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Review

Mitochondrial-targeted therapies in traumatic brain injury: From bench to bedside

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ABSTRACT

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality worldwide, with limited effective therapeutic options currently available. Recent research has highlighted the pivotal role of mitochondrial dysfunction in the pathophysiology of TBI, making mitochondria an attractive target for therapeutic intervention. This review comprehensively examines advancements in mitochondrial-targeted therapies for TBI, bridging the gap from basic research to clinical applications. We discuss the underlying mechanisms of mitochondrial damage in TBI, including oxidative stress, impaired bioenergetics, mitochondrial dynamics, and apoptotic pathways. Furthermore, we highlight the complex interplay between mitochondrial dysfunction, inflammation, and blood-brain barrier (BBB) integrity, elucidating how these interactions exacerbate injury and impede recovery. We also evaluate various preclinical studies exploring pharmacological agents, gene therapy, and novel drug delivery systems designed to protect and restore mitochondrial function. Clinical trials and their outcomes are assessed to evaluate the translational potential of mitochondrial-targeted therapies in TBI. By integrating findings from bench to bedside, this review emphasizes promising therapeutic avenues and addresses remaining challenges. It also provides guidance for future research to pave the way for innovative treatments that improve patient outcomes in TBI.

Introduction

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality among children and young adults, typically resulting from a bump, blow, or jolt to the head, or a penetrating injury that disrupts normal brain function [1]. TBI is a significant public health challenge, affecting 50–60 million people globally and costing the world economy around $400 billion annually [2], approximately 0.5 % of the gross world product. Each year, there are 27.16 million new TBI cases and 7.08 million years lived with disability [3]. In the United States alone, about 1.7 million individuals suffer from TBI annually, with adolescents aged 15 to 19 and adults aged 65 and older being the most susceptible [4]. TBI is a complex disorder characterized by various injury mechanisms, such as extrinsic compression from mass lesions, contusions, and diffuse axonal injury (DAI). Additionally, neuronal injury in TBI can result from mechanisms like ischemia, apoptosis, mitochondrial dysfunction, cortical spreading depression (CSD), and microvascular thrombosis, all of which contribute to diverse clinical presentations [5]. Clinically, TBI severity is often categorized by using the post-resuscitation Glasgow Coma Scale (GCS) scores into mild [14,15], moderate [9–13], and severe [3–6,6,7,7,8]. Severe TBI has mortality rates of 30–40 % and can cause significant physical, psychosocial, and social deficits in up to 60 % of cases [7,8]. Despite promising results from preclinical studies for TBI treatment, only a few treatments have proven effective in clinical settings. This may reflect the heterogeneous nature of TBI and/or an incomplete understanding of the mechanisms underlying secondary neuronal loss.

Over the past few decades, significant progress has been made in understanding the pathophysiological mechanisms of TBI, including primary injury from direct biomechanical forces and secondary injury that contributes to brain damage and death [9]. In response to the primary injury, two critically important cellular events occur: the depletion of energy and the disruption of calcium homeostasis. The first event involves an “ischemia-like” pattern characterized by direct tissue damage and impaired cerebral blood flow and metabolism, leading to ATP

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depletion and failure of energy-dependent ion pumps [9]. The second event involves nerve terminal membrane depolarization, excessive release of excitatory neurotransmitters (e.g., glutamate, aspartate), and activation of NMDA, AMPA, and voltage-dependent calcium and sodium channels. This causes further release of calcium from intracellular stores, resulting in high levels of free intracellular and mitochondrial calcium. This consecutive calcium overload initiates catabolic processes that involve the overproduction of free radicals, activation of cell death pathways, and increased inflammatory mediators, ultimately leading to cell membrane degradation and cell death [10]. Hence, mitochondria, often referred to as the 'ATP powerhouse of the cell', are responsible for an early and critical event and play a pivotal role in the secondary insult of TBI.

Mitochondria are crucial for cell survival and development by producing ATP through oxidative phosphorylation, which is essential for numerous cellular processes [11]. However, mitochondrial dysfunction can significantly impact these cellular functions and lead to various detrimental effects. Damage to mitochondria can result in the increased production of reactive oxygen species (ROS), decreased cellular energy production, and impaired respiration. These changes can trigger apoptosis and contribute to the neuronal loss and impaired neurological functions that are frequently observed in TBI patients [12]. In this comprehensive review, we first examine the various aspects of mitochondrial dysfunction in TBI, exploring its underlying mechanisms and consequences. We then discuss a range of potential therapeutic strategies for mitochondrial dysfunction in TBI that have been investigated in preclinical studies, as well as current therapeutic approaches used in clinical practice. Additionally, we discuss advanced techniques for mitochondrial-targeted therapies as a new avenue for TBI treatment. These techniques include mitochondrial transplantation and mitochondrial-targeted drug delivery systems using nanoparticles, which hold promise for improving outcomes in TBI patients by specifically targeting and restoring mitochondrial function.

Mitochondrial Dysfunction and Oxidative Stress in TBI

Oxidative stress is a key player in the pathophysiology of TBI, occurring when the production of oxygen-derived free radicals surpasses the body's antioxidant defenses [13]. These free radicals such as hydrogen peroxide (H_2O_2), hydroxyl radicals (OH^-), superoxide anions (O_2^-), and peroxyl radicals (ROO^-), can cause severe damage to cellular components [13]. The brain is more prone to oxidative damage due to its high demand for oxidative metabolic activity and limited antioxidant defenses [14]. In the context of TBI, brain levels of O_2^- increase significantly within 60 min to 24 h post-injury [15,16]. Oxidative stress in TBI is closely related to mitochondrial dysfunction, aggravating cellular damage and impairing energy metabolism.

Mitochondria, in particular, are both sources and targets of free-radical oxidation. Their lack of protective histone makes mitochondrial DNA highly vulnerable to damage, resulting in a mutation rate estimated to be 10 to 20 times higher than that of nuclear DNA. This vulnerability leads to bioenergetic deficits characterized by reduced ATP production and increased free radical generation [17]. In TBI, several pathways contribute to the production of ROS, such as the arachidonic acid cascade, mitochondrial leakage, catecholamine oxidation, and neutrophil activity [18,19]. The severity of TBI is directly related to the degree of ROS-induced tissue damage and mitochondrial dysfunction [20,21]. A significant contributor to this oxidative damage is NADPH oxidases (Nox), a group of enzymes specialized in generating ROS. Preclinical studies have extensively examined the pathological effects of elevated Nox levels following TBI. For instance, elevated Nox post-TBI leads to higher ROS production, oxidative damage, larger lesion volumes, and persistent cell death observed up to a year post-injury [22,23], particularly evident in older mice [24]. Among the various Nox isoforms expressed in the brain—Nox1, Nox2, Nox3, and Nox4 [25]. These isoforms are expressed across different brain regions, including the forebrain, midbrain, and hindbrain, and in cell types such as neurons, astrocytes, and microglia [25]. Nox2 is the most extensively studied in the context of neuroinflammation and oxidative stress following TBI [26]. Notably, Nox2 is primarily localized to neurons and microglia [27], where it is responsible for oxidative stress [28] and microglial activation [29] post-injury. In addition to Nox2, emerging evidence emphasized on the role of Nox4 in TBI-induced oxidative stress. While predominantly expressed in astrocytes, Nox4 is also found in neurons [30]. Neurons are vulnerable in TBI, where Nox2 and Nox4 upregulation contributes to oxidative stress and neurodegeneration. Nox2 in neurons is upregulated following TBI and generates superoxide in response to injury-induced stimuli such as cytokines, excitotoxicity, or calcium influx [31]. This ROS production disrupts synaptic function, impairs neurotransmission, and exacerbates mitochondrial dysfunction, perpetuating a cycle of oxidative stress. Similarly, neuronal Nox4 is also upregulated post-TBI, which produces hydrogen peroxide (H_2O_2). This contributes to sustained oxidative damage to DNA, lipids, and proteins, leading to neuronal death and disruption of repair mechanisms [32,33].

Microglia, play a central role in amplifying oxidative stress. Activated microglia exhibit significant upregulation of Nox2 post-TBI, making them the primary contributors to Nox2-dependent ROS production [27]. This persistent activation, observed for months to years after the initial injury, drives chronic neuroinflammation, oxidative damage, and secondary brain injury [24,27,34,35]. Microglial activation exacerbates the neurotoxic environment, compounding the damage initiated by neurons. Astrocytes, typically neuroprotective, also contribute to oxidative stress in TBI, primarily through Nox4 upregulation. While predominantly expressed in astrocytes, Nox4-mediated ROS production impairs crucial astrocytic functions, such as maintaining the BBB and providing metabolic support to neurons [33]. This shift in astrocytic behavior exacerbates neuronal damage and disrupts the oxidative balance in the brain. Together, Nox2 and Nox4 mediate a dual-phase oxidative stress response in TBI: Nox2 drives acute ROS production, while Nox4 sustains prolonged oxidative damage. Although neurons, microglia, and astrocytes all contribute to ROS production, their roles vary in timing, mechanisms, and magnitude. Neurons are especially susceptible due to their high metabolic demands and mitochondrial dysfunction. In contrast, microglia amplify inflammation and oxidative stress, while astrocytes, under injury conditions, shift from neuroprotection to ROS production. These cell-specific contributions highlight the intricate interplay of oxidative stress mechanisms in TBI and their role in driving long-term neurodegeneration.

Repeated TBIs escalate oxidative stress, leading to ionic imbalances and the breakdown of cell membranes due to lipid peroxidation in various brain cells including neurons, glial cells, and vascular cells [36]. This process depletes energy reserves, enhances mitochondrial calcium influx, and exacerbates oxidative metabolism and glycolysis impairment. These disruptions collectively lead to lactate accumulation, acidosis, and edema [36,37]. Despite extensive research on TBI, current treatments do not completely eliminate its consequences. Therefore, therapeutic efforts focus on mitigating secondary injury and managing biochemical contributors. Given the crucial role of oxidative stress in TBI development, antioxidants are being explored as potential treatments.

Post-traumatic antioxidant therapy holds potential, employing agents that either directly scavenge reactive radicals or enhance the antioxidant defense system. The objective is to counteract ROS and RNS, protect neurons from oxidative damage, and facilitate recovery. While no FDA-approved antioxidant therapy is specifically designed for TBI, several antioxidant strategies have demonstrated promising results in preclinical studies, as summarized in Table 1 [28,38–101]. Direct antioxidants like vitamin E, vitamin C, and N-acetylcysteine (NAC) work by donating electrons to neutralize ROS and RNS [62,102,103]. Another approach involves enhancing the activity of intrinsic antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), with investigations underway into compounds that can increase their production. Given the central role of mitochondria in ROS production,

Table 1
Therapeutic approaches targeting antioxidant mechanisms in TBI.

