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REVIEW ARTICLE

Novel Synthetic and Natural Therapies for Traumatic Brain Injury

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Abstract: Traumatic brain injury (TBI) is a major cause of disability and death worldwide. The initial mechanical insult results in tissue and vascular disruption with hemorrhages and cellular necrosis that is followed by dynamic secondary brain damage that presumably results in additional destruction of the brain. In order to minimize deleterious consequences of the secondary brain damage-such as inflammation, bleeding or reduced oxygen supply. The old concept of the -staircase approach- has been updated in recent years by most guidelines and should be followed as it is considered the only validated approach for the treatment of TBI. Besides, a variety of novel therapies have been proposed as neuroprotectants. The molecular mechanisms of each drug involved in the inhibition of secondary brain injury can result as a potential target for the early and late treatment of TBI. However, no specific recommendation is available on their use in the clinical setting. The administration of both synthetic and natural compounds, which act on specific pathways involved in the destructive processes after TBI, even if usually employed for the treatment of other diseases, can show potential benefits. This review represents a massive effort towards current and novel therapies for TBI that have been investigated in both pre-clinical and clinical settings. This review aims to summarize the advancement in therapeutic strategies based on specific and distinct -target of therapies-: brain edema, ICP control, neuronal activity and plasticity, anti-inflammatory and immunomodulatory effects, cerebral autoregulation, antioxidant properties, and future perspectives with the adoption of mesenchymal stromal cells.

Keywords: Pharmacology, biological drugs, traumatic brain injury, secondary brain damage, neuroprotective drugs.

1. INTRODUCTION

Traumatic brain injury (TBI) is a major cause of disability and death worldwide, with an incidence of around sixty--nine million people per year [1]. The initial insult (primary brain injury) is usually followed by a dynamic evolution (secondary brain injury). The long-term effects of TBI are widely influenced by clinical management within the first few hours after the traumatic event [2]. Treatment of TBI requires a multidisciplinary approach, starting from the primary brain injury and continuing through the chronic phase [2]. Novel therapeutic pharmacological strategies have been investigated in the latest years [3].

2. PATHOPHYSIOLOGY OF TBI

The classification of TBI includes various scales and measures. First of all, the Glasgow Coma Scale (GCS), the duration of level of consciousness (LOC) and post-traumatic amnesia (PTA) are useful to assess the clinical severity of TBI. We, therefore, divide TBI in mild (GCS of 13-15 or LOC<1 hour and PTA<24 hours), moderate (GCS of 9-13 or LOC 1-24 hours and PTA 1-7 days) and severe (GCS 3-8, or LOC>24 hours and PTA>7 days) classes. Patients with severe TBI are at higher risk of secondary brain injury, and poor outcome associated with disability, vegetative state, and death. Further classification derives from the areas of lesion: focal injury includes mass lesions such as contusions, subdural hematoma, epidural hematoma and intraparenchymal hemorrhage, whereas diffuse injury includes axonal, hypoxic-ischemic, and microvascular injuries. TBI may also present with both types of damage. Based on the result of brain trauma, we can therefore divide TBI into primary and secondary brain injuries [4]. Primary brain injury causes focal or diffuse brain damage with hypoxia, and massive necrosis involving all cellular elements and blood vessels in the brain. Death of neurons and glial cells in the necrotic area is associated with compromised blood supply and damaged blood-brain barrier (BBB) integrity that can lead to additional intracerebral hemorrhage and edema due to vascular leak-

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age [5]. Although excess edema fluid is moved out of the brain *via* astroglial syncytial systems with involvement of aquaporin-4 (AQP-4) [6], persistent severity of post-injury inflammation with high levels of pro-inflammatory cytokines [7] likely contributes to blood vessel damage and vasogenic edema. Similarly, the pathophysiology of spinal cord injury (SCI) has been recently studied [7], as it is relevant to the understanding of the pathogenesis of human TBI due to the large content of the white matter in the rat spinal cord. While the human brain is very rich in white matter, the rodent brain is not. A massive injury to the white matter such as in human TBI or rat SCI involves the destruction of large amounts of myelin, a potently immunogenic material that initiates severe infiltration by CD68+/CD163-, pro-inflammatory macrophages whose phagocytic activity persists for >16 weeks in the rat SCI and along with high levels of pro-inflammatory cytokines and chemokines contribute to additional irreversible destruction. A neuroprotective therapy, therefore, should primarily address inhibition of the severe and destructive inflammation in the white matter injury [8].

Secondary brain injury also involves several factors, including excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid peroxidation, axon degeneration, and apoptotic cell death [9]. Cytotoxicity and its consequence on redox-regulated processes, pathways and enzymes worsen brain damage. The side products of oxidative metabolism (reactive products-ROS, such as superoxide (O_2^-), hydrogen peroxide (H_2O_2) and the hydroxyl radical (OH^-)) are mainly generated by mitochondria [10]. In the brain around the lesion, Wallerian axonal degeneration is seen within few hours after the traumatic event and also within weeks post-TBI, with infiltration of myelin sheaths by macrophages, proteolysis, excitotoxicity and mitochondrial dysfunction, which may result in secondary axotomy [11]. Moreover, the primary traumatic brain insult and supervening inflammation are associated with the brain tissue reaction integrated as astrogliosis with proliferation and hypertrophy of astrocytes acting to sequester the necrotic and inflammatory lesion from the rest of the CNS tissue [7, 12]. Reactive astrogliosis post-SCI is associated with inhibition and elimination of macrophage-rich destructive inflammation [13, 14] and is involved in the removal of excess edema fluid [7]. The persistent response to TBI is apoptotic cell death of oligodendrocytes and neurons, which may occur until up to one year after the TBI [15]. Excitotoxicity is due to the rapid influx of calcium into the cells with the release of excitatory amino acids such as aspartate and glutamate from presynaptic terminals and may cause BBB damage and neuronal cell death [16]. Glutamate activates both N-methyl-d-aspartate (NMDA) receptor and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors that allow the passage of ions through the ion channels, causing membrane depolarization [16]. The increase of calcium into cytosol causes the activation of the pathways responsible for apoptotic death and impairment of mitochondrial function, thus increasing mortality rate and worsening neurological outcome [17]. Mitochondrial dysfunction contributes to neuronal dysregulation and cell death. Production of reactive oxygen species (ROS), depolarization of mitochondrial membrane and inhibition of adenosine triphosphate (ATP) synthesis are the main mechanisms involved [18]. The activity of nitric oxide synthetase triggered by calcium and the production of reactive oxygen species can induce the formation of peroxynitrite, followed by oxidative damage to protein and lipids [19]. Impaired synaptic plasticity is a consequence of oxidative stress, thus increasing the permeability of mitochondrial membrane and modifying ion transport [20]. These mechanisms are resumed in Fig. (**1**).

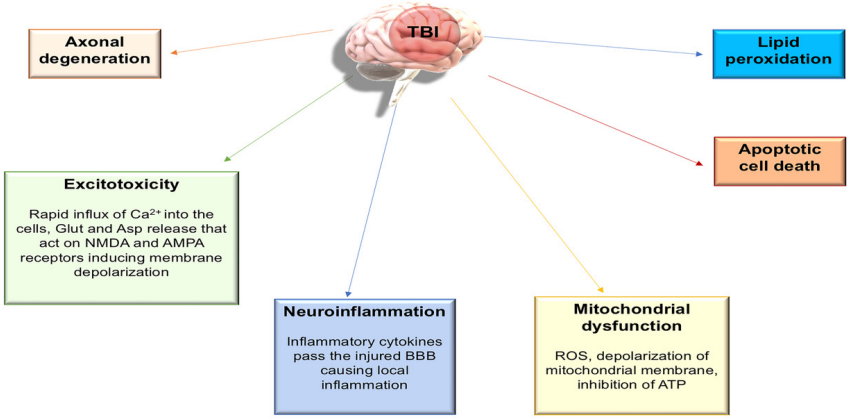

Fig. (1). Mechanisms implicated in secondary brain damage after TBI. As described in the text, we summarized the main mechanisms involved in the secondary brain damage. Excitotoxicity, axonal degeneration, mitochondrial dysfunction, neuroinflammation, lipid peroxidation, and apoptotic cell death. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3. CURRENT THERAPIES FOR TBI

One of the most fearful problems of TBI includes the evolution of intracranial hypertension (HICP). Irrespective of intracranial pressure (ICP) elevation, a "staircase approach" in severe TBI patients should be pursued [2, 21-23]. We, therefore, consider as -tier zero- basic ICU interventions as endotracheal intubation followed by mechanical ventilation, head-up position (15-30°), analgesia and sedation, and normothermia, with the goal of maintaining a cerebral perfusion pressure (CPP) threshold of 60 mmHg, hemoglobin concentration of >7 g/dL, normal serum sodium, and peripheral oxygen saturation (SpO_2) of ≥ 94%. These basic interventions need advanced monitoring, including end-tidal carbon dioxide, a central line placement, an arterial line for invasive continuous pressure monitoring, and a peripheral oxygen saturation device. Tiers -one to -three- includes the interventions suggested only in the case of HICP. Goals of tier 1 include CPP maintenance between 60-70 mmHg and partial pressure of carbon dioxide ($PaCO_2$) between 35 and 38 mmHg, eventually implementing analgesia and sedation, using an intermittent bolus of osmotic agents, placing external ventricular drainage to allow cerebrospinal fluid drainage [24], and implementing electroencephalographic monitoring and prophylactic anticonvulsants if the risk of seizures is deemed high [2, 21-23]. Tier 2 is expected to implement tier 1 interventions as much as mild hypocapnia (32-35 mmHg), neuromuscular paralysis, inotropes or vasopressors to assess if cerebral autoregulation is intact. Once reached tier 3, barbiturate coma, mild hypothermia (35-36°C), hyperventilation ($PaCO_2$ goal of 30-32 mmHg), and secondary decompressive craniectomy may be opted. Further implementation includes an increase of a fraction of inspired oxygen up to 60% or partial pressure of oxygen up to 150 mmHg, CPP>70 mmHg, and a transfusion threshold of <9 g/dL in case of possible hypoxic damage [2, 21-23].

