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Review Article

NEUROPROTECTIVE ROLES OF BDNF AND NGF IN ARSENIC-INDUCED NEUROTOXICITY: MECHANISMS AND THERAPEUTIC IMPLICATIONS

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ABSTRACT

Arsenic-induced neurotoxicity is increasingly recognized as a major global health issue, leading to both developmental and degenerative neurological impairments, therefore, arsenic is becoming one of the potent environmental neurotoxins that can lead to significant health risks, particularly through long-term exposure via water, food, and air. Arsenic exposure can initiate a range of pathological events such as-disruption of mitochondrial function, oxidative stress, apoptosis, and inflammatory processes, which result in neuronal damage and cognitive dysfunction. Conversely, neurotrophins growth factors that regulate neuronal survival, growth, and function, are emerging as promising neuroprotective agents against such neurotoxic effects. This article explores the neuroprotective roles of BDNF (Brain-derived neurotrophic factor) and NGF (Nerve growth factor) in counteracting arsenic-induced neurodegeneration, through the analysis of epidemiology and mechanism-based preclinical studies of last decade.

Arsenic disrupts neurotrophin signaling by inhibiting Trk (Tropomyosin receptor kinase) receptor phosphorylation and downstream survival pathways PI3K-AKT (Phosphoinositide 3-kinase–Protein kinase B), ERK-CREB (Extracellular signal-regulated kinase-cAMP response element-binding protein), thus contributing to neurodegeneration. In animal models, BDNF supplementation exhibited reduction in oxidative stress by 45–60%, neuronal apoptosis declined by about 55%, and improvement in cognitive function up to 40%. Additionally, NGF supplementation shows a 40-55% reduction in apoptosis. By integrating toxicological mechanisms with therapeutic perspectives, this narrative review underscores the potential of neurotrophin-based strategies to mitigate arsenic-related neurodegeneration and highlights future research directions for translational applications.

Keywords: Arsenic, Neurotoxicity, Neurotrophins, BDNF, NGF, Neuroprotection

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INTRODUCTION

Surrounding of the animal kingdom directly or indirectly affect their nervous systems, heavy metal contaminations are emerging as major threat for animal kingdom. Arsenic is among the top five contaminants that affecting health. The earth's crust includes naturally occurring arsenic, which is dangerous in its inorganic trivalent form rather than its biological form. Global arsenic exposure primarily occurs through contaminated drinking water and food, especially in countries such as Bangladesh, India, China, Mexico, Afghanistan, Myanmar, Nepal, The United States, Cambodia, Mongolia, and Chile over 140 million people are estimated to consume water exceeding the WHO provisional guideline of 10 µg/l, making it a critical public health concern. Hence, like other parts of the world, Asia is believed to be more severely impacted by Arsenic contamination [1]. Furthermore, it was ranked as a top priority on the ATSDR (Agency for toxic substances and disease registry's) list until 2020 [2, 3]. Due to its high reducing potential and interactions with various molecules, particularly sulfur, chloride, and oxygen, arsenic can create organic compounds by bonding with carbon-containing molecules [4]. Nearly every individual is now at risk of chronic exposure to either low or high levels of this toxicant. Inhalation and ingestion are the two major routes through which arsenic enters the human body. However, compared to the pentavalent version, trivalent arsenic oxide is more lipid soluble, and it can also be absorbed through the skin to a certain extent. Recent studies indicate that general public exposure to arsenic primarily occurs through the consumption of Arsenic contaminated food and water, while inhalation plays a less significant role. The majority of arsenic that is ingested or inhaled is rapidly absorbed into the bloodstream through the gastrointestinal tract and lungs. Once absorbed, approximately 95% to 99% of trivalent arsenic is processed in the body and binds to hemoglobin within erythrocytes and is subsequently transported to various organs such as liver, kidneys, skin, and lungs. The liver can convert (in a limit) the arsenic that enters the body into a less harmful methylated derivative, which is eliminated through urine [5].