Compound	TBI Model and specie	Dosage and administration	Main findings	References
Chrysin	Closed head weight-drop model; rat	25, 50 or 100 mg/kg; per oral (P.O)	Improved vestibulomotor function, recognition memory, and emotional behavior (depression and anxiety); modulated inflammation, reduced apoptotic index, and regulated Bcl-2 family protein expression.	[38]
Pycnogenol	Cortical contusions model; rat	100 mg/kg; i.p.	Elevated GSH, GPx, SOD, GR, and GST levels; reduced oxidative stress; preserved synaptic proteins.	[39]
Quercetin	Parietal contusion model; rat	30 mg/kg; i.p.	Reduced TUNEL- and ED-1-positive cells, BAX and cleaved caspase-3 proteins, proinflammatory cytokines; increased antioxidant enzyme activity (GSH-Px, SOD, CAT).	[40]
	Marmarou's weight-drop model; mice	50 mg/kg; i.p.	Reduced cerebral edema, apoptosis, and caspase-3 activity; alleviated oxidative stress through PGC-1α pathway mediation.	[41]
Resveratrol	Weight-drop model; rat	100 mg/kg; i.p. post-TBI	Decreased edema and oxidative stress; increased GSH levels; attenuated lesion volume.	[42]
	Feeney's weight drop model; rat	50, 100 mg/kg i.p. Post-TBI	Reduced neuronal loss in hippocampal CA1, CA3, and CA4 regions; ameliorated oxidative stress (reduced MDA, 8-OHdG; increased SOD, GSH-Px activity).	[43]
	Weight-drop model; rat	100 mg/kg i.p. 30 min pre-TBI	Reduced brain edema and serum neuron-specific enolase; ameliorated oxidative stress (increased SOD, GSH; reduced MDA); decreased NLRP3 mRNA/protein via enhanced SIRT1 expression; reduced IL-1β and IL-18 levels.	[44]
	Controlled Cortical Impact (CCI) model; rat	0.05 mg/kg and 0.1 mg/kg b.w.; 7-days post-TBI Oral	Improved cognitive deficits; reduced ROS production; increased total non-enzymatic antioxidant capacity; prevented apoptosis via activation of p38/Nrf2/HO-1 signaling.	[45]
	CCI model; mice	100 mg/kg; Subcutaneous Post-TBI	Reduced IL-6 and IL-12 levels in the cerebral cortex and hippocampus.	[46]
	CCI model; rat	100 mg/kg;	Protected astrocytes from glutamate-induced cytotoxicity; reduced autophagy and apoptosis.	[47]
	Thoracic blast exposure model; mice	25 mg/kg and 50 mg/kg; i.p. Pre-TBI	Improved cognitive and emotional behavior; reduced ROS and endoplasmic reticulum stress; ameliorated inflammation and apoptosis; enhanced Nrf2 signaling; reduced NF-κB and Keap1 activity.	[48]
Riboflavin (Vitamin B2)	Contusion injury model; rat	7.5 mg/kg; i.p.	Improved sensory, motor, and cognitive functions; reduced lesion volume, edema, and reactive astrocytes.	[49]
Nicotinamide	Contusion injury model; rat	500 mg/kg; i.p.	Improved motor and cognitive functions; reduced lesion volume and number of reactive astrocytes	[50]
	Contusion injury model; rat	50 mg/kg; i.p.	Improved sensory, motor and cognitive functions; reduced lesion volume	[51]
	CCI model; rat	50 mg/kg/day; s.c. pump	Improved somatosensory and motor functions; reduced lesion volume	[52]
	CCI model; rat	50 mg/kg plus 150 mg/kg/day; s.c. pump	Improved somatosensory, motor, and cognitive functions; reduced lesion volume and inhibited RAGE, JNK, and inflammatory mediators; regulated apoptotic markers (Bax, Caspase-3, Bcl-2).	[53]
	Stab wound cortical brain injury (SWI) model; mice	250 mg/kg; i.p.	Reversed synaptic protein loss; improved motor and cognitive outcomes.	[54]
α-tocopherol (Vitamin E)	Bilateral frontal cortex lesions model; rats	28.6 μg/day; s.c. pump	Improved spatial learning and memory	[55]
	Mild fluid percussion injury (FPI) model; rats	500 IU/kg; oral	Improved spatial learning and memory; reduced oxidative stress; restored BDNF, synapsin I, CREB, and CaMKII levels; increased SOD and Sir2.	[56]
	Repetitive concussive brain injury (RCBI); mice	2 IU/g; oral	Reduced lipid peroxidation; improved spatial learning and memory.	[57]
	Feeney's weight drop model; guinea pigs	100 mg/kg; i.p.	Suppressed lipid peroxidation	[58]
N-acetylcysteine (NAC)	FPI model; rat	50 mg/kg; i.p.	Reversed cognitive deficits.	[59]
	Closed head injury model; rats	150 mg/kg; i.p.	Increased antioxidant enzyme activities (SOD, GPx); decreased edema and oxidative stress.	[60]
	Cortical contusions model; rat	150 mg/kg; i.p.	Prevented NF-κB, IL-1β, TNF-α, and ICAM-1 expression; reduced brain edema, BBB permeability, and apoptosis.	[61]
	Blast exposure model; rat	500 mg/kg; i.p	Enhanced glutathione (GSH) production and preserved BBB integrity.	[62]
Minocycline plus NAC	Mild CCI model; rat	45 mg/kg Mino + 150 mg/kg NAC; i.p.	Protected oligodendrocytes and promoted M2 microglia.	[63]
Melatonin	Contusion model; mice	1.25 mg/kg; i.p.	Improved grip score.	[64]
	Contusion model; immature rat	5 or 20 mg/kg; i.p.	Reduced neuronal death; alleviated spatial memory deficits	[65]
	Contusion model; immature rat	5 mg/kg; i.p.	Reduced lipid peroxidation.	[66]
	Mild contusion model; rat	50 mg/kg; i.p.	Decreased edema; preserved the structures of neurons, glia, and the neuropil.	[67]
	Feeney's weight drop model modified by Marklund; rat	100 mg/kg; i.p	Reduced MDA, XO and NO levels; Increased GSH level	[68]
	Marmarou's weight drop model; rat	5 or 20 mg/kg; i.p.	Increased SOD and GPx activities; reduced BBB permeability and intracranial pressure.	[69]
	Closed head injury model; mice	5 mg/kg; i.p.	Increased the levels of low molecular weight antioxidants; prevented NF-κB and AP-1 activation	[70]
	Marmarou's weight drop model; rat	5 mg/kg; i.p.	Increased β-carotene, vitamin E and vitamin C.	[71]
	Marmarou's weight drop model; rat	5 mg/kg; i.p.		[72]

(*continued on next page*)

Table 1 (*continued*)

Compound	TBI Model and specie	Dosage and administration	Main findings	References
			Downregulated caspase-3 and caspase-9 expression; prevented mitochondrial membrane depolarization and increase intracellular free Ca^{2+} levels.	
	Marmarou's weight drop model; mice	10 mg/kg; i.p.	Stimulates antioxidant enzymes, reduces oxidative stress, Enhanced autophagy; suppressed mitochondrial apoptotic pathway.	[73]
	CCI model; rat	5 mg/kg; i.p.	Induced mitophagy via mTOR pathway; suppressed inflammation and mitochondrial apoptotic signaling.	[74]
	CCI model; rat	10 mg/kg; i.p.	Restored KCC2 cotransporter expression; activated BDNF/ERK pathway.	[75]
	Repetitive mild traumatic brain injury (rmTBI) model; mice	20 mg/kg	Reduced oxidative stress, neuroinflammation, apoptosis, and lesion volume; activated Nrf2, AMPK, and CREB signaling; ameliorated AD-like changes.	[76]
Estradiol	FPI model; rat	144 μg/kg; i.p.	Improved motor function; decreased mortality but worsened outcomes in females.	[77]
	FPI model; rat	5 mg/kg; i.v	Improved neuronal survival; reduced apoptosis and astrogliosis	[78]
	Marmarou's weight drop model; rat	33.3 μg/kg	Prevented brain edema and BBB disruption; Increased survival and hemodynamic function.	[79]
	Closed-head model; Yucatan swine	0.2 mL/kg; i.v.	Decreased neurological severity, brain infarction, and edema.	[80]
	CCI model; mice	10–80 μg/kg; i.p.	Reduced neurological deficits, brain infarction and edema; decreased neuronal apoptosis; improved spatial memory; attenuate NR2B reduction; reduced oxidative stress and limit activation of ERK1/2 pathway.	[81]
Estrogen	Marmarou's weight drop model; rat	1 mg/kg; i.p.	Decreased neurological severity, and improved ICP and CPP scores	[82]
Progesterone	Cortical contusion injury; rat	4 mg/kg; i.p. and s.c.	Reduced brain edema even after 24 h delayed	[83]
	Bilateral medial frontal cortex injuries; rat	4 mg/kg; i.p.	Inverse relationship between serum progesterone levels and brain edema	[84]
	Cortical contusion injury; rat	4 mg/kg; i.p. and i.v.	Improved spatial learning and memory; decreased neuronal degeneration.	[85]
	CCI model; rat	4, 8 or 16 mg/kg; i.p.	Reduced lesion volume and motor function deficit.	[86]
	Feeney's weight-drop model; rat	16 mg/kg; i.p. and s.c.	Reduced post-injury inflammatory response, brain edema and Evans blue dye extravasation; improved neurological scores	[87]
Dimethyl fumarate	CCI model; mice	80 mg/kg; oral	Improved neurological outcome; reduced brain tissue loss, increased GSH levels.	[88]
	Intracerebral hemorrhage model; mice	10 mg or 100 mg/kg; i.c.v.	Ameliorated inflammation; reduced BBB permeability and improved neurological outcomes by casein kinase 2 and Nrf2 signaling pathways.	[89]
	CCI model; mice	1, 10, and 30 mg/kg; oral	Reduced histological damage and behavioral impairments; increased Bcl-2 expression; upregulated the antioxidant Nrf2/Keap1 pathway, reduced oxidative stress; Regulated the NF-κB pathway; decreased inflammation by modulating neuronal nitric oxide synthase (nNOS), interleukin-1 (IL-1), tumor necrosis factor (TNF-α), cyclooxygenase-2 (COX-2), and myeloperoxidase activity; reduced IBA1 and GFAP expression.	[90]
Fisetin	weight-drop model; mice	25 or 50 or 75 mg/kg; i.p.	Improved neurological function; reduced edema, lesion volume and BBB disruption; increased antioxidant effect via Nrf2-ARE pathway	[91]
Fucoxanthin	weight-drop model; mice	50, 100 or 200 mg/kg; i.g. 0.01, 0.05 or 0.1 mmol/L; i.c.v.	Decreased neurological severity, brain infarction, and edema; increased GPx activity	[92]
Sulforaphane	CCI model; rat	5 mg/kg; i.p.	Alleviated cognitive deficits and oxidative damage.	[93]
Tertiary butylhydroquinone (TBHQ)	CCI model; rat	25 mg/kg; i.p.	Reduced lesion volume, astrocyte hyperactivation and improved spatial learning and memory.	[94]
Apocynin	CCI model; rat	50 mg/kg; i.p.	Reduced brain edema, neuronal autophagy, inflammatory signaling (TLR4, NF-κB, TNF-α, IL-1β) and improved behavioral function.	[95]
	Weight drop model; rat	100 mg/kg; i.p.	Reduced neuronal loss, oxidative stress, BBB disruption and microglial activation.	[96]
	Blast-induced TBI model; rat	5 mg/kg; i.p.	Reduced BBB leakage, microglial activation, and neuronal death; suppressed MMP-3 and MMP-9 expression.	[97]
	CCI model; mice	4 mg/kg; i.p.	Reduced neuronal apoptosis, amyloid-β levels, oxidative stress and microglial activation.	[28]
	Moderate lateral FLP injury (mLFPI) model; mice	5 mg/kg; s.c.	Improved memory function; reduced oxidative stress, inflammation, and lesion volume.	[98]
Alpha-lipoic acid (ALA)	CCI model; rat	100 mg/kg; i.p.	Up-regulated Nrf2 expression and its downstream protein factors; alleviated neuronal cell apoptosis and improved neurobehavioral function.	[99]
Carnosic acid	cerebrovascular injury model; rat	3 mg/kg; i.p.	Enhanced antioxidant pathways (SIRT1, MnSOD, Nrf2); reduced ROS, edema, and neuronal apoptosis.	[100]
	RmTBI; mice	1 mg/kg	Improved neurological function and reduced Gfap/Iba1 expression in white matter.	[101]