3.1. Current use of Osmotic Agents: Targeting Brain Edema

Recent guidelines suggest the possible use of osmotic agents in all steps of the "staircase approach" when deemed necessary [2, 21-23]. No superiority of mannitol over hypertonic saline on long-term efficacy and safety profile has been confirmed. However, 20% mannitol and hypertonic (1.8% or 3%) saline are able to increase plasma osmolality in TBI patients. Both of them should preferably be used in patients with low or normal plasma osmolality to achieve plasma osmolality of 300 – 320 mOsm/kg [25, 26]. It is currently accepted that excess edema fluid is moved out of the brain *via* an integrated system of hypertrophied astrocytes with elevated expression of AQP-4 [27-30]. Mannitol is six--carbon alcohol of mannose sugar, which enhances the flow of water from tissues into interstitial fluid and plasma. Mannitol is not reabsorbed in the renal tubules, increasing the osmolality of the glomerular filtrate, which increases diuresis through inhibition of sodium and chloride reabsorption [31, 32]. Unfortunately, hyperosmolality induced by mannitol leads to renal tubular epithelial cells injury by an increase in oxidative stress, apoptosis and cytoskeleton destruction [31, 33]. The risk for mannitol-induced acute renal failure significantly increases in patients with hypo-or normo-natremic hyperosmolality [31, 34]. Additionally, an increase in plasma osmolality above 313 mOsm/kg H_2O following mannitol administration significantly increases the risk for prolonged QTc interval, cardiac arrhythmia and cardiac ischemia in patients treated for isolated TBI [35]. Hypertonic saline effectively reduces ICP, corrects microcirculation and cerebral blood flow (CBF), and improves brain tissue oxygen tension [36]. An experimental study in rats has also documented that hypertonic saline suppresses the production of proinflammatory cytokines in activated microglia [37]. Despite the beneficial effect of hypertonic saline, the superiority of hypertonic saline over mannitol has not been strongly documented [38, 39].

3.2. Current Anesthetics, Sedative Agents and Analgesics in TBI: Targeting ICP Control

Sedation and analgesia are a current practice for ICU patients, including those with TBI as a basic and usual strategy to put the brain at rest [21]. Sedation is commonly achieved with propofol, while analgesia privileges opioids. The goal of sedation and analgesia in TBI patients is to provide agitation control, tolerance to the endotracheal tube, and to prevent patient-ventilator asynchronies in order to control ICP by suppressing metabolism, reducing oxygen consumption, and achieving an adequate energy balance in the initial phases of TBI (within 48 hours after TBI), and to avoid rebound of HICP later on. The optimal anesthetic should allow a daily neurological wake-up test, limited effects on hemodynamic, vasoreactivity, and myocardial depression. These characteristics make propofol the first choice for this goal, while midazolam, even if effective, reduces the ability to assess a neurological test, but allowing less hemodynamic instability [21].

In 2013, Krzisch *et al.* demonstrated that propofol (that binds gamma-amino butyric $(GABA)_A$ receptor) can induce neurogenesis in adult animals by increasing intracellular calcium and cyclic adenosine monophosphate and enhancing the proliferation of hippocampal cells [40]. Following an ischemic insult, propofol attenuates brain injury by changing neurotransmitters activity, protein expression, apoptosis and brain oxygen supply/demand [41].

In the clinical setting, some authors compared the micro--dialytic effects of propofol or midazolam administration in TBI patients. No differences were found in the cerebral metabolic profile using these drugs [42]. Propofol at the dosage of 3 mg/kg/h and fentanyl at the dosage of 1-2 mcg/kg/h allow reduction of oxygen consumption, facilitate patient-ventilator synchronism, and endotracheal tube tolerance, thus modulating ICP fluctuations [43]. Advantages in using propofol over midazolam are the rapid metabolism, thus facilitating to assess a daily wake-up neurologic test, and not compromising an eventual electroencephalographic exam [21].

In the case of refractory HICP, barbiturates, which are known as gamma-aminobutyric acid (GABA) receptor agon-

ists, can be adopted to suppress cerebral electrical activity, metabolic demand, and brainstem reflexes by acting on CBF, CPP, and cerebral blood volume. Achievement of burst suppression is not the goal of barbiturate administration. The true goal of barbiturates is to control ICP in case of refractory uncontrolled HICP and seizures. Similarly, continuous increments of barbiturate dosage after bust suppression achievement is not recommended, as it is unlikely associated with a further reduction of ICP [44]. Pentothal seems to be less effective than thiopental in reducing ICP. Thiopental should be used by initial bolus administration of 15 mg/kg followed by continuous infusion of 100 mg/kg/die [44].

4. NOVEL PHARMACOLOGIC STRATEGIES FOR TBI: FROM EXPERIMENTAL TO CLINICAL EVIDENCES

There is growing evidence that some medications can improve recovery after neurologic injury [3]. Novel pharmacological treatments for TBI also include drugs primarily employed for different uses. Few clinical trials have investigated whether novel pharmacological therapies can improve secondary brain damage after TBI. A recent systematic review concluded that some novel therapeutic strategies might have a beneficial effect on functional outcomes (statins, N-acetyl cysteine, enzogenol, cerebrolysin, and nitric-oxide-synthase inhibitor), while other drugs did not demonstrate any neuroprotective effects [3]. The following paragraph will discuss the current pharmacological strategies available, either clinical or preclinical, to modulate some of the pathologically activated pathways after TBI. Table **1** resumes the main drugs tested for the treatment of TBI; while in Fig. (**2**), the main receptors of the brain and some drugs that can activate them, are summarized.

4.1. Novel Anesthetics, Sedative Agents and Analgesics in TBI: Targeting ICP Control

Anesthetics and sedatives are used in TBI for the management of these patients, although their therapeutic efficacy is not yet completely accepted. A meta-analysis on sixteen pre-clinical studies in rats or mice demonstrated that anesthetic drugs provide neuroprotection in rodent models of TBI [45].

Table 1. Novel drugs for the treatment of TBI and their effects.

Drug	Class	Traditional Use	Effects in TBI	References
Novel anesthetics, sedative agents and analgesics in TBI: targeting ICP control				
Ketamine	**NMDA antagonist**	-anesthetic -dissociative anesthesia -antidepressant -treatment of seizures	-reduces neurological deficits -inhibits neuronal apoptosis -reduces brain edema	[46-50]
Dexmedetomidine	**α_2-2 agonist**	-sedative and anti-hypertensive drug	-reduces axonal injury and synaptic degeneration -brain edema reduction -inhibits apoptosis and oxidative stress	[51, 56]
Sevoflurane	**Anesthetic vapor**	-anesthetic	-reduces cellular autophagy -reduces neuronal apoptosis	[55, 57, 58]
Xenon	**Noble gas**	-anesthetic	-reduces secondary brain injury	[59-62]
Argon	**Noble gas**	-anesthetic	-protects against hypoxic-ischemic injury	[63-65]
Opioids	**Analgesic**	-analgesic used for moderate-severe pain	-neuroprotective effects -reverse memory deficits -fentanyl is associated with lower ICP than morphine and sufentanyl	[66-69]
Psychostimulants, psycho-depressants and drugs approved for the treatment of memory: targeting neuronal activity and plasticity				
Fluoxetine	**Selective serotonin reuptake inhibitor**	-antidepressant -ansiolitic	--reactivates neuronal plasticity	[71]
Methylphenidate	**Inhibitor of dopamine and noradrenaline reuptake**	-psychostimulant -increase extracellular dopamine, norepinephrine and serotonin levels	-improves cognitive outcomes as mental fatigue, depression, anxiety and other cognitive symptoms	[74-76]
Lithium	**Mood stabilizer**	-mood stabilizer -antidepressant -used for bipolar disorders -antipsychotic	-neuroprotective effects -stimulates neurogenesis *via* multiple signaling pathways -improves dopamine release and soluble N-ethylmaleimide-sensitive factor attachment protein receptor -downregulates pro-apoptotic factors -upregulates neurotrophins and growth factors (brain-derived neurotrophic factor, BDNF)	[77, 78]

(Table 1) contd….

Drug	Class	Traditional Use	Effects in TBI	References
Quetiapine	**Antipsychotic**	-antidepressant -mood stabilizer -sedative	-BBB protection by protecting the integrity of tight junctions and matrix metalloproteinase-9 activity suppression -anti-inflammatory properties - protects the integrity of tight junctions -suppress matrix metalloproteinase-9 activity	[79, 80]
Phenserine tartrate	**Acetylcholinesterase inhibitor**	-antioxidant properties -alleviates glutamate excitotoxicity - effects *via* mitogen-activated protein-kinase-threonine/tyrosine kinases (MAP-K/MEK1/2) cascades -Regulate post-transcriptionally proteins such as amyloid precursor protein and α-synuclein	-alleviates oxidative stress, glutamate excitotoxicity and neuroinflammation processes -reduces programmed neuronal cell death -shift gene pathways leading to neurodegeneration	[81-86]
Galantamine	**Acetylcholinesterase inhibitor**	-Alzheimer disease -dementia	-decreases BBB permeability -increases the synaptic levels of acetylcholine	[87-89]
Memantine	**NMDA agonist**	-reduce cell death -reduce astrogliosis	-reduce astrogliosis, cell death and functional deficit	[85, 86]
Dextroamphetamine	**Central nervous system stimulant**	-attention deficit hyperactivity disorder (ADHD) -narcolepsy -cognitive enhancer -euphoriant	--reduces reuptake of dopamine -norepinephrine agonist -psychostimulant	[90]
PDE4	**Phosphodiesterase-4 inhibitor**	-chronic obstructive broncho-pneumopathy	-increases memory -improves cognitive disfunction	[91]
Ethanol	**Psychoactive drug**	-antiseptic -antidote -medicinal solvent -recreational use	-neuroprotectant -increases inflammation -contrasting results	[92, 93]
Insulin-like growth factor	**Growth factor**	-growth factor	-anti-inflammatory, antioxidative, and anti-ischemic activity -improve vascular and endothelial function -reduce cerebral edema -inhibit microglial activation	[94-96]
Medications with anti-inflammatory and immunomodulatory effects				
Salsalate	**Non-steroidal AI**	-anti-inflammatory -analgesic	-decreases microglia pro-inflammatory response -neuroprotection and neurogenesis	[98, 99]
Steroids	**Steroid hormones**	-anti-inflammatory -analgesic -immunomodulant	-anti-inflammatory regulatory effect -reduces neuronal cells death	[100-103]
Progesterone	**Sexual hormone**	-hormone replacement therapy	-may modulate neuroinflammation	[104-106]
Estrogens	**Sexual hormone**	-hormone replacement therapy	-reduce pathological intracranial pressure and cerebral edema -increase cerebral perfusion pressure and glycolytic metabolism	[107-109]
Bazedoxifene	**Selective estrogen receptor modulator**	-postmenopausal osteoporosis	-neuroprotection Reduces BBB destruction	[110]
Thalidomide	**Chemotherapy drug**	-morning sickness during pregnancy -multiple myeloma -graft-versus-host disease -tuberculosis -sedative	-reduces apoptosis of neurons -reduces oxidative damage -improve functional outcome -neuroprotectant	[111, 112]
Maraviroc	**Antiretroviral drug**	-CCR5 receptor antagonist -treatment of human immunodeficiency virus (HIV) -graft-versus-host disease	-improves motor function -modulates learning and memory -improves cognitive function	[120, 121]

(Table 1) contd….