A family of proteins known as neurotrophins helps neurons grow, survive, and differentiate. In 1988, the word "neurotrophin" was initially came out. After the finding that neurotrophins, which are survival factors, may be secreted by neuronal cells. After a thorough investigation, it was discovered that neurotrophins control the formation, preservation, and death of neurons in both the PNS (Peripheral nervous system) and CNS (Central nervous system), respectively. In mammals, the four key neurotrophins are NGF, BDNF, NT-3 (Neurotrophin-3) and NT-4/5 (Neurotrophin-4/5). NGF was the first of these neurotrophins to be identified by Levi-Montalcini and Hamburger in the 1950s, who found that a protein released by a mouse sarcoma tumor placed near a developing chicken's spinal cord could stimulate neurite outgrowth originating from sympathetic neurons, that protein was later named as NGF [6]. The discovery of novel soluble growth factors was made possible by the discovery of NGF, the first growth factor ever discovered, having nourishing impact on sympathetic and sensory neurons. BDNF, the second identified member of the neurotrophic factor family, was obtained from pig brain after it was demonstrated in 1982 to support the viability of a subgroup of neurons in the dorsal root ganglia. Additional neurotrophin family members, including NT-3 and NT-4/5, have been recognized; each exhibits a distinct pattern of supportive effects on specific neuron subpopulations in the PNS and CNS [7]. NT-3 is highly expressed in the hippocampus and has been shown to enhance BDNF mRNA levels and alter BDNF signaling. It can also promote neurogenesis and synaptic plasticity. NT-4/5 functions similarly to BDNF by attaching itself to TrkB (Tropomyosin receptor kinase B) and encouraging neuronal growth [8, 9]. Although oxidative damage, mitochondrial dysfunction, and inflammation have been well-documented in arsenic-induced

neurotoxicity, the role of neurotrophins such as BDNF and NGF in mediating these effects is not fully understood. While previous reviews have explored neurotrophin involvement in neurodegenerative and psychiatric disorders [6, 10]. They often overlook their potential role in environmental neurotoxic exposures. Similarly, arsenic-related reviews have focused primarily on redox imbalance and inflammatory signaling with limited integration of neurotrophin signaling pathway [11]. This review aims to bridge this knowledge gap by synthesizing recent findings on the modulation of BDNF and NGF in arsenic-induced neurotoxicity and evaluating their therapeutic potential.

Methodology

A wide-ranging literature search was conducted across databases such as PubMed, Google Scholar, and Scopus via keywords such as "Neurotoxicity," "Arsenic," "Neuroprotection," "Neurotrophins," and "BDNF and NGF." Boolean operators (AND/OR) were used to refine the search queries. In addition, the reference lists of relevant papers were examined to identify additional studies not captured in the initial search. The search covered publications of the last decade.

Included studies were peer-reviewed and taken articles that are published in English. The review considered original research articles involving *in vivo* animal models that assessed arsenic-induced neurotoxicity. Review articles relevant to the molecular mechanisms of arsenic toxicity and neurotrophin signaling were also included to support background context and interpretation.

In vitro studies, editorials, conference abstracts, non-peer-reviewed materials, studies not reporting relevant neurotoxic outcomes and articles unrelated to neurotrophins or arsenic-induced neurotoxicity were excluded from this review. No formal quality assessment tools were applied due to the narrative nature of the review.

Arsenic occurrence

A metalloid named arsenic could occur in water, soil, and air due to sources that are both environmental and anthropogenic. It occurs in forms that are inorganic and organic, and it has been found in a variety of oxidation states (−3, 0,+3,+5). Both arsenic (iii) and (v) oxidation states of arsenic are the main considerations of toxicology researchers when it comes to exposure in the environment. As^{5+}(Arsenate) and As^{3+}(Arsenite), which are the more commonly recognized arsenic compounds, represent the negatively charged forms of arsenic acid and arsenous acid, respectively [12]. A major worldwide health issue affecting millions of people is the toxicity of arsenic. As a result of arsenic that comes from geological sources pouring into manufacturing and other industrial operations, in addition to poisoning drinking water in aquifers [13]. The toxicity of arsenic varies widely among mammals, and humans are likely to be more vulnerable than the majority of test animals [14]. Humans, along with a number of other organisms utilize methylation to detoxify inorganic arsenic, mostly forming DMA (Dimethylarsinic acid). DMA is less noxious, less likely to interact with bodily tissue, and more easily excreted through urine compared to inorganic arsenic [13]. The main ways that this metalloid is exposed are through tainted water and food. In many regions, arsenic levels in drinking water exceed recommended exposure limits. According to a tentative WHO recommendation, more than 142 million individuals in 50 countries are exposed to arsenic-contaminated water with concentrations exceeding 10µg/l [15]. Groundwater in several nations, such as India, Bangladesh, Mexico, Chile, China, Argentina, and the United States, naturally contains high levels of arsenic. It a toxicant that affects almost all organs and tissues, it has been linked to serious health consequences, such as skin lesions, multiple forms of cancer, and cardiovascular, respiratory, and gastrointestinal disorders. Additionally, this metalloid poses significant neurotoxic risks, contributing to peripheral neuropathies, encephalopathy, and neurobehavioral alterations [11]. It has also been linked to neurodegeneration. Even though epidemiological and toxicological research has demonstrated the neurotoxic effects of arsenic, this subject is still developing. It ranks as the fifth most prevalent element in the human body and is widely found in water, air, soil, and throughout the geological layers. Arsenic compounds are classified into two categories: iAs (Inorganic) and organic. iAs exists in two primary state-As^{3+} and As^{5+}. In addition to being employed as an alloying element in electronics, iAs is now utilized as a wood preservative in agricultural products and in the treatment of leukemia. The WHO-recommended exposure limits of 10 parts per billion have been exceeded by at least 140 million individuals across 50 nations. The content of iAs in groundwater might surpass 1000 parts per billion in polluted locations [16].