antioxidants designed to specifically target mitochondria, such as MitoQ [104,105], have shown potential by accumulating within mitochondria and providing localized protection against oxidative damage.

Interestingly, several preclinical studies have shown that antioxidant treatments effectively reduce oxidative damage and enhance outcomes following TBI. However, translating these findings into clinical practice has proven difficult. A significant obstacle lies in determining the optimal timing and dosage for administering antioxidants, as early intervention is critical. Additionally, many antioxidants have limited bioavailability and have difficulty penetrating the blood-brain barrier (BBB). To address this challenge, recent research has thus focused on advanced delivery systems like nanoparticle carriers to improve their efficacy. Numerous clinical trials for antioxidant therapies in TBI are currently underway, as detailed in Table 2 [106–109]. It is important to recognize that TBI involves a complex pathophysiological response, and oxidative stress is just one facet. This complexity suggests that effective treatment may require combination therapies that target multiple pathways. Despite challenges in treating the heterogeneous nature of TBI and the need for timely intervention, antioxidant therapies show promise due to their minimal side effects and practicality in clinical settings.

The future of post-traumatic antioxidant therapy hinges on a deeper understanding of how oxidative damage occurs in TBI and the development of targeted therapies. Combining antioxidants with other therapeutic strategies, such as anti-inflammatory agents and neuroprotective drugs, may offer a more comprehensive strategy against TBI-induced damage. Personalized medicine, guided by biomarkers of oxidative stress and individual patient characteristics, may further enhance the effectiveness of antioxidant therapy. In conclusion, post-traumatic antioxidant therapy holds significant potential for improving TBI outcomes. Continued research is essential to overcoming current obstacles and translating promising preclinical results into effective clinical therapies.

Mitochondrial Dysfunction and Apoptotic Pathway in TBI

Apoptosis, or programmed cell death, is another key factor in the pathology of TBI [110,111]. Mitochondrial dysfunction exacerbates apoptotic processes, leading to neuronal loss and tissue damage through disrupted calcium homeostasis, oxidative stress, and inflammatory signaling [112,113]. The interaction between mitochondrial dysfunction and apoptosis explains their combined contribution to the pathological mechanisms of TBI. Mitochondria regulate apoptosis by releasing pro-apoptotic factors such as cytochrome *c*, which activates caspases and leads to cell death. Apoptotic stimuli can further impair mitochondrial function, creating a cycle of cellular dysfunction. Preclinical studies observed apoptosis in various brain regions such as the hippocampus and cortex within 24–48 h post-injury [113–117]. Apoptosis has also been observed in post-traumatic human brain tissue [110,118,119]. These findings explained the relationship between injury characteristics and the extent and distribution of neuronal apoptosis. Apoptosis can be triggered through various pathways, including intrinsic and extrinsic mechanisms, as well as by several molecules. In the context of TBI, both intrinsic and extrinsic apoptotic pathways lead to cell death mediated by caspase-3 (Fig. 1), which selectively eliminates damaged neurons and glial cells.

Mitochondrial dysfunction primarily initiates the intrinsic apoptotic pathway. Following injury, mitochondria release pro-apoptotic factors including cytochrome *c*, apoptosis-inducing factor (AIF), endonuclease G (EndoG), and second mitochondria-derived activator of caspase (Smac) [120]. The B-cell leukemia/lymphoma 2 (Bcl-2) protein family, comprising pro-apoptotic (BAK, BAX) and anti-apoptotic (Bcl-2, MCL1) members, maintains mitochondrial membrane integrity [120]. Imbalances in these proteins cause membrane permeabilization and release of

Table 2
Clinical trials of antioxidant therapies in TBI.

Compound	Trial number	Status	References
N-acetylcysteine (NAC)	NCT03680911	Terminated	https://clinicaltrials.gov/study/NCT03680911?tab=history&a=8#version-content-panel
	NCT03241732	Recruiting	https://clinicaltrials.gov/study/NCT03241732
	NCT04291066	Completed	https://clinicaltrials.gov/study/NCT04291066?tab=history&a=3#version-content-panel
	NCT00822263	Completed	https://clinicaltrials.gov/study/NCT00822263?tab=history&a=3#version-content-panel [106]
	NCT02791945	Completed	https://clinicaltrials.gov/study/NCT02791945?tab=history&a=4#version-content-panel
	NCT01515839	Completed	https://clinicaltrials.gov/study/NCT01515839
	NCT01322009	Completed	https://www.clinicaltrials.gov/study/NCT01322009?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=N-acetylcysteine%20(NAC)&rank=2 [107]
Alpha-lipoic acid	NCT01515839	Completed	https://clinicaltrials.gov/study/NCT01515839?tab=history&a=1#version-content-panel
Pycnogenol	NCT03777683	Completed	https://www.clinicaltrials.gov/study/NCT03777683?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=Pycnogenol&rank=1&tab=history&a=4#version-content-panel [108]
Cytoflavin	NCT04631484	Recruiting	https://www.clinicaltrials.gov/study/NCT04631484?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=Riboflavin&rank=1&tab=history&a=3#version-content-panel
Riboflavin	NCT06260072	Recruiting	https://www.clinicaltrials.gov/study/NCT06260072?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=Riboflavin&rank=2
Nicotinamide	NCT02721537	Completed	https://www.clinicaltrials.gov/study/NCT02721537?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=Nicotinamide&rank=3&tab=history&a=15#version-content-panel
	NCT05958277	Completed (Phase 3)	https://www.clinicaltrials.gov/study/NCT05958277?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=Nicotinamide&rank=1
Minocycline	NCT01058395	Completed	https://www.clinicaltrials.gov/study/NCT01058395?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=Minocycline&rank=1 [109]
	NCT05826912	Not yet recruiting	https://www.clinicaltrials.gov/study/NCT05826912?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=Minocycline&rank=2&tab=history&a=4#version-content-panel
Melatonin	NCT04400266	Recruiting	https://www.clinicaltrials.gov/study/NCT04400266?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=Melatonin&rank=1
	NCT04932096	Recruiting	https://www.clinicaltrials.gov/study/NCT04932096?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=Melatonin&rank=2
	NCT04034771	Completed	https://www.clinicaltrials.gov/study/NCT04034771?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=Melatonin&rank=3
	NCT04731974	Recruiting	https://www.clinicaltrials.gov/study/NCT04731974?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=Melatonin&rank=6
	NCT03732963	Completed	https://www.clinicaltrials.gov/study/NCT03732963?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=Melatonin&rank=7&tab=history&a=2#version-content-panel
Estrogen	NCT00973674	Completed	https://www.clinicaltrials.gov/study/NCT00973674?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=Estrogen&rank=1
	NCT00766038	Completed	https://www.clinicaltrials.gov/study/NCT00766038?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=Estrogen&rank=2
Progestrone	NCT01143064	Completed	https://www.clinicaltrials.gov/study/NCT01143064?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=progestrone&rank=1
Alpha-lipoic acid (ALA)	NCT01515839	Completed	https://www.clinicaltrials.gov/study/NCT01515839?cond=Traumatic%20Brain%20Injury&term=Brain%20Injuries&intr=Alpha-lipoic%20acid%20(ALA)&rank=1