Drug	Class	Traditional Use	Effects in TBI	References
Methylene blue	**$GABA_A$ antagonist**	-methemoglobinemia -urinary tract infections -facilitator of tissutal view	-inhibits microglial activation -reverses mitochondrial damage -reduces neuronal apoptosis -improves BBB integrity -lower lesion volume -improve behavioral functions	[122-126]
Melatonin	**Hormone**	-insomnia -circadian rhythms	-reduces inflammation -increases anti-inflammatory processes -attenuates brain edema -attenuates hyperpermeability	[127-130]
Erythropoietin	**Glycoprotein cytokine**	-stimulation of blood cells production -illicit use as a performance-enhancing drug -hormone activity	-prevents loss of tight-junction protein zonula occludens1 -improves BBB integrity -reduces post-TBI edema -decreases inflammation -glycoprotein cytokine -protein kinase activator	[131-135]
Cannabinoids	**Psychoactive drug**	-nausea due to chemotherapy -neuropathic pain -spasticity	-modulates apoptosis -inflects on neuroinflammation, cell structure and remodeling	[136-139]
Statins	**3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors**	-used for hypercholesterolemia -primary and secondary prevention of cerebrovascular diseases	-immunomodulatory effect -anti-inflammatory properties -less functional disability, improved outcome -lower risk of vasospasm and delayed cerebral ischemia in subarachnoid hemorrhage -suppress the upregulation of major histocompatibility complex class II expression -inhibit inflammatory cell migration into the central nervous system -enhance nitric oxide production -modulate platelet function, the coagulation cascade and increase fibrinolysis (via upregulation of tissue plasminogen activator, inhibition of plasminogen activator inhibitor and reduction in Lp (a) 1 levels)	[140-143]
Metformin	**Biguanide**	-used for type II diabetes mellitus -used for polycystic ovary syndrome	-anti-inflammatory -antioxidative Improves vascular and endothelial functions	[144, 145]
Serp-1	**Myxoma virus-derived immunomodulatory protein**	-serine protease inhibitor -inhibits tissutal and urokinase type plasminogen activators, plasmin, Xa factor, and thrombin	-anti-inflammatory	[146, 147]
Platonin		-antimicrobial -anti-histaminic -used for immune disease in clinical setting	-antioxidant -immunomodulator -inhibitor of platelets aggregation	[148-150]
Anti-hypertensive drugs, inotropes and vasopressors: targeting cerebral autoregulation				
Beta-blockers	**Beta-adrenergic blocking agents**	-used for arterial hypertension -arrythmia -chest pain -heart attack -migraine -tremors	-beta-blockers present protection of cerebral autoregulation and reduce hippocampal neuronal death	[151, 152]
Norepinephrine	**Catecholamine**	-inotropes -increases heart rate and blood pressure	-protectant for cerebral autoregulation -prevents hippocampal necrosis	[154-156]
Dopamine	**Inotropes**	-increases heart rate -increases blood pressure -increases cardiac output	-protects cerebral autoregulation -controls Arousal system	[154-156]

(Table 1) contd….

Drug	Class	Traditional Use	Effects in TBI	References
Novel synthetic and natural compounds for TBI: targeting antioxidant properties				
Antioxidants	**Synthetic and natural antioxidants (see Section 3.5 and *Table 2*)**	-antioxidants with various mechanisms	-improve outcomes -improve recovery and cognitive function -reduce cerebral edema -decrease mortality -selected improve ICP and CPP control -neuroprotective and antiapoptotic properties -protection of BBB integrity	[158-203]

Abbreviations: ICP, intracranial pressure; CPP, cerebral perfusion pressure; BBB, blood-brain-barrier; TBI, traumatic brain injury, AI, anti-inflammatory.

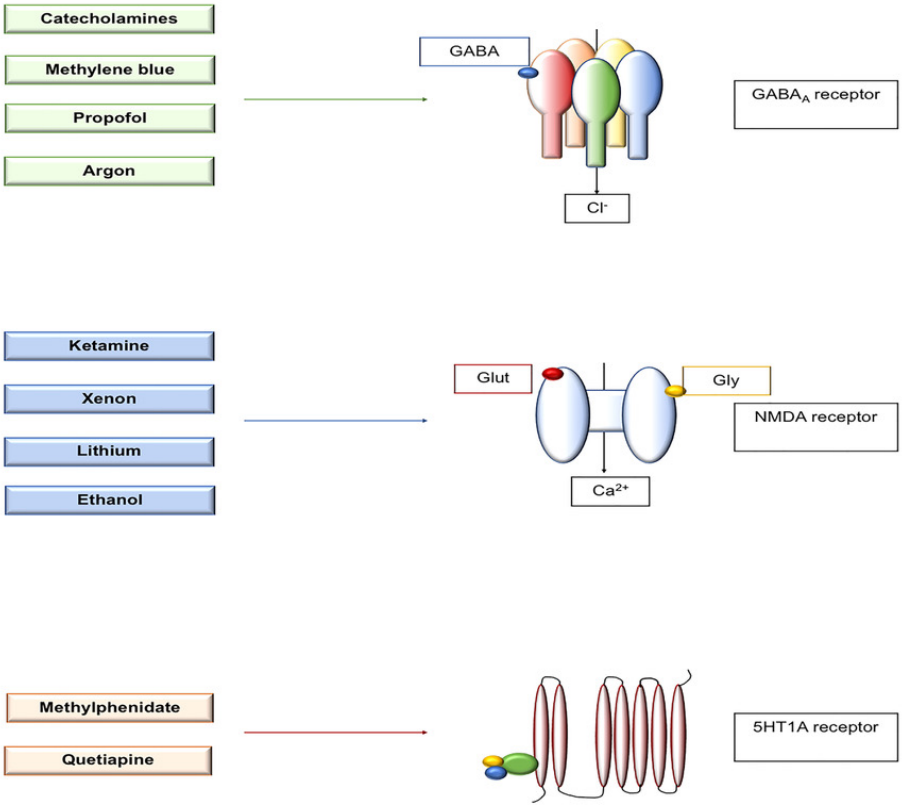

Fig. (2). Receptors activated in the brain as possible target for TBI. GABA$_A$, gamma-amino butyric acid receptor, which is activated by GABA that allows the passage of Cl^- into the cell. It can be modulated by propofol, argon, methylene blue, and catecholamines. NMDA, N-methyl-D-aspartate receptor which can be activated by xenon, lithium, ethanol, ketamine. This receptor is activated by Glutamate (Glut) or Glycine (Gly) binds that allow the passage of Calcium. 5HT1A and B receptors that can be bind by quetiapine and methylphenidate. These receptors are 7-transmembrane fold which acts by activating a G-protein that when phosphorylated activates the intracellular pathway. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Ketamine administration significantly reduced the course of secondary brain injury in TBI mice by binding NMDA receptors, including neurological deficits, neuronal apoptosis and brain edema [46]. Clinical evidence about the possible neuroprotective effects of anesthetic agents are poor; for example, ketamine seems to reduce post-operative cognitive dysfunction and delirium and attenuated refractory status epilepticus [47]; similarly, propofol seems to have equivalent effects [48]. More recent evidences suggested that ketamine exerts a protective effect in TBI patients [49]. The dose of ketamine able to cause spreading depolarization is >1.5 mg/kg/h, while at 0.55 mg/kg/h, it does not induce excitatory effects. Thus, the suggested dosage of ketamine for inhibiting spreading depolarization is between 0.7-1.15 mg/kg/h [50]. However, ketamine alone is not suggested for ICP control, while its administration together with other anesthetic allows to reduce their dose and side effects [21].

Moreover, dexmedetomidine, a selective α_2-adrenoceptor agonist, reduced axonal injury and synaptic degeneration

in the experimental model of TBI in rats [51]. Dexmedetomidine exerted protective effects by decreasing oxidative stress and mitochondrial damage and leading to reduce both cerebral edema and neuronal apoptosis. These mechanisms increased behavioral functions [52] and modified neurological outcomes by modulating Bcl2-associated-X-protein (Bax) expression in the rat's hippocampus [53]. Additionally, neuroprotective effects by modulating PI3K/Akt/mTOR pathway were demonstrated by some authors [54]. Synergic benefits of using both dexmedetomidine and sevoflurane were not detected, although dexmedetomidine seemed to protect from neuronal cells proliferation and neurotoxicity effects induced by sevoflurane [55]. In clinical settings, dexmedetomidine employed at the median dosage of 0.49 mcg/kg/h did not decrease neurological function in TBI patients [56].

Similarly, sevoflurane inhalator administration reduced cellular autophagy and neuronal apoptosis in TBI rats [57]; while on the clinical side, sevoflurane (1-1.5 minimal alveolar concentration) *via* inhalator administration plus remifentanil (2-8 ng/mL) anesthesia was compared to intravenous target-controlled infusion of propofol (3-6 mcg/mL) plus remifentanil (2-8 ng/mL) during emergency surgery for TBI. Intraoperative management included the maintenance of cerebral protection targets in both groups. Neurological outcomes at discharge were comparable between groups [58].

Xenon is a noble gas with neuroprotective properties licensed for human use as an anesthetic gas [59]. In a recent experimental model, xenon showed improvement in long- and -short-term-outcome and survival in mice, significantly reducing secondary brain injury [60]. Its neuroprotective properties have been previously discussed by other pre-clinical models, confirming that it acts by binding the glycine site of the NMDA receptor. A recent meta-analysis on clinical trials comparing traditional volatile anesthesia with xenon anesthesia revealed more stable intraoperative blood pressure, lower heart rate, and faster weaning [61]. Xenon is suggested for neurosurgical procedures to protect the brain from further injury [62].

Attention has also been paid to the use of Argon, which acts on different sites (*e.g.* Argon binds $GABA_A$) [63]. Argon and xenon in pre-clinical models protected the brain against hypoxic-ischemic injury in rats hippocampus [64]. A meta-analysis comparing the effects of Argon in pre-clinical and clinical models concluded that this gas may attenuate the effects of hypoxia and increase tolerance to hypoxia, exerting neuroprotective characteristics [65].

Targeting different channels or enzymes opioids could be another therapeutic strategy for TBI, including calcium, NMDA, and opioids channels or Na+/K+-ATPase. The endogenous neuroprotective mechanism promoted by opioids can be useful in the early phase of brain trauma. The administration of morphine or naloxone reduces neurological deficits, while naloxone exacerbates behavioral manifestations. The activation of *m* and *d* opioid receptor exhibits neuroprotective effects [66], such as for biphalin, which is a dimeric enkephalin-analog that evokes an analgesic response [67]. In experimental data, biphalin presented early neuroprotective effects and reversed memory deficits [68]. A recent systematic review concluded that opioids administration had no significant effects on CPP and meant arterial pressure. Only one study revealed differences in opioid subtypes, suggesting that fentanyl is associated with lower ICP and CPP than morphine and sufentanyl [69].

Data concerning the use of anesthetic, sedative agents, and opioid analgesics interestingly confirm their utility as neuroprotectors, although the role of these drugs for TBI patients is still inconclusive and randomized controlled trials and observational studies are needed to confirm these evidences.

4.2. Psychostimulant, Psycho-depressant Agents and Drugs Approved for the Treatment of Memory Impairment: Targeting Neuronal Activity and Plasticity

After TBI, the initial excitatory/inhibitory balance of the brain circuit is lost. Cognitive symptoms after TBI are frequently determined by changes in network structure in different brain regions. A recent work discovered that neurodegeneration can impact both network activity and neural oscillations to one microcircuit that could influence many connected brain areas [70]. An increasing body of research suggests that many drugs can alleviate cognitive dysfunction and promote recovery after TBI [70].