Neurotoxic effects of arsenic on the nervous system

Effects on gestational development and growth

We currently lack a comprehensive knowledge of iAs neurotoxicity throughout pregnancy and development. However, it has been shown by toxicological and epidemiological investigations that encounter with iAs during development has affects the cognitive and intellectual performance are discussed in table 1. Moreover, even below the current safety recommendations, iAs exposures have been linked to reduced overall IQ and alterations in memory function. Children in Bangladesh, the United States, and Mexico are affected by iAs concentrations in water between 5 and 50 ppb, exhibiting neurobehavioral alterations, including decline in long-term storage, motor function, IQ, cognitive function, and language abilities. NaAsO2 (Sodium Arsenite) exposure during pregnancy increases its accumulation in the brain of offspring mice and disrupts their memory and learning processes. Additionally, behavioral abnormalities and abnormal prefrontal cortical region development in adult-born offspring are caused by prenatal exposure of mice to NaAsO2 [17].

Effects on the adult nervous system

Numerous studies have shown a strong link between iAs exposure and changes in adult mental health and cognitive function, although epidemiological evidence regarding the effects of iAs exposure in adults remains limited, as presented in table 1 [18]. These effects include peripheral nerve dysfunction, delayed nerve signal transmission, nerve damage, and sensory processing changes [19]. Following a single exposure to iAs, four individuals developed peripheral neuropathy, which manifested as severe disturbances in sensory nerve action potentials and decreased motor conduction velocity. In the sciatic nerves of rats exposed to iAs, neurofilament and fibroblast proteins also abolished. Additionally, iAs exposure in rats causes oxidative damage, demyelination, and structural abnormalities in peripheral nerve axons, which may result in reduced information transmission from peripheral sensory receptors to the CNS [20].

Neural degeneration

Neurodegeneration cannot be shown by exposure to iAs alone, according to several studies. Yet, the neurotoxic effects of iAs may be correlated with or work in concert with the molecular causes of neurodegeneration, including inflammation, ROS (Reactive oxygen species) imbalance, and disruption of mitochondrial function. A case-control study found that higher concentrations of iAs and DMA, along with reduced selenium levels in urine, were linked to a heightened risk of developing AD (Alzheimer's disease). iAs has the ability to cause dementia and vascular damage *in vivo* [21]. Chronic iAs exposure causes behavioral deficits in rats along with elevated BACE-1 (β-secretase 1) activity, Aβ (Amyloid-β) formation, and RAGE (Receptor for advanced glycation end products) Expression. In transgenic AD animal models, iAs has been correlated with bioenergetic dysfunction and disruptions in redox metabolism, exacerbating Aβ accumulation and phosphorylated Tau immunoreactivity [22]. When iAs are mixed with other heavy metals, their pro-amyloidogenic effects are amplified, and it is linked to linked to oxidative damage and neuroinflammation. Consequently, iAs raises pro-inflammatory cytokine levels in astrocytes, which are correlated with increased BACE-1 and APP (Amyloid precursor protein) levels. Although it does not directly cause neurodegeneration *in vivo*, iAs can synergize with dopamine to cause neurotoxicity and increase the biomarkers of proteotoxic stress, leading to the accumulation and oligomerization of α-synuclein, a primary pathological characteristic of PD (Parkinson's disease). According to these results, exposure to iAs may make people more vulnerable to neurodegeneration [17].