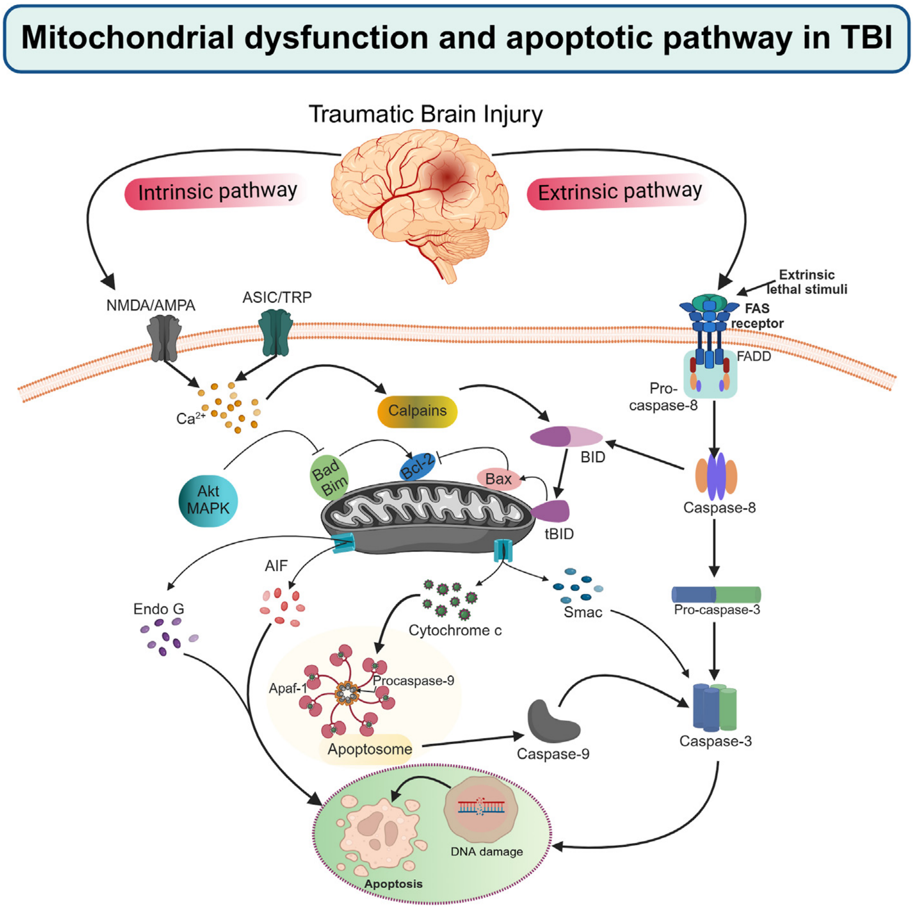

Fig. 1. *Mitochondrial Dysfunction and Pathways of Apoptosis in Traumatic Brain Injury (TBI).* Schematic representation illustrating mitochondrial dysfunction and its role in the intrinsic and extrinsic apoptotic pathways in TBI. Mitochondrial dysfunction is triggered by cellular insults such as calcium overload, oxidative stress, and mechanical injury. These events lead to the activation of Bid, which is cleaved into tBid. tBid translocates to the mitochondria, where it activates Bax while inhibiting Bcl-2, resulting in the release of cytochrome *c* and second mitochondria-derived activator of caspase (Smac) into the cytosol. Cytochrome *c* participates in the intrinsic apoptotic pathway by forming the apoptosome complex with Apaf-1 and caspase-9, which subsequently activates caspase-3. Smac enhances apoptosis by inhibiting inhibitor of apoptosis proteins (IAPs), thereby ensuring sustained caspase-3 activation. The activated caspase-3 leads to DNA fragmentation and apoptosis. Additionally, mitochondrial release of apoptosis-inducing factor (AIF) and endonuclease G (Endo G) triggers caspase-independent cell death by inducing chromatin condensation and DNA cleavage. In parallel, the extrinsic apoptotic pathway is initiated by external death signals, such as the binding of Fas ligand (FasL) to their respective death receptors. This activates the death-inducing signaling complex (DISC) and caspase-8, which directly activates caspase-3. Caspase-8 also amplifies the intrinsic pathway through the cleavage of Bid into tBid, thereby enhancing mitochondrial-mediated apoptosis (See text for abbreviations). This figure is created with BioRender.com.

apoptotic activators [121]. Cytochrome *c* forms the apoptosome with apoptotic protease-activating factor-1 (Apaf-1) and procaspase-9, which activates caspase-9. Caspase-9, in turn, activates caspase-3, leading to DNA fragmentation and cell death [122]. Caspase-3 also activates enzymes like poly (ADP-ribose) polymerase (PARP), involved in DNA repair [123]. Smac promotes caspase activation by neutralizing inhibitor-of-apoptosis proteins (IAPs) [124]. Additionally, caspase-independent mechanisms involving AIF and EndoG contribute to cell death, particularly in severe TBI with compromised bioenergetics [125,126]. These studies emphasize the role of mitochondrial dysfunction following TBI in initiating the intrinsic apoptotic pathways and the subsequent cascades leading to cell death, as well as potential intervention points to prevent apoptosis.

The extrinsic apoptotic pathway, also known as "the death receptor pathway," involves specific cell surface receptors that trigger apoptosis when they bind to their corresponding ligands. This pathway initiates outside the cell and is significant in various cell types, including neurons. The primary death receptors involved in this pathway include the tumor necrosis factor receptor (TNFR) and Fas receptor (FasR), also known as CD95 or APO-1 [127]. When extracellular signaling molecules such as tumor necrosis factor (TNF) or Fas ligand (FasL) bind to their respective receptors on the cell surface, it triggers a cascade of events leading to apoptosis. The binding of these ligands to the receptors induces receptor trimerization, which then recruits adaptor proteins such as Fas-associated death domain (FADD) and TNF receptor-associated death domain (TRADD). These adaptor proteins are crucial in transmitting the apoptotic signal from the cell surface to the intracellular machinery. Upon binding to the receptor-ligand complex, FADD and TRADD facilitate the formation of the death-inducing signaling complex (DISC). The DISC serves as a platform for procaspase-8 activation (and procaspase-10 in some cases). Within the DISC, procaspase-8 is cleaved into its active form, caspase-8. Activated caspase-8 can directly cleave and activate downstream effector caspases, such as caspase-3, caspase-6, and caspase-7, which execute the cell death program by degrading key cellular components and promoting DNA fragmentation. Additionally, activated caspase-8 can cleave Bid, a pro-apoptotic Bcl-2 family member, into its truncated form, tBid. tBid translocates to the mitochondria, where it promotes mitochondrial outer membrane permeabilization (MOMP), leading to the release of cytochrome *c* and other pro-apoptotic factors into the cytosol [128]. This crosstalk between the extrinsic and intrinsic pathways amplifies the apoptotic signal and ensures the efficient execution of apoptosis. The significance of the extrinsic pathway in TBI is underscored by a study showing that TNF-α and Fas knockout exhibited reduced brain lesions and improved memory performance following controlled cortical impact (CCI) injury [129], emphasizing the critical role of death receptors in mediating cell death.

Molecules such as Akt and the MAPK/ERK pathway, along with proteins like SIRT1, play a crucial role in regulating neuronal apoptosis after TBI. Akt, also known as protein kinase B (PKB), promotes cell survival and growth by inhibiting apoptosis. It phosphorylates and inactivates pro-apoptotic factors like Bad, thus preventing them from inducing cell death [130]. Akt can also phosphorylate procaspase-9, inhibiting its activation and the apoptotic cascade [131]. This prevents the activation of downstream caspases and maintains cellular integrity following TBI. The MAPK/ERK pathway, involving mitogen-activated protein kinases (MAPKs) and extracellular signal-regulated kinases (ERKs), is essential for transducing extracellular signals into cellular responses like growth, differentiation, and survival. Activation of this pathway can promote cell survival by upregulating anti-apoptotic proteins and downregulating pro-apoptotic factors. This pathway also influences transcription factors that control the expression of genes involved in cell survival and apoptosis, significantly impacting the cellular response to injury and promoting recovery. SIRT1, a sirtuin

Table 3
Therapeutic approaches targeting apoptotic pathways in TBI.

Compound	TBI Model and specie	Dosage and administration	Main findings	References
Andrographolide (ANDRO)	hypoxia injury model; mouse cortical astrocytes cultured cell;	10 μM	Promoted autophagy and protected against hypoxia injury.	[134]
FTY720	weight-drop model; mice	0.5 mg/kg; i.p.	Reduced endothelial cell apoptosis; improved BBB permeability; attenuated astrocytes and microglia activation; improved neurological function and increased the survival rate of mice.	[135]
	weight-drop model; mice	0.5 and 1 mg/kg; i.p.	Improved neurobehavioral function; alleviated brain edema; modulated Bcl-2, Bcl-xL, Bax, and cytochrome *c*.	[136]
Omega-3 polyunsaturated fatty acid	weight-drop model; rat	2 mL/kg; i.p.	Attenuated neuronal apoptosis; enhanced autophagy; increased NAD^+/NADH ratio and SIRT1 activity and increased Beclin-1 deacetylation.	[137]
	Feeney's weight-drop model; mice	2 mL/kg; i.p.	Attenuated neurological scores; alleviated cerebral edema; attenuated neuroinflammation, necroptosis, and neuronal cell death.	[138]
Luteolin	Marmarou's weight-drop model; mice	10, 30, and 50 mg/kg; i.p.	Ameliorated neurological deficits, brain water content, and neuronal apoptosis; restored level of MDA and GPx activity.	[139]
Baicalin	weight-drop model; mice	50, 100, and 150 mg/kg; i.p.	Improved motor function; reduced cerebral edema; alleviated BBB disruption; enhanced autophagy and ameliorated mitochondrial apoptotic pathway	[140]
	weight-drop model; mice	50, 100, and 150 mg/kg; i.p.	Improved neurobehavioral function; alleviated brain edema; reduced apoptosis; upregulate Bcl-2; downregulated Bax and caspase 3 and restored MDA, GPx and SOD via Akt/Nrf2 pathway.	[141]
Quercetin	weight-drop model; rat	50 mg/kg; i.p.	Attenuated brain edema, attenuated neuronal apoptosis by ERK 1/2 pathway inhibition and Akt serine/threonine protein kinase phosphorylation.	[142]
	Marmarou's weight-drop model; mice	20, 50 and 100 mg/kg; i.p	Reduced neuronal apoptosis; ameliorated mitochondrial lesions; restored cytochrome *c*, malondialdehyde and superoxide dismutase in mitochondria via PGC-1α pathway.	[41]
Valporic acid	Controlled cortical impact (CCI) model; rat	400 mg/kg; i.p	Attenuated brain edema; reduced contusion volume and the rate of neuronal apoptosis; partly blocked capase-3 activity. Upregulated ERK and Akt expression	[143]
Salidroside	CCI model; mice	(20, or 50 mg/kg); i.p	Improved functional recovery; reduced brain tissue damage; reduced neuronal death, apoptosis, and brain edema; decreased cleaved caspase-3, cytochrome *c*, and Smac; increased Akt phosphorylation and Bcl-2/Bax ratio.	[144]
pifithrin-μ pifithrin-α	CCI model; rat	2 mg/kg, i.v.	Lowered p53 mRNA expression; pro-inflammatory cytokines (IL-1β and IL-6); autophagic marker localization (LC3 and p62) and decreased PINK-1 and SOD2 mRNA levels.	[145]
Alpha-lipoic acid (ALA)	weight-drop model; rat	20 or 100 mg/kg; intragastric	Downregulated caspase-3 expression; improved neuronal survival; restored malondialdehyde levels and glutathione peroxidase activity; increased Bcl-2-associated protein translocation to mitochondria and reduced cytochrome *c* release into the cytosol.	[146]

family protein, also regulates apoptosis by deacetylating substrates like p53, inhibiting its pro-apoptotic activity and promoting cell survival. SIRT1 also influences other pathways involved in cellular stress responses and apoptosis, contributing to its protective effects in TBI [132]. The tumor suppressor p53 translocates to mitochondria in the rodent ischemia model, interacts with Bcl-XL in rodent ischemia models, and activates intrinsic apoptotic pathways [133]. This interaction triggers the release of cytochrome *c* and other pro-apoptotic factors from mitochondria, promoting cell death in response to severe cellular stress or damage.