Neuronal plasticity is a process that involves trophic mechanisms such as neurogenesis and synaptogenesis and atrophic processes. Neuronal plasticity is typical of the postnatal evolutive period but can also be mediated by drugs commonly adopted for the treatment of neuropsychiatric disorders. Neurotrophic factors include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and -4 [71]. Neurotrophins bind to Trk and p75 family receptors to promote neuronal survival and plasticity. Antidepressants were discovered to increase BDNF mRNA expression and to prevent downregulation of these receptors. Other antidepressants act by phosphorylating the TrkB receptor. Fluoxetine was found to promote recovery from stroke and brain trauma in an animal model. Fluoxetine may reactivate critical plasticity in many cortical regions and recovery of amblyopic vision in adult rodents, but similar effects on humans are unclear. In a recent clinical trial, fluoxetine and placebo were equally effective in the recovery of amblyopic vision, raising concerns on this effect [71].

Following TBI, cognitive and neuropsychiatric symptoms are very commonly observed. However, there are no specific pharmacological strategies currently approved by the Food and Drug Administration for the treatment of such symptoms in TBI [72]. Neurological manifestations after TBI include difficulties in attention and concentration, and memory problems, that reach 10-33% of TBI patients in the recovery phase [73]. Psycho-stimulant agents are commonly employed for the treatment of "attention deficit hyperactivity disorder" [74]. Among psychostimulants, methylphenidate is the most commonly used [74]. Its mechanism of action involves the inhibition of dopamine reuptake, thus in-

creasing extracellular dopamine levels, as well as norepinephrine and serotonin [74]. Following TBI, an asymmetric allocation of attention has been identified. In these patients, methylphenidate seemed to be an effective treatment for attentional post-traumatic dysfunction [75]. A recent meta-analysis of ten randomized clinical trials evaluated the effect of methylphenidate on outcomes. Methylphenidate improved cognitive outcomes (mental fatigue, depression, anxiety and other cognitive symptoms), although it exerted significant effects on heart rate [76].

Lithium is a drug commonly employed to treat psychiatric disorders that may exert beneficial effects on brain function. Lithium increases synaptic density, modulates dopamine neurotransmission, and inhibits glycogen synthase kinase-3 [77]. A recent animal study demonstrated that lithium improved dopamine release after TBI and soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor, which are implicated in neurotransmitters exocytosis. Additionally, lithium did not increase synaptic density and did not inhibit the glycogen synthase kinase-3 pathway [78], as previously reported [77]. In animal models, lithium administration did not increase the abundance of synaptophysin or post-synaptic density protein-95 levels, especially when lithium is administered in a period of one week after injury [78].

Quetiapine is an antipsychotic drug that shows anti-inflammatory properties. Quetiapine provides BBB protection by protecting the integrity of tight junctions and matrix metalloproteinase-9 (MMP9) activity suppression [79]. Many other drugs have been proposed for the treatment of anxiety and depressant symptoms after TBI, although current treatments have not been considered very effective. Currently, a randomized controlled trial is investigating the efficacy of receiving or not antidepressants on anxiety and depressant symptoms by using specific scales [80].

Phenserine tartrate (PhenT), originally developed for Alzheimer's treatment, presents effective neuroprotective properties [81]. PhenT alleviates oxidative stress, glutamate excitotoxicity and neuroinflammation processes by increasing neurotrophic factor levels and brain acetylcholine levels [82]. This drug has shown to be able to reduce programmed neuronal cell death and shift gene pathways toward neurodegeneration. PhenT effects are mediated *via* mitogen-activated protein-kinase-threonine/tyrosine kinases (MAPK/MEK1/2) cascades and can post-transcriptionally regulate proteins such as amyloid precursor protein and α-synuclein [83, 84]. Memantine, usually employed for the treatment of Alzheimer, seems to be able to reduce astrogliosis, cell death and functional deficit in *in-vitro* and *in-vivo* models of TBI [85, 86].

Galantamine is a natural or synthetic compound approved for Alzheimer disease. Post-injury administration of galantamine may also decrease BBB permeability. Galantamine elevates the synaptic levels of acetylcholine and is a positive allosteric modulator for the nAChR7 receptor [87, 88]. In animal models of TBI, galantamine decreased systemic inflammation, reduced the loss of hippocampal GABAergic neurons, and ameliorated memory function [89].

Dextroamphetamine is one of the novel candidates for the pharmacological treatment of TBI patients. It is a norepinephrine agonist and a blocker of the reuptake of dopamine, usually prescribed for the treatment of attention deficit hyperactivity disorder [90]. Literature revealed that psychostimulants like dextroamphetamine and methylphenidate enhance recovery, neurologic functionality and improve rehabilitation.

Phosphodiesterase-4 (PDE4D) is a family of cyclic AMP hydrolyzing enzymes involved in memory formation. Evidences come from an experimental setting, in which animals were treated with a negative allosteric modulator of PDE4D called D159687 three months after TBI. In non-injured rats, D159687 did not implement animals' memory, while in TBI rats, D159687 reversed the learning and memory deficits, improving cognitive dysfunction [91].

Ethanol intoxication is frequently observed in TBI patients, accounting for up to 55% of them. Ethanol acts as its neuroprotectant effect by suppressing ErbB signaling in parvalbumin-positive interneurons. It also acts by inhibiting the activation of NMDA receptors. In fact, in an experimental model, ethanol administration before TBI enhanced behavioral recovery and the administration of ErbB inhibitors was able to revert the beneficial effects of ethanol administration [92]. Contrasting results indicated the possible impaired neurological recovery and accentuated inflammation in animals treated with ethanol after TBI [93].

Another drug proposed for ameliorating neurobehavioral recovery following TBI is the insulin-like growth factor-1 (IGF-1), which is able to improve the generation of immature neurons in the hippocampus [78]. The administration of IGF-1 stimulates the downstream signaling in the post-TBI brain [94]. Moreover, Wang *et al.* documented that the administration of IGF-1 variants correlated with the vulnerability and the neuropsychiatric outcome of post-TBI patients [95]. Of note, IGF-1 activates intracellular signaling by enhancing the pathways-phosphatidylinositol 3-kinase/ protein kinase B (PI3K/Akt) and mitogen-activated protein kinase/ extracellular signal-regulated kinase (MAPK/ERK), which play pivotal roles, such as managing glucose utilization, neurogenesis, synaptic plasticity and angiogenesis [96].

4.3. Medications with Anti-inflammatory and Immunomodulatory Effects

The focal inflammatory response is activated within few minutes after brain injury, with subsequent release of danger signals (like damage-associated molecular patterns (DAMPS), adenosine triphosphate, heat shock proteins, high-mobility group box-1 (HMGB1) and so on) [97]. After the injury, microglia, astrocytes, and endothelial cells are activated, and neutrophils, monocytes, and lymphocytes and the complement system are then activated and cells recruited into the lesion, liberating cytokines, chemokines and ROS that contribute and amplify to the inflammation process. Microglia acts by maintaining the BBB integrity. Finally, monocytes, macrophages and T cells are recruited to the brain and the inflammatory process can also extend away from the surround-

ing area. Dysregulation of the immune system can also activate the coagulation cascade, causing micro-thrombosis and micro-bleeding, associated with BBB breakdown [97], Fig. (**3**). The inflammatory and immune response associated with brain injury should consider possible systemic involvement until life-threatening conditions [97]. Modulation of the inflammatory and immune response may be a promising therapeutic target for future researches. Immunomodulators are medications that regulate or normalize the immune system. Thus, the usage of immunomodulant/immune-stimulant agents may affect the final outcome of TBI patients. The above-mentioned immune-response modulators are examples of new targets treatments for TBI. Recently, many studies on TBI have been referred to the use of substances with immunomodulatory properties that may affect the response of the immune system of varying degrees.

Salsalate is a non-steroidal anti-inflammatory drug, which is classified as non-acetylated salicylate [98]. Salsalate inhibited inflammatory gene expression in a microglia cell line [99]. Importantly, salsalate decreased microglia proinflammatory response by the inhibition of NF-κB signaling by blocking the activation of inhibitor of NF-kB kinase-α and-β and reducing the expansion of activated microglia. In summary, animal model salsalate promotes neuroprotection and neurogenesis, with significant recovery of motor function.