Table 1: Overview of inorganic arsenic-induced neurotoxicity in humans and animal models

Subject	Exposure conditions	Dose/Duration	Reported neurotoxic outcomes	References
Human (Adult)	Long-term exposure in Bangladesh	129–265 µg/l	Progressive reduction in plasma cholinesterase, an enzyme linked to liver and neural function.	[23]
	Indian population; decreased exposure from 190.1 to 37.94µg/l over 5 y	190.1 to 37.94 µg/l for 5 y	Increased cases of neuropathy, eye irritation, and respiratory symptoms.	[24]
	Chronic exposure in India	129 µg/l	Elevated neuropathy-related markers like miR-29a and PMP22.	[25]
	Single arsenic dose	250–20,000 µg/l single dose	Peripheral nerve impairment, slower motor signals, and abnormal sensory responses.	[1]
	Sub-chronic	10,000-50,000 µg/l/7 mo	Peripheral nerve disturbances manifest as ongoing weakness, numbness, or pain.	[26]
Human (Child)	Bangladesh	10 µg/l	Impaired coordination and fine motor function.	[27]
	Mexico	µgAs/g creatinine	Deficits in verbal intelligence, comprehension, and memory.	[1]
	Mexico	>50 µg/l	↓cognitive, visual-spatial, and motor performance.	[28]
	U. S.; exposure.	>5µg/l/7.3 y	Lower IQ, memory, and reasoning abilities.	[29]
Rats (Wistar)	Wistar, prenatal to 4 mo.	3000µg/l	Behavioral issues and elevated Alzheimer's biomarkers.	[30]
	Acute exposure	15–20 mg/kg/single dose	Structural protein loss and cytoskeletal abnormalities.	[31]
	Sub-acute exposure	10 mg/kg/30 days	↑ Lipid peroxidation, ↓ NCV, conduction area, myelin thickness, axonal area and perimeter.	[32]
Mice	CD-1 mice, (pregnancy exposure)	20,000 µg/l/during gestation	Altered transporter/receptor expression in brain regions; memory impairment.	[33, 34]
	C57BL/6 strain	100,000 µg/l	Reduced synaptic transporters and receptors in striatum.	[35]
	Swiss Webster, chronic exposure	100 µg/l	Increased neurodegeneration markers in striatum and cortex.	[36]

Abbreviations: ↑: Increase; ↓: Decrease; µg/l: micrograms per liter; NCV: Nerve conduction velocity; µgAs/g: micrograms arsenic per g of creatinine; miR-29a: MicroRNA-29a; PMP22: Peripheral myelin protein 22.

Mechanisms underlying arsenic-induced toxicity

Arsenic-mediated oxidative stress mechanisms

Arsenic toxicity is primarily driven by the production of oxidative stress, as evidenced by several *in vitro* and *in vivo* studies. After exposure, it has been demonstrated that ROS, including superoxide anion radical and hydrogen peroxide, increase in a variety of tissues. A very complicated cycle links oxidative stress and inflammation. ROS can activate several transcription factors, which in turn enhance the expression of pro-oxidant and antioxidant enzymes, as well as inflammatory cytokines [37]. Moreover, they can activate and attract phagocytic leukocytes to inflammatory areas, where they can release enzymes that intensify oxidative stress and raise inflammation. Inflammation and oxidative stress are major contributors to chronic illnesses as shown in [fig. 1]. Therefore, several *in vivo* models, especially at lower doses or shorter durations, have shown no significant increase in ROS generation, suggesting that arsenic-induced oxidative stress may be tissue-specific or dose-dependent. These discrepancies may reflect compensatory antioxidant responses or limitations in detection sensitivity [38].

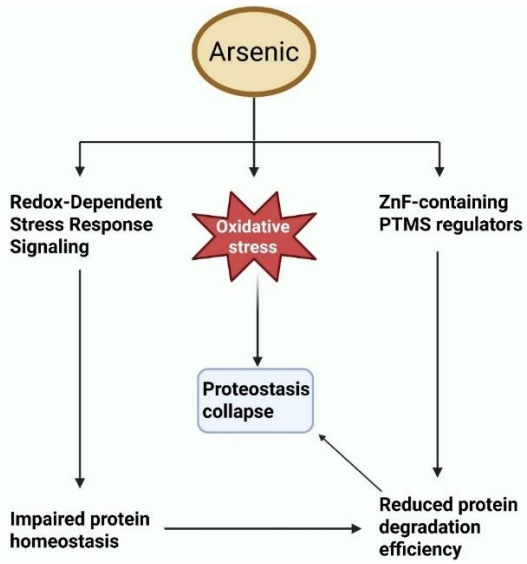

Fig. 1: Oxidative stress pathways triggered by arsenic: interference with ZnF (Zinc Finger) proteins and redox-responsive stress response pathways, resulting in disrupted proteostasis, compromised protein stability, and diminished protein degradation efficiency

The following are several ways that arsenic is thought to cause oxidative damage in cells: (i) It is commonly known that arsenic changes mitochondria, reduces membrane potential, and weakens the mitochondrial membrane. These structural changes serve as key locations for excessive superoxide anion generation, initiating a cascade of reactions that culminate in elevated free radical formation. The oxidative defense mechanism breaks down, and harmful symptoms show up when oxidative stress levels keep rising [39].