In summary, apoptosis following TBI involves a complex interplay of intrinsic and extrinsic pathways, with both caspase-dependent and caspase-independent mechanisms contributing to cell death. Regulating these pathways can influence the activity of various apoptotic proteins, affecting TBI outcomes by either promoting or inhibiting cell death. Understanding these pathways is crucial for developing therapeutic strategies to reduce neuronal loss and improve outcomes in TBI patients.

Inhibition of apoptosis has emerged as a promising treatment strategy for TBI. One key aspect of apoptosis is its minimal activation of the immune system during cell death, allowing surrounding cells to remain relatively unaffected. Consequently, targeting neuronal apoptosis appears to be a reasonable approach to limit collateral damage following TBI. Numerous studies have shown improved neurological outcomes by inhibiting the mitochondria-dependent apoptosis pathway, as detailed in Table 3 [41,134–146]. Modulating apoptosis at various levels could offer potential therapeutic targets, such as regulating Bcl-2 family proteins or using caspase inhibitors. For instance, broad-spectrum caspase inhibitors like Z-VAD-FMK have shown neuroprotective effects in experimental TBI models by reducing neuronal death and improving functional outcomes [147]. Additionally, the specific caspase-3 inhibitor Ac-DEVD-CHO has also been effective in preventing endothelial cell apoptosis and reducing angiographic vasospasm in acute brain injury [148]. While clinical trials of caspase inhibitors in TBI are yet to be conducted, their ability to mitigate secondary brain injury warrants further preclinical and clinical investigation.

Mangiferin, a bioactive compound found in mangoes, has demonstrated significant neuroprotective effects by influencing mitochondrial apoptotic proteins. It reduces Bcl-2 protein expression while increasing BAX expression, thus lowering levels of cytochrome *c* and cleaved caspase-3 [149]. In a TBI model, mangiferin has further shown efficacy in reducing cortical damage by inhibiting the nucleotide-binding leucine-rich repeat receptor (NLR) family pyrin domain-containing protein-3 (NLRP3) inflammasome [150]. Its favorable safety profile and beneficial effects on human serum lipid profiles [151] demonstrate its potential as a therapy to reduce apoptosis in TBI.

Neuroglobin (Ngb) has also gained much attention in TBI research due to its role in pathology. Studies indicate that Ngb expression increases post-injury and remains elevated for several days [152]. This increase in Ngb expression is also associated with a reduction in lesion size in various models of brain injury [153]. In a rat model of TBI, Ngb mRNA levels in the cerebral cortex peak at 30 min and 48 h post-injury, coinciding with significant reductions in the Bax/Bcl-2 ratio. These findings suggest that Ngb may protect neurons from apoptosis after TBI by modulating the Bax/Bcl-2 pathway [154]. Moreover, Ngb treatment has been associated with decreased levels of pro-apoptotic factors, including BAX, caspase-9, and caspase-3 [155], highlighting its potential as a neuroprotective agent.

Overall, antiapoptotic strategies in TBI—such as caspase inhibitors and natural compounds like mangiferin and Ngb—offer promise for improving outcomes by mitigating apoptotic pathways that contribute to neuronal loss and dysfunction.

Mitochondrial Dynamics in TBI

Mitochondria dynamics are essential for maintaining mitochondrial size, shape, and distribution. It involves cycles of fission, fusion, and mitophagy, which are crucial to meeting cellular energy needs. This dynamic process is regulated by a complex system of proteins known as the mitochondrial quality control (MQC) system. The MQC system balances the processes of fission, fusion, and mitophagy, ensuring cellular homeostasis and function. In neurological disorders, dysfunctional mitochondria often show significant alterations in the gene and protein expression of MQC components, leading to cellular damage [156]. However, in physiological conditions, damaged or dysfunctional mitochondria are segregated by fission and removed via mitophagy [157]. However, in pathological conditions, fusion initially protects mitochondria by fusing with healthy ones to restore function, but prolonged stress can inhibit fusion, stimulate fission, and result in mitochondrial fragmentation and apoptosis [157]. Several GTPase proteins, including dynamin-related protein (Drp1), regulate mitochondrial fission and fusion [158]. Drp1, a key protein in mitochondrial fission, is recruited to the outer mitochondrial membrane upon phosphorylation. Inhibiting Drp1 has been shown to reverse mitochondrial morphological changes, reduce ROS, mitigate BBB disruption, and decrease apoptosis [159]. In TBI models, increased Drp1 expression correlates with changes in mitochondrial length post-injury [160,161]. Post-TBI astrocytic mitochondrial dysfunction, driven by Drp1 dysregulation, favors fission over fusion [162]. Conversely, mitochondrial fusion is regulated by mitofusin-1 and 2 (Mfn1 and Mfn2) on the outer mitochondrial membrane and optic atrophy 1 (OPA1) on the inner membrane [157]. In addition to mitochondrial fission, TBI pathology also exhibits excessive fusion leading to mitochondrial respiratory dysfunction and increased ROS production [160]. Following TBI, a shift from fission to fusion is observed over time, with increased expression of fusion-related genes like OPA1, Mfn1, and Mfn2, and decreased Drp1 expression [163]. These studies highlight the involvement of mitochondrial fission in the pathological process of TBI.

Another critical component of MQC is mitophagy, a process that removes damaged mitochondria through autophagy. Although mitophagy is typically cytoprotective, excessive activation under severe pathological stress due to injury can be lethal [164]. Mitophagy helps alleviate injury and cellular dysfunction by maintaining mitochondrial dynamics in rodent TBI models and removing dysfunctional mitochondria [165]. The mitophagy pathway involves several proteins, including PTEN-induced putative kinase 1 (PINK1), Parkin, Bcl-2 interacting protein-3 (BNIP3) and NIX, which mediate fission-related mitophagy pathway, particularly under conditions of mitochondrial damage and autophagy [166]. FUN14 domain-containing 1 (FUNDC1), a protein located in the outer layer of mitochondrial membranes, can also serve as a mitophagy receptor. The protein level of FUNDC1 was upregulated and peaked 12 h after intracerebral hemorrhage (ICH). Knockdown of FUNDC1 suppresses mitophagy, potentiates inflammation, and exacerbates ICH injury [167]. In TBI models, increased autophagy markers indicate upregulated mitophagy as a primary mechanism for eliminating damaged mitochondria [168]. Proper regulation of mitochondrial dynamics is essential for maintaining mitochondrial health and cellular homeostasis.

In this regard, several agents have been used to modulate mitochondrial dynamics in TBI, summarized in Table 4 [74,165,168–174]. One commonly used treatment target is mitochondrial division inhibitor 1 (Mdivi-1), an inhibitor of Drp1. Mdivi-1 has shown efficacy in experimental TBI by mitigating autophagy dysfunction and activating mitophagy [160,165,175], thereby protecting against BBB disruption and cell death. Additionally, Mdivi-1 has demonstrated neuroprotection by alleviating TBI-induced behavioral deficits, reducing brain edema, mitigating mitochondrial morphological changes, and decreasing cell death [176,177]. These studies identify Mdivi-1 as a potential therapeutic compound to reduce brain damage in TBI.

Mitochondrial fission could also be targeted through indirect molecular regulators like rapamycin. Rapamycin, an mTOR inhibitor restores mitochondrial function by reducing excessive mitochondrial fission and enhancing neuroprotection post-TBI [171]. Although there are currently no clinical trials of rapamycin for TBI patients, it is an approved drug with known pharmacokinetics [178] and is expected to be available in clinical research for TBI treatment in the future.

Targeting mitochondrial fusion as a treatment strategy has also shown effectiveness in restoring mitochondrial function. For instance, mitoquinone (MitoQ) was found to enhance neurological and cognitive functions 30 days post-injury in the CCI model. MitoQ also decreased the activation of astrocytes and microglia, accompanied by improved axonal integrity and neuronal cell count in the cortex [105]. Mechanistically, MitoQ reduces astrocytosis, microgliosis, dendritic, axonal shearing, and increases the expression of antioxidant enzymes. Administration of MitoQ following repeated mild TBI represents an efficient approach to ameliorate repeated mild TBI neurological and cellular outcomes with no observable side effects [104]. Activation of another fusion protein, OPA1, by celastrol also showed beneficial effects in ICH model [179]. Indirect activation Mfn1/2 by using the SIRT3 agonist Honokiol (HNK) improved mitochondrial morphology and function by inhibiting apoptosis and attenuating inflammation after brain injury [180,181]. These studies highlight the therapeutic potential of targeting various proteins related to mitochondrial fusion.

Enhancing mitophagy pathways with mitophagy activators like Resolvin D1 has also demonstrated promise in mitigating cognitive impairment by protecting astrocyte mitochondria after TBI [169]. Novel

Table 4
Therapeutic approaches targeting mitochondrial fission, fusion, and mitophagy in TBI.

Compound	TBI Model and specie	Dosage and administration	Main findings	References
Resolvin D1	Controlled cortical impact (CCI) model; mice	15 μg/kg; i.p	Ameliorated brain edema; cognitive impairment; suppressed neuroinflammation and neuronal loss; eliminated extra mitoROS and improved the supportive function of astrocytes.	[169]
IL-10	CCI model; rat	Overexpress	Inhibited inflammatory response; reduced neuronal degeneration and death	[170]
Rapamycin	weight-drop model; mice	3 mg/kg; i.p	Attenuated neuroinflammation; mitochondrial damage; inhibited NLRP3 inflammasome activation.	[171]
Melatonin	CCI model; rat	5 mL/kg; i.p	Reduced inflammation; dampened the secretion of pro-inflammatory cytokines; ameliorated neuronal death and behavioral deficits,	[74]
Midvi-1	weight-drop model; mice	3 mg/kg; i.p	Alleviated loss of mitochondrial membrane potential, ROS production, ATP reduction, BBB disruption and cell death.	[165]
	CCI model; rat	1 mg/kg; i.c.v	Aggravated neurological manifestations and neuronal apoptosis.	[168]
Nitroxide antioxidant CTMIO and DCTEIO	weight-drop model; rat	40 mM aqueous solutions; oral	Alleviated ROS production; improved tissue repair and neurological function.	[172]
Triiodothyronine	CCI model; mice	20 μg/100 g/day for 14 days; subcutaneous	Reduced ROS production; prevented neuronal death; induced neurogenesis and neuroprotection.	[173]
Cardiolipin siRNA	CCI model; rat	30 nmol; intracerebral infusion	Induced endogenous neuroprotection, prevented neuronal apoptosis and behavioral deficits.	[174]

strategies, such as the transplantation of mesenchymal stem cells (MSCs) overexpressing IL-10, enhance mitophagy and reduce neuronal degeneration and death in a rat model of TBI [170]. Inactivators of p53, pifithrin-μ and pifithrin-α mitigated TBI-induced neuronal damage by modifying oxidative stress, neuroinflammation, and mitophagy [145]. Furthermore, cell therapies, such as human umbilical cord mesenchymal stem cell (HucMSC) transplantation, activate mitophagy and promote neuronal repair, offering another avenue for improving TBI outcomes [182]. Despite the wealth of preclinical studies targeting mitochondrial dynamics, no translational therapies have yet reached clinical application. Given the complexity of mitochondrial regulation, combined therapies targeting multiple facets of mitochondrial function may synergistically enhance therapeutic outcomes and mitigate neuronal damage in TBI.