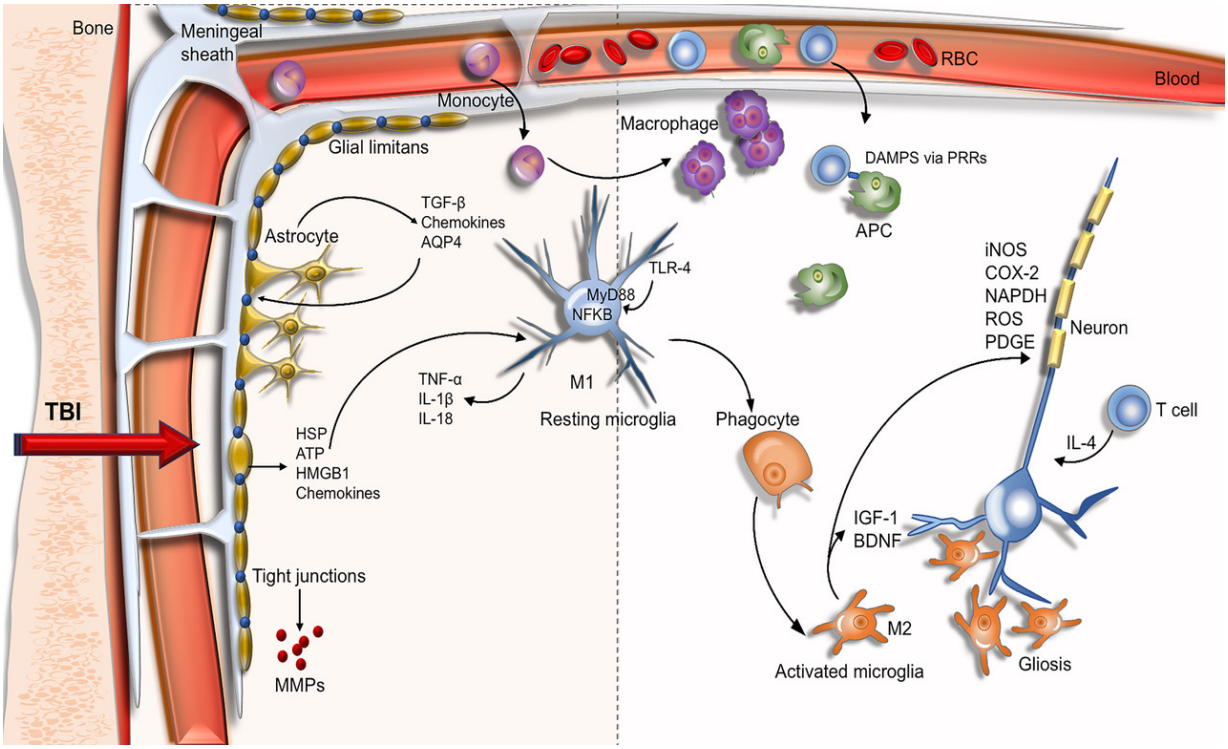

Fig. (3). Mechanisms implicated in inflammation after TBI. Following a brain insult, BBB disfunction and cerebral blood vessels alterations are frequent. Tight junction proteins are altered like as pial and intracerebral blood complex. Changes in expression of the tight junctions are accompanied with up-regulation of matrix metalloproteases (MMPs), involved in BBB alteration. Astrocytes become reactive and start proliferating while providing astrogliosis. Cytokines and chemokines are then released by astrocytes, altering the BBB and increasing the expression of transforming growth factor-β (TGF-β) and expression of the water channel aquaporin-4 (AQP4) that is altered after TBI and may contribute to cerebral edema and disruption of the BBB. Meanwhile, innate and adaptive immune responses are activated, converging in element of the complement pathway with the release of proteolytic enzymes. The innate immune response is mainly mediated by the interaction between antigen-presenting cells (APC) and damage-associated molecular patterns (DAMPS) *via* pattern recognition receptors (PRRs) expressed by a large variety of immune cells including polymorphonucleates, natural killer lymphocytes, macrophages, and dendritic cells. After interacting, APC product chemokines and cytokines. Particularly after TBI, among DAMPS, high-mobility group box 1 chaperone protein (HMGB1) that regulates DNA transcription, adenosine triphosphate (ATP), heat-shock proteins (HSP), and chemokines are liberated promoting inflammation and oxidative stress. Microglia can be polarized into M1 and M2. M1 microglia is associated with the production of pro-inflammatory cytokines and chemokines, and typically involves a tolle-like receptor-4 (TLR-4) signaling after binding to tumor necrosis factor-α (TNF-α), and involving MyD88 and the transcription of NF-kB, thus producing cytokines and chemokines (TNF-α, interleukin-1β (IL-1β), IL-18),; while M2 activated microglia express insulin-like growth factor-1 (IGF-1) and brain-derived neurotrophic factor (BDNF) promoting oligodendrogenesis and neurogenesis, suppressing inflammation and contributing to tissue repair. Microglia activation causes nicotinamide adenine dinucleotide (NADPH) oxidase, inducible nitric oxide synthases (iNOS) and cyclooxygenase (COX-2) synthasis, resulting in reactive product of oxygen (ROS), nitric oxide (NO), prostaglandin-E2 (PGE2). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Steroids are well-known endogenous molecules, which are able to modulate the inflammatory response. The inflammatory process plays a pivotal role in facilitating secondary brain injury *via* the production of inflammatory cytokines and interleukins. Pre-clinical and clinical studies have shown an acute increase of cortisol levels in serum and cerebrospinal fluid in response to TBI, thus suggesting a possible anti-inflammatory regulation effect and reduced neuronal cell death of the brain-injured tissue [100, 101]. An experimental study on mice concluded that hydrocortisone administration in TBI can reduce the pro-inflammatory response, particularly by reducing the number of circulating lymphocytes that remained stocked into the lymphoid tissues. This study suggested that exogenous administration of cortisol in the early phase after TBI could play a protective role against the enhanced immune response [102]. Moreover, experimental evidences identified dexamethasone as a possible inhibitor of the expression of Ras homolog family member (Rho)-A and-B proteins (involved in leukocyte migrations) in the injured cortex and hippocampus a few hours after TBI [103].

Progesterone is a hormone with neuro-steroidal properties that has been shown very promising in preclinical models of TBI. Progesterone efficacy in TBI has been related to its intrinsic neuroprotective function [104]. A meta-analysis investigated the effect of progesterone on the Glasgow Outcome Scale, mortality and adverse events in acute TBI patients. Two-phase III trials and three phase II trials were included in the final analysis. No significant difference was observed in the favorable outcome (relative risk (RR) 1.07, 95% confidence interval (CI) 0.91-1.27, p=0.41) and mortality rate (RR 0.85, 95% CI 0.65-1.13, p=0.27) between progesterone and placebo groups, with a moderate quality of evidence [105]. These results were confirmed by another meta--analysis performed in 2019 on eight randomized controlled trials that observed reduced mortality (RR 0.59; 95%CI 0.42-0.81, p=0.001) and better neurological outcome at 3 months (RR 1.51; 95%CI 1.12-2.02, p=0.007), that did not persist at 6 months [106]. Taken together, these findings do not guarantee sufficient evidence concerning progesterone use for the management of TBI.

Estrogens play an important role in the protection of the central nervous system. Among estrogen subtypes, estrogen sulfate (E_2-SO_4) is the most abundant and effective in mammals and humans, playing a pivotal role in neuronal activity, neuronal networking and synaptogenesis [107]. A recent experimental study on Dawley rats after TBI induction, showed that estrogen sulfate administration reduces pathological intracranial pressure, cerebral edema, increases cerebral perfusion pressure and glycolytic metabolism [107]. Another experimental model of TBI on rats demonstrated that Tamoxifen, a drug primarily involved in binding the estrogen receptors, could be a useful neuroprotectant in TBI rats. Its mechanism of action is the bind of the estrogen receptor-α on neurons and glia, leading to reduced neuroinflammation and apoptosis of these cells [108]. In 2016, 17α-ethinylestradiol-3-sulfate (EE-3-SO_4) was employed for the treatment of TBI in a rat model. EE-3-SO_4 significantly lowered intracranial pressure levels and brain edema, while rising cerebral perfusion pressure and partial brain oxygenation pressure. These pre-clinical findings supported the possible clinical use of EE-3-SO_4 (at the dosage of 1 mg/kg in Sprague-Dawley rats) for treating TBI in the early phase. No peripheral effect of this drug was described [109].

Lan *et al*. documented that bazedoxifene, a third-generation selective estrogen receptor modulator, presented neuroprotection by inhibiting the activation of the MAPK/NF-κB signaling pathway [110]. Importantly, bazedoxifene reduced BBB disruption by increasing both occludin, TJs and ZO-1 levels which are normally decreased 24 hours after TBI. This discovery is terrific, since BBB dysfunction may lead to brain edema and neuronal death and cause subsequent long-term TBI complications, such as cognitive and psychological impairments.

Thalidomide analog -3,6′-dithiothalidomide (3,6′-DT) presented good brain penetration by inhibiting the synthesis of TNF-α, pro-inflammatory cytokines expression, reducing apoptotic neurons in the cortical contused regions, suppressing microglia activation, and reducing oxidative damage [111]. These findings suggested that 3,6'-DT significantly decreases the loss of cortical tissue and improves functional outcomes in a rat model. Moreover, it inhibits pro-inflammatory cytokines by blocking cytokine receptors, thus resulting in a major neuroprotective treatment [112].

The BBB "breakdown" after TBI activates the coagulation cascades, resulting in decreased blood flow [113]. Compromised integrity of the BBB results in blood-borne factors such as thrombin, albumin and fibrinogen, entering the brain and promoting microglia activation, proliferation, and production of pro-inflammatory factors [114]. HMGB1 is recognized as DAMPS and stimulates a wide variety of receptors for advanced glycation end-products (RAGE), toll-like receptor-4 (TLR)-4 and TLR-2 [115]. It also upregulates the production of proinflammatory cytokines *via* NF-κB and MAP-K-signaling pathways. HMGB1 plays an important role in the disruption of BBB after TBI [116]. Anti-HMGB1 mAb therapy protects against BBB disruption and reduces brain edema [117, 118]. Importantly, this monoclonal antibody suppresses the activation of glia cells, the expression of proinflammatory cytokines, and the inflammatory cascade [119].

Likewise, the administration of drugs that are used in other diseases which act on specific pathways involved in destructive processes after TBI can present potential benefits. The C-C chemokine receptor5 (CCR5) antagonist-maraviroc, approved by Food and Drug Administration for Human-immunodeficiency virus (HIV) treatment, presented beneficial effect on motor function following stroke and TBI. The inhibition of CCR5 receptor-signaling modulated learning, memory, and plasticity processes in hippocampal and cortical circuits [120]. Thus, CCR5 antagonist reduced learning deficits and amplified cognitive function [121].

Methylene blue is a drug usually applied for the treatment of poisoning such as those caused by cyanide, carbon

monoxide, as well as methemoglobinemia [122]. Its mechanism of action includes the binds of $GABA_A$ receptors in the brain [123]. In 2016, Zhao *et al.* explored the mechanism of action of methylene blue on neuroprotection in a mouse model of TBI. The methylene blue group showed higher surviving neurons than the other groups and lower lesion volume, also inhibiting microglial activation [124]. Regarding the timing, acute administration of methylene blue improved neuroinflammation and behavioral functions [125]. Likewise, administration of methylene blue 24 hours after TBI exerted neuroprotective effects and reduced the lesion volume on quantitative magnetic resonance [126]. A recent experimental study on mice showed that methylene blue treatment was able to reverse mitochondrial damage, reduce neuronal apoptosis and improve BBB integrity after TBI [122]. Unfortunately, human clinical studies are no yet available on this drug, although experimental evidences are really promising.

Melatonin is a hormone secreted by the pineal gland with antioxidant and anti-inflammatory properties [127]. Experimental evidence demonstrated that exogenous melatonin administration alleviated early brain damage after TBI and neurobehavioral deficits in mice [127]. Moreover, exogenous melatonin administration reduced inflammation and increased anti-inflammatory properties, through the modulation of IL-10, IL-4, superoxide dismutase, glutathione, glutathione peroxidase, IL-1β and tumor necrosis factor levels [127]. It was also able to enhance autophagy, thus inhibiting mitochondrial apoptotic pathways with subsequent protection against secondary brain damage [128]. Secondary brain damage is characterized by a hyperpermeability status followed by brain edema (modulated by MMP9), proteolytic enzymes and pro-inflammatory cytokines) and possible secondary intracranial hypertension. In this setting, melatonin showed brain protection attenuating hyperpermeability *via* MMP9 inhibition [129]. Human studies on exogenous melatonin use after TBI are only focusing on sleep disorder, although evidences revealed an increased level of endogenous melatonin in the cerebral spinal fluid after TBI, thus suggesting its potential role on oxidative stress and metabolic functions [130]. Taken together, preclinical evidences suggest its possible role to attenuate brain edema and hyperpermeability after TBI, although further studies are required to elucidate its real usefulness.

Erythropoietin is a glycoprotein cytokine that stimulates the production of blood-red cells in anemic and hypoxemic patients. Its neuroprotective effects have been recognized for a long time, although its potential role on TBI patients has been recently proposed [131]. Erythropoietin expression may be upregulated by oxygen tension but also may be promoted by Xenon or agents blocking inflammation of cerebral microglia [132]. Brain effects of erythropoietin have been explored on TBI rats by Blixt *et al*. [131]. In this study, erythropoietin significantly prevented the loss of tight junctions protein zona occludens-1 (ZO-1) and BBB dysfunction, also attenuating vasogenic edema [131]. Millet *et al.* showed the reduction of post-traumatic edema, mitochondrial modulation and reduced caspase-3 expression [133]. Moreover, erythropoietin resulted in decreased inflammation in the injured brain, thus increasing the expression of the anti-inflammatory interleukin (IL)-10, and decreasing proinflammatory cytokine levels [134]. Erythropoietin seemed to be protective also against acute lung injury secondary to TBI in a human study. Erythropoietin-derived peptide decreased total bronchoalveolar lavage proteins and histological signs of pulmonary damage, acting on macrophages and cytokines modulation [135]. Taken together, these evidences suggest that erythropoietin treatment could be effective for modulating the secondary brain damage after TBI, as well as secondary systemic injurious effects.

