitive mechanism improving cognition and memory; these are the two major areas affected by TBI. Reduction of Neuroinflammation: Bacopa group antagonized pro-inflammatory cytokines & enhanced anti-inflammatory cytokines to report a fatty for brain remodeling. Green Tea Extract (Epigallocatechin Gallate - EGCG) Antioxidant & Anti-inflammatory: EGCG which is the main catechin found in green tea provides significant antioxidant & anti-inflammatory properties, which reduces secondary injury in TBI. Promotion of Neurogenesis: Scientific publications also reveal that EGCG helps in promoting neurogenesis, as well as synaptic plasticity helping recovery of cognitive deficit.

- **Mind-Body Practices:** Yoga and Mindfulness: Both of them have been widely suggested to be used as an add-on therapy in TBI. Yoga assists in enhancing physical and mental performance and lessening tension, on the other hand, mindfulness-based cognitive therapy has benefits on self-esteem and mental clarity (Neurology Live).
- **Tai Chi and Qi Gong:** These are believed to better balance, reduce stress, and increase general well-being, though data is less compelling and thus should not be ruled out nonetheless.
- **Acupuncture and Acupressure:** They are part of the systematic treatment employed in the Chinese traditional medicines for pain control and stress alleviation of TBI individuals. A review shows that acupuncture enhances wakefulness and other faculties in patients suffering from TBI.
- **Neuromodulation and Rehabilitation:** Neuromodulation methods for instance TMS and tDCS are reported to have been seen to help in cognitive rehabilitation and improve other disorders for example depression and anxiety in TBI patients according to Practical Neurology.
- **Inpatient Rehabilitation:** Through this, it has been found that the management approach of using physical, occupational, and spoken language therapies in the centers of rehabilitation leads to better functional prognosis in patients with TBI.
- **Fibrin-Targeting Immunotherapy:** Scientists from the Gladstone Institutions have found a new approach that involves the use of a monoclonal antibody that targets fibrin, a clotting protein that, when formed in the brain, can cause dangerous inflammation usually after TBI. Working on the same biochemical pathway as the coagulant effects on fibrin, this treatment is effective in preventing inflammation with no impact on the clotting process and, therefore, aims at decreasing neurodegeneration for better outcomes. This immunotherapy, first used to treat conditions such as multiple sclerosis & Alzheimer's in mice is now being used on human beings for the safety tests phase one.
- **Macrophage-Based Therapy:** A working group from the Wyss Institute at Harvard has developed an innovative strategy regarding macrophages, a kind of immune cell, for the treatment of TBI. It is worth pointing out that they cultivated "backpacks" the proteins that enable macrophages to stay in the anti-inflammatory state, attaching to them and increasing their function, reducing inflammation. When these macrophages were altered and given to TBIs in pigs, the outlook lessened the severity of the lesion, decreased the amount of bleeding, and lessened inflammation without any ill effect. It is conceivable that this effective method will one day be suitable for use in humans and other inflammatory diseases.
- **Stem Cell Therapy:** Offering promise in preclinical research, this therapy sometimes offers patients discomforting symptoms that can be difficult to manage. Among them, two kinds of stem cells, namely the (NSCs) neural stem cells and the (MSCs) mesenchymal stem cells deserve special attention. MNs derived from NSCs can regain the neurons and glial cells and restore functional loss and injury in animal models. MSCs include those isolated from bone marrow, adipose tissue, and umbilical cord blood; it has the capabilities of regulating inflammation, supporting the formation of new blood vessels, and releasing neurotrophins that are important in sustaining neurons and new neuron development; this is from DVC Stem.
- **(HBOT) Hyperbaric Oxygen Therapy:** it's, a process of breathing O_2 in a chamber with higher pressure than the usual atmospheric pressure, is another non-pharmacologic treatment. This therapy raises the oxygen levels bringing blood to the brain assisting in the healing process and minimizing the effect of brain swelling. Some studies prove the effectiveness of HBOT with the improvement of global cerebral metabolism and decrease of edema in TBI with better objectively assessed cognition and overall quality of life among TBI patients.
- **Rehabilitation Programs:** Physical, occupational, speech therapy, and other services continue in the rehabilitation process of TBI. These programs are designed to fit the client's specific requirements and can help enhance the capacity to interact and perform appropriate tasks in home and community settings as well as meet the medical and psychological needs arising out of TBI.

Abbreviations

Transcranial magnetic stimulation- TMS, Deep Brain Stimulation (DBS), non-steroidal anti-inflammatory pills – NSAIDs, Traumatic brain injury -TBI, controlled cortical impact -CCI, glutamic acid -Glu, 5-hydroxytryptamine -5-HT, 5-hydroxy indole acetic acid -5-HIAA, mitochondrial permeability transition pores -mPTPs, Tumor necrosis factor-alpha-TNF-α, C-reactive protein -CRP, glial fibrillary acidic protein -GFAP, neuron-specific enolase -NSE, loss of consciousness -LOC, post-traumatic amnesia -PTA, Glasgow Coma Scale -GCS.

Conclusion

In this review diagnosis, treatment, and possibility of other approaches presented in the aspect of TBI, the review concludes optimistically. It focuses on the use of better imaging for identification, individualized treatments from medicines to physiotherapy, and searching for other non-conventional treatments such as Chinese herbs. Thus, there is a focus on the treatment and rehabilitation of TBI patients suffering acc to the needs of the patient, with an emphasis on the long-term perspective and comprehensive rehabilitation approach that implies the use of both allopathic and complementary/alternative medicine.

Herbal medicine shows promising neuroprotective potential in traumatic brain injury (TBI) research, but challenges remain in ensuring quality control and clinical application. Due to the complex chemical constituents, efficient separation methods, like column chromatography, are difficult, complicating clinical use. Preclinical evaluations must be rigorous and systematized. While the efficacy of traditional herbal medicine is historically proven, improved quality control methods are essential. Additionally, the combination of acupuncture and drug therapy could offer future therapeutic advancements for TBI.

Conflict of Interest: None

Source of Funding: None

Authors Contributions: None

Acknowledgement: None

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