Mitochondrial Biogenesis Dysfunction in TBI

Mitochondrial biogenesis, the process involving the growth and division of existing mitochondria, plays a critical role in maintaining mitochondrial homeostasis [156]. Impairments in mitochondrial biogenesis can lead to significant mitochondrial and cellular dysfunction [156]. This complex process involves various proteins, including mitochondrial energy and nutrient sensors, as well as transcription factors, cofactors, and nuclear receptors [183]. A key regulator of mitochondrial biogenesis is peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). PGC-1α integrates upstream signals to initiate a mitochondrial gene program essential for mitochondrial biogenesis [184]. It recruits transcription factors that promote the transcription of nuclear-encoded genes required for this process. Activation of PGC-1α leads to the activation of nuclear respiratory factors (NRFs), which, in turn, promote the transcription of mitochondrial genes [185]. These genes are then transported to the mitochondrial matrix, where they stimulate mitochondrial DNA replication and gene expression [186]. GC-1α also interacts with various other transcription factors, including peroxisome proliferator-activated receptors (PPARs), thyroid hormone receptors, glucocorticoid receptors, estrogen receptors, mitochondrial transporters, and antioxidant proteins [186]. Its expression is highly responsive to physiological cues signaling increased cellular metabolic needs, such as oxidative stress and cell division [187]. However, neurological conditions like brain injury demonstrate reduced PGC-1α expression [188,189]. Unlike other neurological diseases, mitochondrial biogenesis is severely impacted in TBI. Given that mitochondrial biogenesis is a main regulator of mitochondrial DNA, targeting this process could be crucial for counteracting mitochondrial dysfunction and improving overall mitochondrial health.

Targeting mitochondrial biogenesis involves several therapeutic strategies. Activation of PGC-1α facilitates the transcription of nuclear-encoded genes necessary for mitochondrial biogenesis, including ATP synthase, cytochrome *c*, and mitochondrial transcription factor A (TFAM) [190]. This process promotes mitochondrial DNA replication and gene expression, thereby enhancing mitochondrial function. Various pharmacological agents can effectively modulate these regulatory pathways effectively, summarized in Table 5 [45,191–196]. For instance, AICAR, an AMPK activator, mimics the effects of AMP to stimulate PGC-1α activity, promoting mitochondrial biogenesis and improving spatial memory in TBI models [191]. Additionally, sirtuin-activating compounds (STACs) like resveratrol (RSV) enhances the SIRT1-PGC-1α axis, ameliorating cognitive deficits and reducing oxidative stress and apoptosis in TBI rodent models [45]. The safety and pharmacokinetics of RSV have been extensively studied in human clinical trials [197] suggesting its potential translational value.

Activation of melanocortin 1 receptor (MC1R) could also be beneficial, as numerous reports have demonstrated that MC1R exerts brain protective effects via multiple signaling pathways, including AMPK/SIRT1/PGC-1α [198]. One candidate synthetic agonist of MC1R, Nle4-D-Phe7-α-Melanocyte stimulating hormone (NDP-MSH), has shown improvement in neurological deficits, reduction in brain edema, and decreased neuronal apoptosis [192]. Another agonist, BMS-470539, has also shown promise in TBI by reducing infarct area, brain atrophy and improving both short- and long-term neurological deficits [193]. Furthermore, heat shock protein 22 promotes mitochondrial biogenesis via the AMPK-PGC-1α signaling pathway thus offers neuroprotection in TBI [199]. Another protein, mitochondrial uncoupling protein 2 (UCP2), interacts with PGC-1α to regulate mitochondrial biogenesis and metabolism, showing potential therapeutic benefits [200], its overexpression has been shown to inhibit inflammatory cytokines and activate cell survival factor after cerebral ischemia [194]. Furthermore, its use in TBI has demonstrated neuroprotection by regulating mitochondrial ROS production, protecting neurons from damage and death [201]. Similarly, irisin, a cytokine secreted by skeletal muscles, enhances mitochondrial biogenesis by promoting UCP2 expression on neuronal mitochondrial membranes post-TBI, thereby reducing neuroinflammation and neuronal apoptosis [195,196]. Clinical studies have shown that low serum irisin levels are associated with poor early functional outcomes in ischemic stroke patients [202]. Therefore, irisin may have neuroprotective effects in the human body as well, supporting its promising role in neuroprotection, particularly in conditions like TBI.

In conclusion, targeting mitochondrial biogenesis pathways represents a promising approach for mitigating neuronal damage and improving neurological outcomes in conditions like TBI. Future research

Table 5
Therapeutic approaches targeting mitochondrial biogenesis in TBI.

Compound	TBI Model and specie	Dosage and administration	Main findings	References
AICAR	Controlled Cortical Impact (CCI) injury; mice	500 mg/kg; i.p.	Increased AMPK phosphorylation; enhanced long-term memory	[191]
Resveratrol	CCI model; rat	0.05 mg/kg and 0.1 mg/kg; i.p.	Reduced ROS generation; suppressed apoptosis; improved cognitive function	[45]
Nle4-D-Phe7-α-Melanocyte stimulating hormone (NDP-MSH)	CCI model; rat	50 μg/mouse; i.p.	Reduced neuronal death; improved neurological deficits; alleviated brain edema; improved BBB permeability and motor function	[192]
BMS-470539	Neonatal hypoxia-ischemia brain injury model; rat	50 μg/kg 160 μg/kg 500 μg/kg; intrnasally	Reduced the percent infarct area, brain atrophy and inflammation; improved short- and long-term neurological function	[193]
Uncoupling protein 2	Middle Cerebral Artery Occlusion (MCAO) model; mice	UCP2 Tg mice (Overexpression)	Reduced infarct volume; attenuated IL-6 increase; preserved Bcl-2 expression; upregulated cell cycle gene expression; increased non-cleaved caspase-3 levels; decreased non-cleaved caspase-9 levels.	[194]
Irisin	CCI model; mice	10 μg/kg; i.v	Increase survival rate; improve neurological score; alleviates brain edema; improved BBB integrity; inhibited inflammation and oxidative stress; reduced mitochondrial apoptosis; regulated UCP2 expression.	[195]
	Intracerebral hemorrhage (ICH) model; mice	80 μg/kg, 250 μg/kg, and 750 μg/kg; intranasally	Inhibited microglia/macrophage pro-inflammatory polarization; promoted anti-inflammatory polarization; inhibited neutrophil infiltration; suppressed neuronal apoptotic cell death	[196]

exploring these pathways, particularly focusing on agents like irisin, holds potential for developing novel therapies that enhance mitochondrial function and support neurological recovery.

Mitochondria-related Inflammation in TBI

Mitochondria serve as central regulators of cellular energy metabolism and immune responses, acting as integrative hubs that link bioenergetics with immune signaling [203]. Their role becomes particularly significant in the context of TBI, where mitochondrial dysfunction drives neuroinflammation [204]. Damage to mitochondria triggers the release of mitochondrial damage-associated molecular patterns (mtDAMPs), including mitochondrial DNA (mtDNA) and ATP, which are detected by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs). This activation leads to the activation of inflammasomes, especially the NLRP3 inflammasome, which processes pro-caspase-1 into its active form (Fig. 2). The active caspase-1 then matures inflammatory cytokines, such as IL-1β and IL-18, thereby amplifying the inflammatory response [205,206]. Mitochondrial ROS exacerbate these inflammatory pathways, causing additional damage to neuronal cells and perpetuating inflammatory signaling. One critical pathway linking mitochondrial dysfunction to neuroinflammation is the NF-κB signaling cascade. ROS and mtDAMPs activate the IκB kinase (IKK) complex, leading to the degradation of IκBs. This allows NF-κB to translocate into the nucleus, where it activates the transcription of pro-inflammatory genes, including cytokines, chemokines, and adhesion molecules. These pro-inflammatory factors not only disrupt the BBB but also facilitate the infiltration of peripheral immune cells, further intensify the inflammatory response. Additionally, NF-κB enhances NLRP3 inflammasome expression, establishing a feedback loop that sustains chronic inflammation [207]. Mitochondrial dysfunction also intersects with apoptotic pathways, linking inflammation and cell death. Mitochondrial outer membrane permeabilization (MOMP) allows the release of cytochrome *c* into the cytoplasm, which activates caspase-9 and subsequently caspase-3-mediated apoptosis [208]. While caspase-3 is a hallmark of apoptosis, it also interacts with inflammasome components like gasdermin D (GSDMD), contributing to pyroptotic cell death. This interplay between apoptosis and pyroptosis releases additional intracellular damage signals, which further propagate inflammation.

Moreover, glial cells, including microglia and astrocytes, play a central role in the neuroinflammatory response driven by mitochondrial dysfunction. Microglia, highly sensitive to mtDAMPs, adopt a reactive