Endocannabinoids have recently been demonstrated as powerful anti-inflammatory drugs with a not completely understood mechanism. Endocannabinoids act binding the cannabinoid receptors (CBR)-1 and-2, which are hyperactivated during the first 72 hours after TBI in murine models [136]. The administration of a selective agonist for CBR-2 receptor, attenuated macrophage polarization toward pro-inflammatory subtype M1, increased M2 anti-inflammatory polarization, and improved TBI neurobehavioral outcome [136]. Modulation of endocannabinoid degradative enzymes (*e.g.*, monoacylglycerol lipase, fatty acid amide hydrolase), receptors (CBR-1 and CBR-2) and their ligands (*N*-arachidonoylethanolamide and 2-arachidonyl glycerol) have been effective on the intracellular response to TBI (*e.g.*, modulating apoptosis, excitotoxicity, neuroinflammation, cell structure and remodelling) [137]. A phase III trial focused on the efficacy and safety of dexanabinol in TBI patients, suggested that this cannabinoid does not modify either TBI outcome or the control of intracranial pressure [138]. Dexanabinol is a synthetic cannabinoid analog, with pleiotropic properties. In experimental models, dexanabinol decreased oxygen reactive species, and improved ICP and CPP control [138, 139]. In an international multicenter analysis on 861 patients with severe TBI, researchers investigated the effect of a single intravenous dose of dexanabinol within 6 hours of injury, showing that there was no significant reduction of ICP or worsened clinical outcome. In summary, available evidence does not suggest cannabinoids use in clinical practice for TBI patients, although experimental studies seemed promising.

Statins are medications generally employed for treating hypercholesterolemia. Recently, anti-depressant and neuroprotectant effects of statins have been supposed. Immunomodulatory and anti-inflammatory properties of statins were demonstrated in the experimental murine model. An experimental study on anesthetized TBI rats demonstrated that statins can attenuate TBI by reducing neuronal apoptosis microglia, and tumor necrosis factor (TNF)-α expression, thereby resulting in a reduction of depressive-like symptoms [140]. These results were confirmed by another study on rats, which demonstrated that simvastatin is able to reduce inflammation and provide significant protection against cognitive dysfunction in the acute phase after TBI, while no improvement was detected after 4 days [141]. The administration of Atorvastatin modulates neuroinflammation processes

via altering peripheral leukocyte invasion and the alternative polarization of microglia/macrophages. Significantly increase the proportion of regulatory T cells (Tregs) in brain, and main effector cytokines IL-10 and transforming growth factor (TGF)-β1 [142]. In the clinical setting, the use of statins before TBI was associated with improved outcomes. Although both experimental and clinical studies agreed on the utility of statins to improve outcomes, these findings need further investigations to be confirmed, especially in the clinical setting [143].

Metformin is an oral hypoglycemic drug with pleiotropic neuroprotective effects due to its anti-inflammatory, antioxidative, and anti-ischemic activity, which may also improve vascular and endothelial function [144]. In a rat model, metformin improved neurological deficits and neuronal apoptosis and reduced cerebral edema. Moreover, it inhibited microglial activation, thus reducing pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6. At the nuclear level, metformin inhibited the translocation into the cellular nucleus of nuclear factor (NF)-κB p65 and the phosphorylation of ERK1/2 and p38-MAPK, suggesting that its efficacy on TBI is related to both inflammatory modulation and specific intracellular pathways activation [145]. A randomized controlled trial on 30 trauma patients demonstrated that metformin administration significantly reduces S100b and neutrophil to lymphocyte ratio [144].

Serp-1 is a secreted glycoprotein, a *serine* proteinase *in*hibiter, that targets both thrombotic and thrombolytic pathways. Serp-1 inhibits tissutal- and urokinase-type plasminogen activators, plasmin, factor Xa, and thrombin with high anti-inflammatory properties [146]. Serp-1 blocked early activation and infiltration of monocytes/macrophages and T--cells in a wide range of animal models of vascular inflammation and trauma. Moreover, Serp-1 significantly reduced intimal inflammation and cluster differentiation (CD)11b+ cell infiltrates in arteries after implant. Serp-1 reduced Th (Thelper)1, Th17, and Treg in splenocytes and vascular inflammatory lesions, with IL-1β reduction [147]. Serp-1 is also able to bind the urokinase receptor and filamin-B, an actin-binding protein, in monocytes, therefore increasing IL-10 in other models of inflammatory vasculitis. The neuroprotective activity of Serp-1 by early inhibition of the inflammatory cascade in spinal injury is promising for anti-inflammatory treatment in TBI patients.

Platonin presents interesting antioxidant activity. Platonin is a cyanine photosensitizing dye with previously described antimicrobial and antihistaminic activities [148]. Platonin reduces the production of pyrogenic cytokines from peripheral mononuclear cells and activates the immunomodulator properties of macrophages. Platonin shows neuroprotective antiapoptotic properties by reducing caspase-3 activation and caspase-3 mRNA expression. In addition, platonin downregulates ROS production and, importantly, elevates hemeoxygenase-1 (HO-1)-mRNA expression, which finally reduces the lesion volume after TBI [149]. Additionally, the supplementation with branched-chain amino acids such as nitrogen, leucine, isoleucine, valine and arginine in TBI patients improved recovery from a vegetative or minimally conscious state by the reduction of oxidative stress and the enhancement of iron metabolism [150].

4.4. Anti-hypertensive Drugs, Inotropes and Vasopressors: Targeting Cerebral Autoregulation

Beta-blockers have been tested in pigs demonstrating protection of cerebral autoregulation and reduced hippocampal neuronal death by inhibiting IL-6 release after TBI [151]. A recent meta-analysis investigated the efficacy of beta-blockers on outcome in 2005 TBI patients and 6240 controls extracted from 9 observational studies. Reduced in-hospital mortality was shown in the TBI group treated with beta-blockers (Odds Ratio 0.39, 95%CI 0.27-0.56; $p<0.00001$), although the quality of evidence was very low [152]. In summary, beta-blockers administration could be useful for maintaining cerebral autoregulation and improving neurological outcomes after TBI, although further studies are needed to confirm this hypothesis.

Catecholamines are frequently employed in critically ill patients for maintaining hemodynamic stability. Norepinephrine showed protective effects on cerebral autoregulation and prevented hippocampal necrosis in an experimental model of TBI [153]. Likewise, dopamine protected cerebral autoregulation and prevented hippocampal necrosis after TBI *via* ERK-MAPK pathway [154]. This suggests that drugs, which act on catecholamines levels in the brain (*e.g.*, antidepressants, bupropion and so on) can also modulate cerebral autoregulation. The potential role of dopamine was recently investigated both in clinical and pre-clinical studies. It can act as protecting cerebral autoregulation [155]. Catecholamines seem to be also involved in the control of the Arousal system, since the induction of sleep and sedative states with the use of α2 receptor agonist (*e.g.* dexmedetomidine) and $GABA_A$ allosteric modulators (such as zolpidem) seems to involve histamine and noradrenergic systems commonly involved in Arousal [156].

4.5. Novel Synthetic and Natural Compounds for TBI: Targeting Antioxidant Properties

Researchers all over the world have investigated the role of substances with antioxidants properties as novel therapeutic agents to decrease oxidative stress and to slow the cellular damage caused by reactive products. Antioxidants may target the production of reactive species of oxygen in mitochondria or act by nicotinamide adenine dinucleotide phosphate inhibitors. Both mechanisms may potentially decrease secondary injury and improve clinical outcomes [157]. Several substances often of natural origin show antioxidant effects. Their antioxidant mechanisms are associated with the impact on mitochondria's pathways and enzymes. However, it is worth mentioning that during TBI, the BBB is damaged, explaining why endothelial targeted strategies against oxidative stress seem interesting. In fact, the use of endothelial targeted antioxidant enzymes, with conjugates of the antioxidant enzyme catalase, linked to anti-ICAM-1 antibodies, may be in the future one of the novel treatments to improve

neurological outcomes in TBI. In fact, a recent study demonstrated that anti-PECAM-1/SOD provided anti-inflammatory effects [158]. Therefore, the use of substances with antioxidant properties may slow the destruction processes in the brain and affect the final result or the occurrence of complications. There is growing evidence that neuroinflammation and oxidative stress importantly contribute to neurological deficits and posttraumatic epileptogenesis, except for cytotoxicity, neuronal and glial damages [159]. Importantly, 1/3 of epileptic patients after brain trauma show uncontrolled seizures. Therefore, the use of inhibitors of ROS-generating enzymes may be implemented to alter the vicious circle of oxidative stress and cytotoxicity. As mentioned above, the administration of antioxidants intensifies the activities of endogenous antioxidant enzymes or inhibits the various prooxidant enzymes, finally leading to ROS reduction. The NADPH-oxidases (NOXs) are a family of enzymes that plays an important role in redox signaling and initiating immunity. NOX upregulation is observed in post-TBI brain and resulted in brain injury, ischemia/re-perfusion, epilepsy and a huge variety of pathological conditions [160]. Inhibition of NOX2 activity after TBI attenuated injury-induced increases of markers of astroglial and microglial activation, decrease neuronal loss in the neocortex and hippocampus, and improve functional recovery [161]. Eastman *et al.* concluded that nitric oxide synthases (NOS) inhibitor affect both inflammation and epileptogenesis after brain injury and may improve outcomes after TBI. Moreover, Hall *et al.* documented the preclinical efficacy of antioxidant agents in the inhibition of reactive species that induced lipid peroxidation and protein damage. It is worth noting that there are growing numbers of substances with natural antioxidant properties. The available literature is increasing the number of experimental studies relating to the efficacy of these substances in TBI. The pro-oxidant mechanism following TBI is represented in Fig. (**4**).

4.5.1. Synthetic Compounds

The administration of anti-intracellular adhesion molecule (ICAM)-1/catalase interferes with the oxidative stress response to TBI, and thus decreases cerebral hydrogen peroxide production, markers of protein nitrosylation, finally preserving or protecting BBB integrity [162]. Researchers interested in antibodies as targeted for antioxidant enzyme therapy speculated that these may optimize the treatment strategies in the therapeutic window for intervention. Specific, by using endothelial endosomes that markedly enhance the protective effect of antioxidant enzymes.