(ii) The electron transport activity within mitochondria, particularly at complexes I and III, is a major contributor to O_2^- (Superoxide anion) formation. Arsenic-induced suppression of succinate dehydrogenase and impairment of oxidative phosphorylation contribute to excess O_2^- formation and oxidative stress [40].

(iii) ROS can also be produced by arsenic through processes that include NADPH (Nicotinamide adenine dinucleotide phosphate) oxidase. The e- from internal NADPH are transferred across the membrane by this membrane-bound enzyme, where they combine with oxygen molecules to produce O_2^- [41]. In cultured human endothelial cells, arsenic functions as an external stimulus that activates Ras family proteins, such as cdc42, leading to the stimulation of NADPH oxidase and subsequent production of ROS [42].

(iv) Additionally, arsenic can produce ROS by interfering with the NOS (Nitric oxide synthase) enzyme system. L-arginine and molecular oxygen are converted into NO (Nitric Oxide) by NOS iso-enzymes without generating superoxide [43]. This connection is broken by arsenic exposure, which results in ROS.

(v) Under normal conditions, the metabolism of Arsenic (III) to Arsenic (V) promotes the production of H_2O_2 (Hydrogen peroxide) [44].

(vi) Dimethylarsinic peroxyl radicals, which are metabolic byproducts of DMA, are among the intermediate arsine species that are produced during the generation of ROS [45].

(vii) Methylated 3+organic arsenicals undergo an antioxidative reaction with SH-(Sulfhydryl groups) proteins and prevent them from functioning, which causes oxidative stress [46]. Elevated ROS can also damage nuclear and mitochondrial DNA (Deoxyribonucleic acid), inducing base modifications, strand breaks, and cross-linking. This activates DNA damage response pathways such as p53 (Tumor protein p53) and PARP (Poly (ADP-ribose) polymerase), which can lead to neuronal apoptosis or impaired gene transcription essential for synaptic function. In the brain, such DNA damage contributes to hippocampal atrophy and cognitive dysfunction seen in arsenic-exposed models [47].

Mitochondrial dysfunctions

The operation of other cellular machinery and mitochondria has a complicated interaction that impacts cell viability. Cells rely on mitochondria for energy, and they play crucial roles in the electron transport chain and oxidative phosphorylation [48]. They are yet another significant generator of free radicals in cells. When animals are exposed to xenobiotics like arsenic, their mitochondrial function is disrupted [49]. This is demonstrated by the suppression of mitochondrial oxygen consumption, which results in a disordered membrane potential. A discrepancy in energy expenditure and consumption results from reductions in ATP (Adenosine triphosphate) synthesis and membrane stability [50]. Numerous earlier investigations have revealed that mitochondrial impairment and redox imbalance are the main mechanisms by which arsenic causes neurotoxicity [51]. There have been significant efforts to look at a variety of molecular processes in neuropathological studies in arsenic-induced mitochondrial dysfunction [52]. Studies indicate that arsenic disrupts mitochondrial respiratory function, leading to an overproduction of ROS in several cell types, including neurons [53]. Twelve weeks of arsenic exposure has been found to compromise the function of key mitochondrial enzymes in the brain, particularly those associated with complexes I, II, and IV. Through competition with phosphate because of their similar chemical structures, arsenate can have a major effect on the generation of ATP. This process is called arsenolysis, and it occurs as part of glycolysis. Within this metabolic process, phosphate and G3P (D-glyceraldehyde-3-phosphate) are normally linked by enzymes to generate 1,3-BPG (1,3-bisphosphoglycerate). In addition to the conventional 1,3-BPG, 1-As-3PG (Anhydride 1-arsenato-3-phosphoglycerate) is formed when arsenate is present because phosphate is substituted with arsenate. The arsenic–oxygen bonds are, on average, around 10% longer than phosphorus–oxygen bonds, making the resulting anhydride unstable and prone to hydrolysis into $As^{5+}$and 3-phosphoglycerate [54]. The generation of ATP is depleted by these steps. Glycolysis produces ATP when phosphate is present, but this is greatly impaired when $As^{5+}$is present.