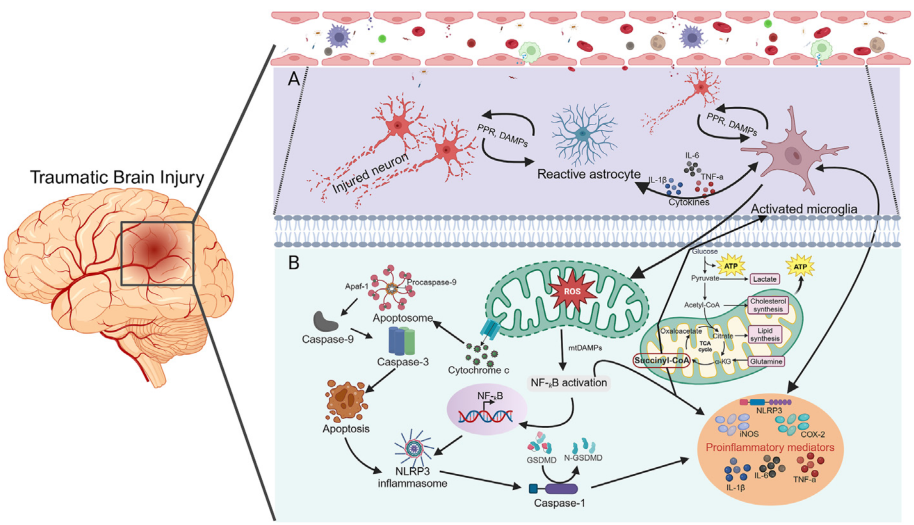

Fig. 2. *Mitochondrial Dysfunction and Inflammation in Traumatic Brain Injury (TBI)*. Mitochondrial-Driven Inflammation and NF-κB Signaling Pathways Mediating NLRP3 Inflammasome Activation in TBI. **(A)** Post-traumatic brain injury (TBI) inflammatory responses begin with blood-brain barrier (BBB) disruption, facilitating the infiltration of immune cells into the brain. Damaged neurons release damage-associated molecular patterns (DAMPs), which are detected by microglia and astrocytes, triggering an inflammatory cascade. Microglia adopt a pro-inflammatory M1 phenotype, releasing cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), which stimulate astrocytes to produce additional cytokines and chemokines, further intensifying inflammation. Mitochondrial damage-associated molecular patterns (mtDAMPs) exacerbate the response, activating microglia to produce reactive oxygen species (ROS) and engage in chronic maladaptive activation, causing neuronal damage. Reactive astrocytes lose their neuroprotective functions, including glutamate buffering and neuronal energy support, and instead release inflammatory mediators such as IL-1α, CXCL10, and complement protein C3. The crosstalk between reactive microglia and astrocytes amplifies inflammation, impairs synaptic repair, and worsens neuronal injury, driving neurotoxicity progression in TBI. **(B)** DAMPs and cytokines activate Toll-like receptors (TLRs) and cytokine receptors, leading to the activation of the NF-κB signaling pathway. NF-κB translocates into the nucleus to promote the transcription of pro-inflammatory genes and components of the NLRP3 inflammasome. Activation of the NLRP3 inflammasome leads to the cleavage of pro-caspase-1 into active caspase-1, which processes pro-IL-1β into its mature form. These inflammatory cytokines, alongside mitochondrial ROS, sustain neuroinflammation and exacerbate neuronal damage. Additionally, mitochondrial outer membrane permeabilization (MOMP) releases cytochrome *c* into the cytosol, linking mitochondrial dysfunction to apoptosis via caspase-9 and caspase-3 activation. Caspase-3 also contributes to pyroptotic cell death through gasdermin D (GSDMD), releasing further DAMPs and perpetuating the inflammatory response (See text for abbreviations). This figure is created with BioRender.com.

phenotype, producing ROS, releasing pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6), and engaging in phagocytosis [204]. Microglia also transform from a ramified (resting) to an ameboid (activated) morphology, and once activated, they become morphologically indistinguishable from recruited blood-derived macrophages. In this state, they secrete pro-inflammatory cytokines and free radicals, which are cytotoxic to neurons and can contribute to neurodegeneration after TBI [209]. While their initial activation is protective by containing injury and clearing debris, prolonged activation becomes detrimental, driving chronic neuroinflammation and neuronal damage [209]. Recent research emphasizes their constant interaction with surrounding neurons, where they detect neuronal injuries and support recovery by modulating cellular calcium levels [210]. In TBI, glial crosstalk has been shown to accelerate brain injury progression [211]. Microglia, activated in response to TBI, trigger alterations in astrocytes characterized by increased secretion of pro-inflammatory factors, disrupted mitochondrial function, and a failure to nurture neurons or eliminate foreign agents, which collectively lead to neurotoxicity and neuroinflammation [211]. Reactive astrocytes, under the influence of reactive microglia, lose their protective functions, such as glutamate buffering and neuronal energy support, while releasing inflammatory mediators like IL-1α, CXCL10, and C3 [212]. This pathological interplay between reactive microglia and astrocytes amplifies inflammation and neurotoxicity, hindering synaptic repair and exacerbating neuronal damage in TBI.

The role of mitochondrial metabolism further underscores its influence on innate immune responses. Beyond ATP production, the tricarboxylic acid (TCA) cycle generates intermediates with significant immunomodulatory roles. For example, the production of ROS and Byproducts of the TCA cycle, including citrate, itaconate, and succinate, regulate the secretion of inflammatory cytokines, antimicrobial responses, and immune cell activation [213]. The precise mechanisms underlying the regulation of these metabolic products in modulating innate immune responses are complex and still require further investigation. For instance, Succinate, as a key metabolite, stabilizes hypoxia-inducible factor 1-alpha (HIF-1α), promoting inflammatory signaling, which contributes to the pro-inflammatory environment typically seen in TBI [214]. Elevated succinate levels are associated with chronic inflammation and modulate immune cell responses [215], particularly in hypoxic conditions, which are common in TBI due to tissue injury and reduced cerebral blood flow. In contrast, itaconate exerts anti-inflammatory effects by inhibiting succinate dehydrogenase (SDH), reducing ROS production, and modulating transcription factors like NRF2, alleviating oxidative stress and mitigating neuronal damage. In mouse cranial window models, itaconate significantly improved hemodynamics while reducing leukocyte adhesion. Further, itaconate supplementation increased survival in mice experiencing TBI and hemorrhagic shock [216]. Furthermore, Glycolytic and oxidative phosphorylation pathways also impact immune cell polarization. In TBI, the shift to aerobic glycolysis in microglia supports their pro-inflammatory phenotype, while mitochondrial dysfunction disrupts oxidative phosphorylation and exacerbates inflammation [217]. This metabolic dysregulation, including alterations in succinate metabolism, contributes to chronic neuroinflammation and delayed recovery.

Collectively, the interaction between mitochondrial dysfunction, inflammasome activation, and immune metabolism underscores mitochondria's key role in TBI-induced neuroinflammation. Therapeutic strategies targeting these pathways, such as NF-κB inhibitors, antioxidants, and mitophagy enhancers, offer potential for mitigating inflammation and promoting recovery in TBI and other neuroinflammatory disorders, highlighting new avenues for intervention. For instance, for therapeutics, mitochondrial transfer showed its promises in reducing inflammation and restoring cellular metabolism. Transferring mitochondria from mesenchymal stem cells (MSCs) to T cells has shown the ability to direct gene expression toward regulatory T cell activation, potentially promoting anti-inflammation [218]. Similarly, mitochondrial transfer showed its promises in reducing inflammation and restoring cellular metabolism. Transferring mitochondria from mesenchymal stem cells (MSCs) to T cells has shown the ability to direct gene expression toward regulatory T cell activation, potentially promoting anti-inflammation [218]. Similarly, mitochondrial transfer from neural stem cells (NSCs) to inflammatory mononuclear phagocytes was able to alleviate inflammation and restore cellular metabolism, supporting the realizable therapeutic potential of mitochondrial transfer [219]. A number of pharmaceutics also showed promises. Melatonin was shown to curb inflammation, and reduce neuronal death and behavioral deficits in TBI [74]. Morin, a natural polyphenol, which enhances autophagy, was shown to reduce inflammation and apoptosis, and improve memory deficits after mild TBI in animal studies [220]. Additionally, enhancing mitophagy through either pharmaceutic agents or genetic manipulation to regulate inflammasome activation has the potential to prevent mitochondrial damage-associated molecular patterns (mtDAMP) release and subsequent aggravation of inflammation. These strategies highlight the potential of mitochondrial dynamics and bioenergetics as the interventional targets, supporting the need for future research in these areas.

Mitochondrial Dysfunction and the BBB in TBI

Mitochondria in cerebrovascular endothelial cells play a crucial role in regulating BBB opening [221]. The interplay between mitochondrial dysfunction and the BBB is critical and has been extensively studied in the context of TBI pathology [222]. Brain capillary endothelial cells, which constitute the BBB, exhibit a mitochondrial density that is twice that of systemic capillaries [223]. This high density reflects the significant energy demands required to maintain BBB integrity and brain homeostasis [224]. Physiologically, mitochondria generate the necessary ATP to support tight junctions and selective transport mechanisms, crucial for protecting the brain from harmful substances while allowing essential nutrients to pass.

Mitochondrial dysfunction, however, leads to pathophysiological events results in the opening of the BBB [225,226], prolonged neurological deficits, and higher mortality rates in TBI [227]. Mitochondria also play a vital role in maintaining ion gradients and facilitating chemical transport between the blood and brain extracellular fluid, further supporting BBB function [221]. For instance, lipopolysaccharide (LPS)-induced mitochondrial dysfunction in cerebrovascular endothelial cells has been shown to increase BBB permeability, exacerbating outcomes in conditions like acute stroke [221]. Another study demonstrates that uncoupling the electron transport chain (ETC) can compromise oxidative phosphorylation, exacerbating stroke outcomes by increasing oxidative stress and disrupting ATP production [228], emphasizing the importance of mitochondrial integrity.

Another function of mitochondria that impacts BBB function is body temperature regulation. Hypothermia resulting from mitochondrial impairment in brain endothelial cells after brain injury has been shown to worsen outcomes [229]. Maintaining mitochondrial function in brain endothelial cells is crucial for preserving BBB integrity and improving outcomes in brain diseases. In this context, a novel specific aptamer (VCAM-1) targeting cerebrovascular endothelial cells after ischemic stroke has been identified [230], providing a potential therapeutic approach for mitigating mitochondrial dysfunction and preserving BBB integrity.

One molecular mechanism underlying these processes involves miR-34a, a microRNA implicated in apoptosis, cell cycle regulation, and stress response [231]. MiR-34a plays a significant role in regulating BBB permeability and mitochondrial function by targeting mitochondrial-related genes, reducing oxidative phosphorylation and ATP production, and contributing to BBB disruption [232]. Numerous studies have identified an association between post-stroke increases in miR-34a levels and mitochondrial dysfunction [233,234]. Mechanistically, increased levels of miR-34a post-stroke are associated with reduced cytochrome *c* levels, leading to increased BBB permeability and mitochondrial dysfunction [232,235]. Furthermore, elevated miR-34a levels post-stroke are associated with decreased expression of ETC genes NDUFS8, COX5b, and ATP5a1, leading to increased reactive oxygen species (ROS) formation and further oxidative damage [236]. These studies highlight the impact of miR-34a on BBB integrity involves complex interactions with mitochondrial function, particularly in regulating oxidative phosphorylation and apoptosis. Consequently, preserving mitochondrial function and mitigating miR-34a′s effects are crucial strategies for maintaining BBB integrity and improving outcomes in TBI and related conditions. Further research is needed to fully elucidate the mechanisms by which miR-34a and mitochondrial dysfunction impact the BBB, offering potential therapeutic targets for enhancing brain protection in TBI.

Novel Approaches to Mitochondria-Targeted Drug Delivery

Recent advances in nanomaterials have enabled precise targeted delivery of therapeutics, increasing the efficacy of treatments and minimizing adverse effects on non-target tissues [237]. Nanoparticles, liposomes, extracellular vesicles (EVs), micelles, and polymers are the most commonly used carriers that possess large surface areas and exhibit excellent electronic, steric, optical, and biological properties, making them ideal for targeted drug delivery. Such characteristics allow them to cross various physiological barriers, including the BBB [238]. Their effectiveness can be further enhanced by their ability to adsorb onto the capillary walls, leading to a higher local concentration through the solubilization of surfactants, increased bypass transport, and endocytosis by endothelial cells, all of which have already been showing promises in treating a variety of diseases.