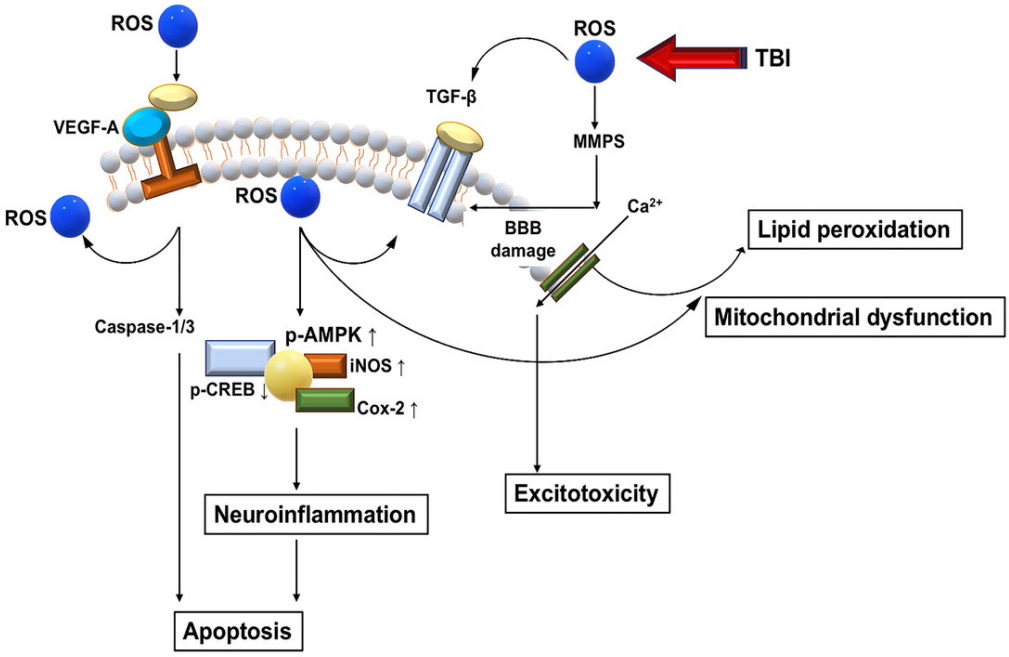

Fig. (4). Pro-oxidant mechanisms after TBI. Pro-oxidant mechanisms after TBI include the liberation of reactive products of oxygen (ROS), nitric oxide (NO), prostaglandin-E2 (PGE2). Changes in expression of the tight junctions are accompanied with up-regulation of matrix metalloproteases (MMPs), involved in BBB alteration, while increasing the expression of transforming growth factor-β (TGF-β), and vascular endothelial growth factor-A (VEGF-A). After TBI, levels of adenosine monophosphate-activated protein kinase (pAMPK), inducible nitric oxide synthases (iNOS) and cyclooxygenase (COX-2) synthasis are increased, while cAMP response element binding protein (pCREB) is decreased. Moreover, caspase 1-3 expression is increased leading to neuronal apoptosis and neuroinflammation. Other mechanisms include the increase of intracellular Calcium (Ca^{2+}) that hyperactivates excitotoxicity, lipid peroxidation and mitochondrial dysfunction. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Likewise, ethanolamine derivative, which is a new diethylethanolamine-derivate with a neuroprotective effect, in a recent rat model increased overall motor activity and decreased the impairment of motor coordination function [163]. In daily practice, TBI patients are often treated with drugs that contain the ethanolamine structure and possess neuroprotective and nootropic effects. Drugs as deanol aceglumate, choline alfoscerate, and citicoline normalized cholinergic transmission in the central nervous system, importantly decrease inflammation and oxidative stress and stimulate neurogenesis and angiogenesis [164, 165].

Succinate is a synthetic compound of natural origin. Succinate therapy, by using micro-dialysis, supports the mitochondrial energetic metabolism by lowering lactate/pyruvate ratio, increases PCr/γATP ratio, and the translocation to better energetics. Succinate enhances brain NADH/NAD+ redox state, which intensify glucose utilization, leading to the increase of pyruvate and moving glutamate into the mitochondria [166].

Neuroprotective mechanisms after brain trauma have also been demonstrated by other substances acting *via* different mechanisms. Among that, salubrinal (selective phosphatase inhibitor of p-eIF2α), Dl-3n-butylphthalide, N-acetyl-seryl-aspartyl-lysyl-proline, larixyl acetate, and succinate could be included. Salubrinal reduces the stress of endoplasmic reticulum, autophagy and apoptosis by decreasing the number of C/EBP-homologous-protein $(CHOP)^+$/$TUNEL^+$ and $CHOP^+$/$LC3^+$ cells [167]. Dl-3n-butylphthalide has anti-inflammatory, anti-oxidative, and mitochondrion-protective functions [168], improving the expression of tight junction proteins and inhibiting mitochondrial apoptosis by suppressing the expressions of autophagy related-7, Beclin1 and LC3II. The N-acetyl-seryl-aspartyl-lysyl-proline is a peptidic fragment of Thymosin-β4, which suppresses the TGF-β1/NF-kB-signaling pathway and upregulates sensorimotor functional recovery probably by reducing the volume of cortical lesions, and the loss of hippocampal neuronal cells [169]. It also reduces fibrin accumulation and improves angiogenesis and neurogenesis. Larixyl acetate is an inhibitor of transient-receptor-potential-channel-6 with protective effects against systemic endothelial dysfunction after TBI [170]. Recent data suggest that larixyl acetate can reduce systemic vascular damage and acute hypoxia-induced vasoconstriction [171].

The use of recombinant Wnt3a, activator of Wnt/β--catenin pathway, promotes neuroprotection and neural regeneration following TBI. Intranasal administration of Wnt3a activator suppresses autophagic activity in neurons and markers as light chain 3II, Beclin-1. The Wnt3a experimental treatment reduced caspase-3, matrix metalloproteinase 9 (MMP-9) markers and apoptosis. Longer duration of treatment with Wnt3a, induced higher levels of β-catenin, glial-derived growth factors and vascular endothelial growth factor. Wnt3a finally improved neurogenesis and angiogenesis [172] and promoted neuronal regeneration as axonal regeneration of cortical neurons [173].

Omeprazole is a synthetic compound that is well known for its efficacy on acid reflux, acting as a proton pump inhibitor. Patients with TBI are at higher risk of stress ulcers (Cushing's ulcers), associated with higher levels of plasma cortisol [174]. Besides, recent experimental studies evidenced that a protective effect of omeprazole in TBI is represented by its anti-oxidant and anti-apoptotic properties [175]. Significant reduction of malondialdehyde levels and activity of caspase-3 after omeprazole administration was found.

4.5.2. Natural Compounds

The Na+/K+-ATPase, together with oxidative stress, plays an important role in secondary brain damage. Importantly, Na+/K+-ATPase is responsible for controlling ion gradients across plasma membranes. It is also one of the main consumers of ATP in neurons [176]. TTHL is a natural plant-derived compound isolated from Combretum leprosum Mart, *Combretaceae*, that inhibits Na+/K+-ATPase. TTHL reduces pain signaling by glutamatergic, opioid and serotonergic systems. It activates Gi/o protein and opens specific K+ channels. It possesses an anti-convulsant effect. The protective effect of TTHL is presented by the induction of glutamatergic maintenance, possibly by the interaction with NMDA and the inhibition of protein kinase-C-mediated phosphorylation of the Na+/K+-ATPase-α1 subunit [177].

Guanosine, an endogenous neuroprotective nucleoside, also protects again neuronal damage, inflammatory response and brain edema by impacting glutamate uptake, Na+/K+-ATPase and glutamine synthetase activity [178]. Of note, potassium aspartate treatment attenuates brain edema and ameliorates BBB integrity. It also reduces ATP loss and increases the activity of Na+/K+-ATPase [179]. Disproportion between mitochondrial fusion and fission is associated with neurodegeneration by dysregulating the production of energy. Particularly, mitochondrial fission is related to the post-TBI destruction of the central nervous system. This process is modulated by dynamin-related protein-1 [180]. In experimental data, the administration of Mdivi-1, a selective inhibitor of Dynamin-related protein-1, provides the reduction of H_2O_2-induced mitochondrial membrane potential dissipation. Midivi-1 reduces the volume of cortical lesions and the blood-brain barrier permeability. Therefore, the inhibition of caspase-3 suppresses oxidative stress and finally provides brain protection and improves behavioral functions [181, 182].

Resveratrol is one of the natural compounds extracted from fruits, which shows antioxidative, antiapoptotic, anti-inflammatory and neuroprotective mechanisms. Resveratrol is also a mediator for regulating the activation of p38/MAPK-signaling [183]. Among antioxidants of natural origin, some vitamins, such as vitamin E and vitamin C, cannaboids, amino acids, N-acetylcysteine and enzogenol, also exhibit antioxidant properties. In a review, Shen *et al.* summarized that the clinical antioxidants use to improve outcomes after TBI, improve recovery and cognitive function, stabilize edema and decrease mortality [184]. A high dose of vitamin C reduces the progression of perilesional edema. In addition, vitamin E importantly decreases mortality rate and improves functional outcomes [185].

Xanthohumol has been shown to limit the size of cerebral injury in a model of stroke in the rat [186]. It is a flavonoid extracted from the flower of hops, a beer additive with potent anti-inflammatory activity demonstrated in a variety of animal models [187-190]; and its administration in high doses resulted in no toxic effect in rodents [191, 192], indicating it as a promising neuroprotectant for TBI.

Baicalin is a 7-D-Glucuronic acid-5,6-dihydroxyflavone, bioactive flavone isolated from the radix of *Scutellaria baicalensis*. In an animal model of TBI, Baicalin administration notably ameliorated neurobehavioral function, reduced brain edema, and apoptosis. Baicalin activated antioxidative enzymes and presented this neuroprotective effect *via* activating the Akt/Nrf2 pathway [193].

N-acetylcysteine is the precursor of the antioxidant glutathione, which possesses neuroprotective effects and anti-inflammatory properties [184], but antioxidants properties also derived by ursolic acid [194] that is a pentacyclic triterpene, which is found in common herbs and plants. Ursolic acid presents a neuroprotective effect in TBI, reducing brain edema and neurological insufficiencies by activating the Nrf2 pathway, increasing the expression of NQO1 and HO-1 and incrementing the levels of protein kinase B [195].

Huperzine-A is a natural alkaloid isolated from the Chinese herb Huperzia serrata, which inhibits acetylcholinesterase, thereby increasing synaptic acetylcholine levels [196]. In experimental data, huperzine-A reduced lipid peroxidation and increased the activity of endogenous antioxidant enzymes [197].

Moreover, an interesting effect was showed by kaempferol, a stimulator of the mitochondrial Ca^{2+}-uniporter channel. Chitturi *et al.* documented protective effects within the first 72 hours after TBI by a decreased level of pyruvate and tricarboxylic acid cycle flux and higher levels of N-acetyl aspartate. Therefore, kaempferol improved mitochondrial functional integrity and neural viability [198, 199].

The superoxide radical scavenger polyethylene glycol--conjugated superoxide dismutase (PEG-SOD) and the 21-aminosteroid lipid peroxidation inhibitor tirilazad were evaluated in phase III trials in brain-injured patients. The results did not show an improvement in 6-month survival and neurological recovery. Besides, tirilazad, in a post-hoc analysis, significantly improved the survival of male patients with traumatic subarachnoid hemorrhage.