Arsenolysis also affects ATP synthesis at the oxidative phosphorylation stage in the mitochondria [55]. When succinate is present, ADP (Adenosine-5-diphosphate) and $As^{5+}$are used to create ADP– As^{5+}at the submitochondrial level [56]. When arsenate is present instead of phosphate, ADP– $As^{5+}$is created because of structural similarities with phosphate. ADP-As^{5+}, in contrast to ATP, is unstable and undergoes further hydrolysis, which results in a considerable reduction in ATP. Dehydrogenase activity was suppressed in mice exposed subchronically to low levels of arsenic trioxide. DNA from the nucleus and mitochondria encode these complexes. More research is needed to describe molecular mechanisms that result in altered gene expression when exposed to arsenic. The mechanisms leading to mitochondrial membrane failure are activated by cellular metabolism and calcium. The alterations in membrane stability, lipid profile, cytoskeletal structure, and reactive species that contribute to cellular dysfunction may all be further explained by these two variables [57]. There is little scientific proof of a connection between neurotoxicity and intracellular calcium levels and dysfunctional mitochondria.

Inflammation

With prolonged arsenic exposure, neurotoxic effects arise, including the disruption of myelination, which impairs neuronal integrity and communication. Arsenic exposure leads to ROS imbalance, triggering the initiation of oxygen-derived free radicals and nitrogen-derived free radicals, which results in cellular damage and initiates cellular inflammatory activity in the CNS [54]. This pro-inflammatory environment stimulates microglia and astrocytes, triggering the production of cytokines like IL-1β (Interleukin-1 beta), IL-6 (Interleukin-6), and TNF-α (Tumor necrosis factor-alpha), which further amplify neurotoxicity [58]. Prolonged arsenic exposure is associated with disruption of myelination, impairing neuronal integrity and communication. When pathogenic anti-myelin T-cells are activated, meningeal damage and macrophage invasion occur, both of which contribute to demyelination. This process results in a loss of trophic support to neurons, leading to decreased nerve conduction velocity and impairments in both motor and sensory functions, as shown in [fig. 2] [54].

Apoptosis

By triggering MAPK (Mitogen-activated protein kinase) signaling, which is primarily mediated by JNK (c-Jun N-terminal kinase), p38 (Tumor protein p38), and ERK (Extracellular signal-regulated kinase), arsenic exposure causes caspase-dependent death in neuronal cells as shown in [fig. 3]. These kinases react to oxidative stress triggered by arsenic, resulting in mitochondrial dysfunction and apoptotic cascade activation. Apoptosis in arsenic toxicity can proceed via both the intrinsic (mitochondrial) and extrinsic (death receptor) pathways. The intrinsic pathway involves mitochondrial membrane permeabilization and cytochrome c release, activating caspase-9 [59]. In contrast, the extrinsic pathway involves activation of death receptors like CD95 (also known as Fas) or TNF-α, which recruit adaptor proteins (e. g., FADD-FAS-associated protein with death domain) to activate caspase-8. Both cascades converge on caspase-3, leading to programmed cell death [60]. Interestingly, some studies report necrotic features such as cell swelling, plasma membrane rupture, and inflammatory infiltration in cortical neurons exposed to high arsenic doses. This suggests that the type of cell death may depend on arsenic dose, cell type, or energy availability. In some cases, necroptosis, a regulated form of necrosis, may be involved. Understanding this balance between apoptosis and necrosis is critical for targeting protective therapies [61]. Additionally, arsenic disrupts intracellular Ca^{2+} (Calcium) homeostasis, promoting endoplasmic reticulum stress and mPTP (Mitochondrial permeability transition pore) opening. This enhances apoptotic signaling by elevating the levels of key pro-apoptotic factors such as cytochrome c and AIF (Apoptosis-inducing factor) [17].