Nanoparticles can be manufactured using various methods and tailored to match the drugs to be delivered and their ultimate targets. Each type of nanocarrier offers distinct advantages. Liposomes are known for their biocompatibility and ability to encapsulate both hydrophilic and hydrophobic drugs, while EVs, which are naturally occurring vesicles, offer low immunogenicity and high biocompatibility. Nanocrystals, which have recently gained attention [239], not only enhance the efficiency of drug delivery but also minimize toxicity to healthy tissues and organs. Lipophilic cations, such as triphenylphosphonium, dequalinium, and rhodamine 123, exhibit strong affinity for mitochondria due to their ability to exploit the mitochondrial membrane potential, allowing for selective targeting and accumulation within the mitochondria [240]. This specificity is crucial for diseases where mitochondrial dysfunction plays a significant role, such as brain diseases. The unique properties of these nanocarriers and lipophilic cations have enhanced treatment efficacy while minimizing potential side effects for patients facing these challenging conditions.

Nanoparticles have notably demonstrated their ability to mitigate mitochondrial oxidative stress and strengthen mitochondrial defense mechanisms. For instance, nanoparticles loaded with resveratrol and functionalized with triphenylphosphonium have shown remarkable efficacy in Alzheimer's disease models [241] by reducing oxidative stress and improving neuronal health. Nanoparticle-based methods have also shown promises in myocardial ischemia-reperfusion injury, with nanoparticle designed for the delivery of cyclosporin A infused with the peptide SS31 showing substantial protective effects against oxidative damage and mitochondrial dysfunction [242], while minimizing the adverse effects of cyclosporin A. A new type of nanoparticle, a hybrid nanozyme, has also been shown to mitigate mitochondrial oxidative stress and reduce myocardial ischemia-reperfusion injury by mimicking natural enzymes and effectively neutralizing mitochondrial ROS specifically [243]. The growing body of experimental evidence emphasizes the potential of nanoparticles and nanozymes in targeting conditions linked to oxidative stress and mitochondrial dysfunction.

Recently, a nanoparticle based on a polymer PGLA containing a small interfering RNA (siRNA) molecule designed to inhibit the production of tau protein—a key molecule in the pathophysiology of Alzheimer's disease—showed promises in TBI patients. Polysorbate 80 was chosen as the coating material based on pharmacodynamic studies with healthy murine models. The particle showed excellent penetrance to the parenchyma regardless of the integrity of the BBB in TBI mice models. Compared to traditional intravenous injections and nanoparticles without the coating material, this new particle showed threefold higher brain accumulation of siRNA and a 50 % reduction in tau. The therapeutic effects persisted even when the agent was given at later time points, with no reduction in tau seen in mice given siRNA using a conventional delivery system [244], highlighting the potential of nanoparticles in mitigating the aftermath of TBI.

In addition to these innovative drug delivery approaches, mitochondrial transplantation [245] and blood substitution therapy [246] have shown significant promise in preclinical studies for rescuing the brain from ischemic damage in mice. These emerging therapeutic strategies offer novel avenues for mitigating brain injury and enhancing recovery. Mitochondrial transplantation involves the direct delivery of healthy mitochondria into damaged brain tissue. This method aims to restore mitochondrial function in affected neurons, potentially reversing or alleviating the damage caused by ischemia [245]. By providing a source of functional mitochondria, this approach can help restore ATP production, reduce oxidative stress, and improve neuronal survival. Experimental studies have demonstrated that mitochondrial transplantation can enhance cellular energy metabolism and reduce neuronal loss in animal models of ischemic stroke, suggesting a promising therapeutic potential. Blood substitution therapy, on the other hand, involves replacing damaged or dysfunctional blood components with substitutes or modified blood products designed to improve oxygen delivery and mitigate ischemic injury [246]. This therapy may also enhance the perfusion of oxygen and nutrients to brain tissue, thus reducing the extent of ischemic damage. In murine model, blood substitutes can effectively restore cerebral blood flow and improve outcomes in models of ischemic brain injury [246]. These substitutes are often designed to mimic the oxygen-carrying capacity of red blood cells or to provide additional protective factors that support brain tissue recovery. Both mitochondrial transplantation and blood substitution therapy represent cutting-edge strategies that address different aspects of ischemic brain injury. Their successful application in animal models highlights their potential as effective treatments for ischemic conditions, offering hope for new therapeutic options in the management of TBI and other neurological disorders. Further research and clinical trials will be essential to evaluate their safety, efficacy, and potential for translation into human medicine.

Emerging technologies in mitochondrial-targeted therapy for TBI

Mitochondria-targeted metal-organic frameworks (MOFs), liposomes, and exosomes hold a significant promise for the treatment of TBI. MOFs are frameworks with metal ions coordinated to organic ligands and serve as a versatile platform for drug delivery due to their high surface area, tunable porosity, and ability to encapsulate a wide range of therapeutic agents. Their efficacy has already been proven in cancer treatments, and now their application in neurological disorders, including TBI, is being examined. Their efficacy has already been proven in cancer treatments [247], and now, their application in neurological disorders, including TBI, is being examined.

Liposomes and exosomes are also being investigated for their therapeutic potential in TBI. Liposomes are spherical vesicles consisting of lipid bilayers and are already being used for targeted drug delivery, with 15 approved products on the market [248]. Yet, none are approved in TBI. Liposomes offer several advantages, including biocompatibility, capacity to carry both hydrophilic and hydrophobic drugs, and surface modifiability to enhance specificity. Exosomes, naturally occurring extracellular vesicles used for cell-to-cell communication, are also being investigated for their therapeutic potential in TBI. Although none of the exosome-based agents are FDA-approved, several hundred clinical trials are being conducted. Exosomes offer unique advantages, such as low

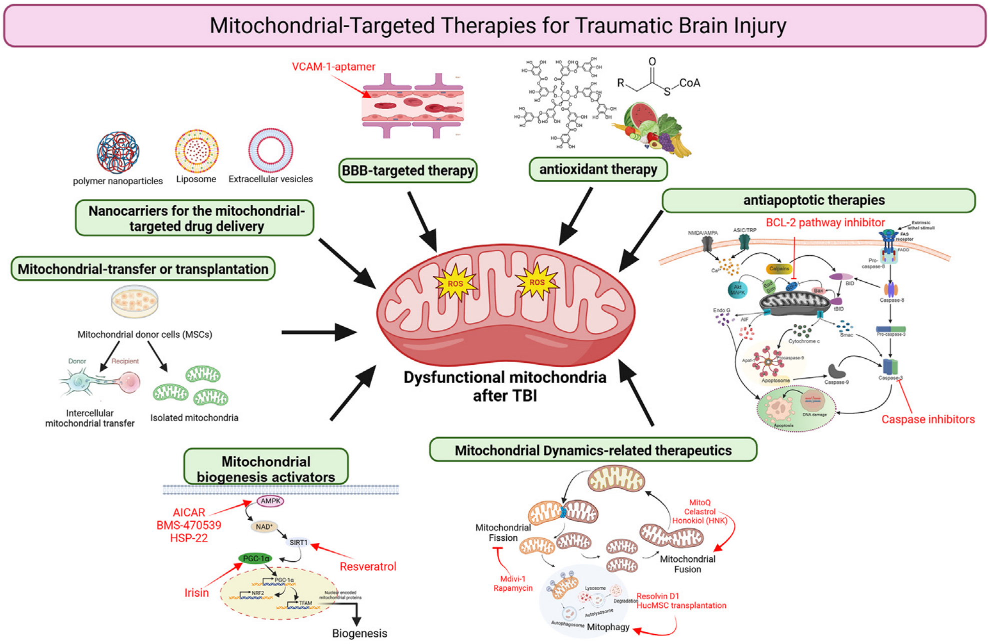

Fig. 3. Therapeutic Approaches Targeting Mitochondrial Function in Traumatic Brain Injury. Overview of various therapeutic strategies aimed at improving mitochondrial function in the context of traumatic brain injury. The therapies are categorized into antioxidants, antiapoptotic agents, mitochondrial dynamics modulators, and mitochondrial biogenesis activators, mitochondrial transfer or transplantation, BBB targeted therapies and nanocarriers for mitochondrial targeted drug delivery. Targeted agents are highlighted in red. The figure also emphasizes the emerging approach of mitochondrial transfer or transplantation, which involves transferring healthy mitochondria to injured cells to restore cellular function. Nanocarriers for mitochondrial-targeted drug delivery are highlighted as a promising method for delivering therapeutic agents directly to mitochondria, enhancing treatment efficacy (See text for abbreviations). This figure is created with BioRender.com.

immunogenicity, high biocompatibility, and high penetrance across biological barriers, including the BBB. Their biocompatibility is exemplified by a clinical trial where mesenchymal stem cell (MSC)-derived exosomes were given to five patients with ischemic stroke through intraparenchymal injection, and none of the subjects suffered from adverse reactions [249]. In addition to their ability to affect intercellular communication, such advantage of being able to directly inject or deliver exosomes to the injury site with minimal adverse consequences makes them particularly promising candidates in treating TBI.

All of these technological advances—mitochondria-targeted MOFs, liposomes, and exosomes—might significantly impact TBI treatment strategies. These advanced nanocarriers can enhance the precision and efficacy of delivery, improving both short- and long-term outcomes with minimal adverse effects.

In summary, mitochondrial-targeted therapies hold significant promises in advancing the treatment of TBI (Fig. 3). Mitochondria, as key regulators of cellular metabolism and homeostasis, are critically involved in TBI pathophysiology, where their dysfunction leads to dysregulation of mitochondrial dynamics, bioenergetics, and inflammatory responses—each representing viable therapeutic targets. Recent advancements in nanoparticles and bioparticles have enhanced target specificity and minimized off-target effects. Lipophilic cations and peptide-based strategies have demonstrated efficacy in preclinical models, providing promising approaches to reduce oxidative stress, inflammation, and neurodegeneration in TBI. Additionally, emerging nanomaterials such as metal-organic frameworks, liposomes, and exosomes are being explored for TBI treatment, with clinical trials already confirming their safety and potential efficacy. Future research may benefit from further optimizing mitochondria-targeted drug delivery systems for TBI, including refining nanoparticle formulations, exploring novel biomaterials, and deepening our understanding of mitochondrial biology in the TBI context.

Author Contributions

ST: Writing- original draft, tables, and figure. SW: Writing – review & editing. CHL: Writing – review & editing. BSKY: Writing – review & editing. AG: Writing – review & editing, Funding acquisition. HC: Writing – review & editing Funding acquisition. XR: Conceptualization, Supervision, Writing – review & editing. content of the work Funding acquisition.

Declaration of competing interest

The authors have no declarations of interest to disclose.

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