Citicoline acts by stimulating phospholipase-A2 and decreasing hydroxyl radical generation after cerebral ischemia [200]. Besides, a large number of compounds with neuroprotective effects are of natural origin. The properties of these natural agents are mainly based on their anti-inflammatory and antioxidant activities, that act *via* different pathways in TBI.

Hydrogen gas or water (H_2) was adopted in rats' models for protecting against the pro-oxidant activity. Inhalation of H_2 or *via* intraperitoneal injection in rats improved neurological outcomes after TBI by regulating the oxidative cascade. Moreover, H_2 was able to reduce the level of miR-21 expression by intraventricular infusion, while upregulation of miR-21 was noted in the traumatic foci. H_2 treatment improved BBB integrity, brain edema, and neurological performance in rats [201-204]. Other natural compounds and their effects are reported in Table **2** [205-231].

4.6. Future Directions

Mesenchymal stromal cells (MSCs) may be considered a promising strategy for TBI treatment, due to their plastic properties but mainly due to their paracrine effects [232]. So far, since pre-clinical studies showed promising anti-inflammatory, anti-oxidative and neuroregenerative properties, clinical studies with MSCs should be considered for the treatment and repair of neuronal cells in TBI patients. In recent data, MSCs stimulate the secretion of bioactive factors, including cytokines, small molecules, and cargo-bearing exosomes [232]. Early infusion of MSCs improves functional and structural outcomes [233]. In addition, animals study presented that MSCs infusion leads to the release of growth factors and stimulates endogenous neurogenesis with proliferation, especially in subventricular and sub-granular zones [234]. The therapeutic effect of MSCs depends on dose, route and therapeutic window. Recent data documented that migration of MSC depends on specific crosstalk with injured brain tissue (*e.g.*, *via* stromal-derived factor-1, a chemokine) expressed in astrocytes, neurons and endothelial cells and C-X-C chemokine receptor4 (receptor of stromal-derived factor-1 expressed on MSCs) [235]. Importantly, MSCs decrease the apoptosis of astrocytes in the ischemic boundary zone [236]. In experimental models of stroke, MSCs induced post-ischemia astrocytes proliferation. Gao *et al.* documented that these processes may involve "activation of mitogen-activated protein kinase/extracellular signal-regulated kinase and phosphoinositide 3-kinase/threonine-protein kinase pathways" [237]. In an experimental TBI model of rats, at 24 hours after TBI, MSCs with hypertonic glycerol (25%) or mannitol (25%) were administered *via* the right internal carotid artery. The administration of mannitol resulted in increased BBB disruption, although the rats treated with mannitol showed improved motor function. Since the administration of mannitol caused more BBB disruption, MSCs passed more in the injured brain tissue than in the glycerol or phosphate-buffered saline groups, enhancing the possible role of MSCs as a new frontier for the treatment of TBI [238]. Thus, concluding that MSCs administration elicits upregulation of brain-derived neurotrophic factor, vascular endothelial growth factor and basic fibroblast growth factor. Recent data suggested that the administration of human mesenchymal stem cell-derived exosomes improves BBB integrity. Exosome-treated animals presented significantly smaller lesion size, decreased ICP, and increased CPP. It also decreased albumin extravasation and higher levels of laminin, claudin-5 and ZO-1 [239].

Table 2. Other natural agents tested for the treatment of TBI.

Substance	Class	Properties	Effect in TBI	References
Sinomenine (7,8-didehydro-4-hydroxy3,7-dimethoxy-17-methyl-9a,13a, 14a-morphinan-6-one)	Active alkaloid extracted from the plant *Sinomenium acutum*	-antiallergenic, -anti-inflammatory -cytoprotective -neuroprotective effects in cerebral ischemia, intracerebral hemorrhage, and neurodegenerative diseases	-decrease brain water content -decrease apoptosis in brain tissue -alleviate oxidative stress -suppress the apoptotic pathway (via the inhibition of Bax translocation and Cyt c release from the mitochondria)	[205-207]
Breviscapine	Ingredient of flavonoid glycosides extracted from *Erigeron breviscapine*	-reduction of vascular resistance -improvement of microcirculation -inhibition of platelets aggregation -anti-apoptotic -synaptogenesis	-inhibit the GSK3β pathway to promote neurobehavioral function (reduction of motor disability by increased expression of phospho-Ser9-GSK3β and decreased expression of phosphor-Try216-GSK3β -enhance expression of synaptic marker synaptophysin (SYP) and weakened expression of pro-apoptotic caspase3 -improve neurobehavior function	[208-210]
Curcumin	Derived from *Curcuma longa* plants	-anti-apoptotic -antioxidative -antitumor -anti-inflammatory -anti-convulsive	-ameliorate brain water content, -reduce oxidative stress and apoptosis (elevated Bcl-2 content, increased the expression of heme-oxygenase 1 (HO1) and NAD(P)H: quinone oxidoreductase 1 (NQO1) *via* the activation of the Nrf2-ARE pathway) -improve neurological severity score -improve neurological function (effects by maintaining glutathione levels)	[211]
Gallic acid	Natural phenolic compound purified from a number of plants	-antioxidant -anti-inflammatory -anti-tyrosine	-decrease brain IL-1β, IL-6, TNF alpha 48 hr after TBI -improve memory and long-term potentiation indexes	[212, 213]
Formononetin	Plant-isolated compound	-anti-tumor -anti-inflammatory -anti-dyslipidemia	-induce neuronal IL10 expression	[214-217]
Isoliquiritigenin	Natural flavonoid with a chalcone structure	-anti-tumor -antioxidative -anti-diabetic potential	-reduce inflammatory (via prevent macrophage activation and suppress NF-κB activation) -prevent neurofunctional deficits -decrease water content in brain -maintain the integrity of the BBB (upregulation of TJs and AJs by suppressing the PI3K/AKT/GSK-3β signaling pathway)	[218-220]
Quercetin	Natural aglycone flavonoid occurring in fruits and vegetables, including apples, red onions and berries	-anti-inflammatory -antiproliferative -anti-atherosclerotic -antioxidative	-alleviate cerebral edema -decrease neuronal degeneration -reduce oxidative stress in the mitochondria -improve motor function -attenuate o neuronal apoptosis (via inhibition of extracellular signal-regulated kinase 1/2 phosphorylation and activated Akt serine/threonine-protein kinase phosphorylation)	[221-224]
Icariin	Natural agent from *Epimedii herba*	-neuroprotective -neuroplastic	-upregulate the brain-derived neurotrophic factor, synaptophysin and postsynaptic density protein 95 expressions.	[225]
Creatine	Naturally occurring guanidino compound consumed in diets containing fresh meat and fish	-antioxidative	-delay creatine supplementation: -reduce EEG and behavior seizures -exhibit a sustained effect on seizures after TBI -reduce brain excitability post-TBI by restoring the impaired GABAergic function.	[226, 227]
Tetrahydrocurcumin	Derived from curcumin by hydrogenation, with phenolic and β-diketone moieties as curcumin	-antioxidant -anti-apoptotic	-alleviate ischemia-reperfusion injury and autophagy -improve neurological function -decrease cerebral edema -decrease neuronal degeneration (via promoted the expression of Nrf2 and downregulation of expression of Bcl-2, Bax)	[228-231]

TBI, traumatic brain injury; GABA, Gamma-amino butyric acid; BBB, blood-brain-barrier; SYP, synaptophisin; EEG, electroencephalogram.

CONCLUSION

The molecular mechanisms involved in secondary brain injury can result as a potential target for the early and late treatment of TBI. Moreover, the administration of drugs, which act on specific pathways involved in the destructive processes after TBI, even if usually employed for the treatment of other diseases, can show potential benefits. However, these therapies remain limited to pre-clinical evidences, and only a few of them have been investigated in clinical trials. Moreover, mesenchymal stromal cells seem very promising for the treatment of TBI in the next future.

LIST OF ABBREVIATIONS

AMPA	=	α-amino-3-hydroxy-5-methyl-4-isoxazole Propionate
ATP	=	Adenosin-triphosphate
Bax	=	Bcl2-associated-X-protein
BBB	=	Blood Brain-barrier
BDNF	=	Brain-derived Neurotrophic Factor
CBR	=	Cannabinoid Receptors
CBF	=	Cerebral Blood Flow
CCR5	=	C-C Chemokine Receptor5
CD	=	Cluster Differentiation
CI	=	Confidence Interval
CHOP	=	C/EBP-homologous-protein
CPP	=	Cerebral Perfusion Pressure
E_2-SO_4	=	Estrogen Sulphate
EE-3-SO_4	=	17α-ethinylestradiol-3-sulfate
GABA	=	Gamma-amino Butyric Acid
GCS	=	Glasgow Coma Scale
HICP	=	Intracranial Hypertension
HIV	=	Human-immunodeficiency Virus
H_2O_2	=	hydrogen Peroxide
HO-1	=	Hemeoxygenase-1
ICAM-1	=	Intracellular Adhesion Molecule
ICP	=	Intracranial Pressure
IGF	=	Insulin-like Growth Factor
IL	=	Interleukin
LOC	=	Level of Consciusness
MAPK	=	Mitogen-activated Protein-kinase
MAPK/MEK1-2	=	Mitogen-activated Protein-kinase-threonine/tyrosine Kinases
MMP9	=	Metalloproteinase-9
MSC	=	Mesenchymal Stromal Cells
NF-kB,	=	Nuclear factor kappa B
NMDA	=	N-methyl-d-aspartate
NOXs	=	NADPH Oxidase
NOS	=	Nitric Oxide Synthases
NT	=	Neurotrophin
O_2^-	=	Superoxide
OH^-	=	Hydroxyl Radical
PDE4D	=	Phosphodiesterase-4
PTA	=	Post-traumatic Amnesia
PEG-SOD	=	Polyethylene Glycol-conjugated Superoxide Dismutase
PhenT	=	Phenserine Tartrate
PI3K/Akt	=	Pathways-phosphatidyl-inositol 3-kinase/protein Kinase B
RAGE	=	Receptor for Advanced Glycation End-products
Rho	=	Ras Homolog Family Member
ROS	=	Reactive Products of Oxygen
RR	=	Relative Risk
TBI	=	Traumatic Brain Injury
TGF	=	Transforming Growth Factor
Th	=	T Helper Cells
TLR	=	Toll-like Receptor
TNF	=	Tumor Necrosis Factor
Treg	=	T Regulatory Cells
ZO-1	=	Zonula Occludens-1
3,6′-DT	=	Thalidomide Analog -3,6′-dithiothalidomide

AUTHORS' CONTRIBUTION

DB, conceptualization, writing - review & editing; DSG, writing - review & editing; WD, writing – review & editing; FFC, conceptualization, supervision; PLS, conceptualization, supervision; IB, conceptualization, supervision; NP, conceptualization, supervision; PRMR, conceptualization, supervision; PP, conceptualization, supervision; CR, conceptualization, supervision, project administration. All authors participated in the conception and design of the study, revising it critically for important intellectual content, and final approval of the version submitted.

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