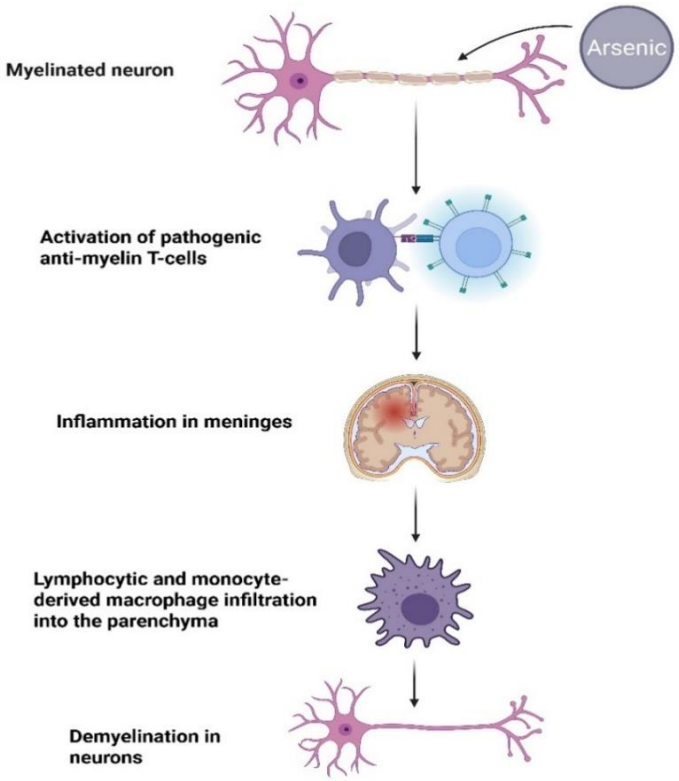

Fig. 2: Pathogenic anti-myelin T-cell activation causes demyelination, subsequently leading to inflammation of the meninges and infiltration of the brain parenchyma by lymphocytes, as well as macrophages derived from monocytes, which ultimately deprives neurons of trophic support

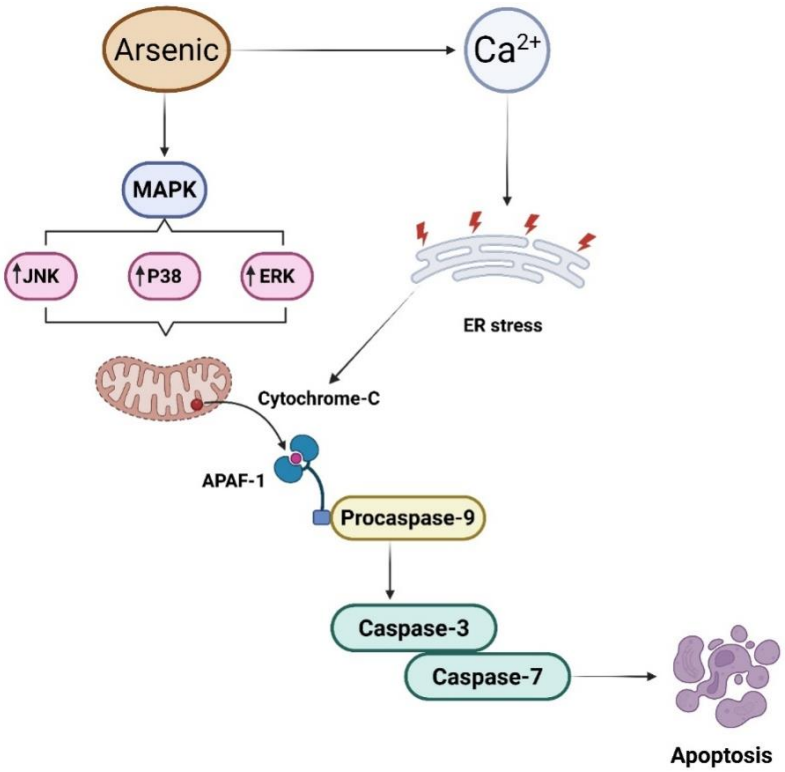

Fig. 3: Arsenic exposure triggers caspase-dependent apoptosis in neuronal cells via MAPK signaling (JNK, p38, ERK), oxidative damage, and mitochondrial dysfunction. Cyt-C release activates caspases, contributing to neuronal apoptosis, further amplified by ER stress and disrupted Ca^{2+} homeostasis. MAPK: Mitogen-activated protein kinase; JNK: Jun N-terminal kinase; ERK: Extracellular signal-regulated kinase; APAF-1: Apoptotic protease activating factor-1

Effects on nerve conduction

Numerous mechanisms for arsenic-induced neurotoxicity have been identified, as shown in [fig. 4]. The speed at which an electrical impulse passes through a neuron is measured by motor and sensory nerve conduction [62]. During a NCV (Nerve conduction velocity) test, electrodes placed on the skin are used to stimulate a specific nerve. This examination evaluates the extent of nerve damage and impaired function. A decline in neural transmission velocity in the sural-saphenous region, which plays a role in conveying sensory information from the skin, has been recognized as an initial sign of prolonged arsenic-related peripheral neuropathy. Prolonged arsenic exposure has been linked with reduced nerve conduction velocity in Taiwanese adolescents [63]. The median, sural, ulnar, and saphenous nerves all exhibited a significant reduction in nerve conduction in those who were exposed to arsenic long-term. CMAPs (Compound muscle action potentials) were also affected. It has been shown that the NCV of taller patients (>163 cm) is lower than that of shorter subjects. Sensory nerves exhibit greater sensitivity compared to motor nerves in symmetrical peripheral neuropathy, according to several studies, and the larger arm neurons are significantly impacted [54]. Axis cylinders disintegrated, and the number of myelin fibers decreased as a result of myelin breakdown and resorption on the distal part of nerves brought on by arsenic exposure. Arsenic exposure is associated with encephalopathy and impairments of superior brain functioning, according to several additional investigations [64]. Besides its direct effects on neuronal systems, arsenic has been shown to induce oxidative stress, inflammation, and tissue damage in non-neuronal organs. In a rat model, Arsenicum album administration resulted in elevated HDL (High-density lipoprotein) levels and mild liver and kidney toxicity, potentially linked to underlying oxidative and inflammatory responses [65].

Epigenetic modifications in arsenic neurotoxicity

Arsenic-induced neurotoxicity involves not only oxidative and inflammatory processes but also epigenetic changes such as DNA methylation, histone modification, and miRNA (microRNA) regulation. Chronic arsenic exposure has been shown to induce global hypomethylation and gene-specific promoter hypermethylation in brain tissues, leading to altered gene expression patterns linked to neurodevelopment and neurodegeneration [66].

Specifically, miRNAs such as miR-124, miR-29a, and miR-210 are dysregulated by arsenic and have been implicated in pathways related to neuronal apoptosis, inflammation, and synaptic plasticity. These miRNAs can also regulate neurotrophin signaling components such as Trk receptors and downstream PI3K/AKT cascades, suggesting a functional cross-talk between arsenic-induced epigenetic changes and neurotrophin-mediated protection [67].

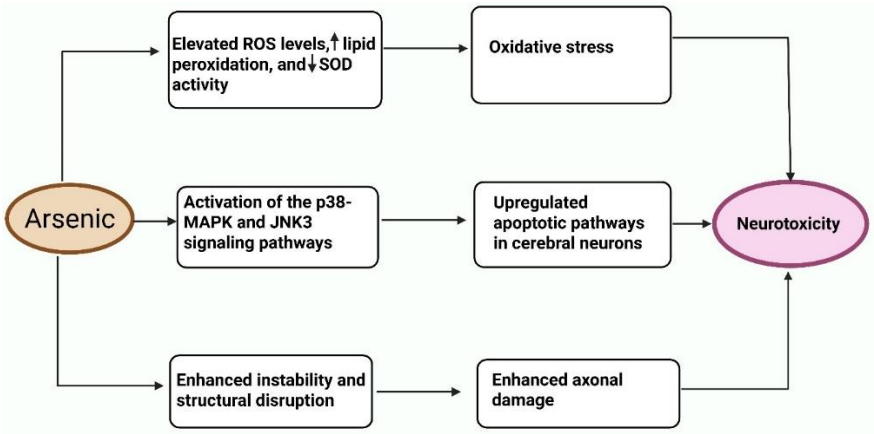

Fig. 4: Schematic representation of the key molecular and cellular mechanisms involved in arsenic-induced neurotoxicity. Arsenic exposure initiates a cascade of neurotoxic events through three major pathways: (i) increased oxidative stress due to ROS imbalance and decreased antioxidant defense; (ii) activation of p38-MAPK and JNK3 signaling pathways leading to neuronal apoptosis; and (iii) cytoskeletal instability and axonal degeneration, all contributing to neuronal dysfunction

Table 2: Summary of major neurotrophins involved in arsenic-induced neurotoxicity and their neuroprotective roles

Neurotrophins	Receptor	Functions	Arsenic-induced disruption	Protective role	References
BDNF	TrkB	Supports synaptic plasticity, cognition, and neuron survival	Inhibits TrkB phosphorylation, suppresses PI3K-Akt, RAS-MEK-ERK, and PLCγ pathways	70–80% reduction in memory impairment	[10, 69, 70]
NGF	TrkA	Promotes survival and differentiation of sensory neurons	Arsenic impairs NGF-mediated signaling, affecting survival pathways	40-55% reduction in apoptotic motor neurons	[6, 71, 72]
NT-3	TrkC	Involved in neurogenesis, BDNF signaling, and synaptic plasticity	Disrupted expression under arsenic exposure, indirect BDNF suppression	Boost neuronal and oligodendrocyte differentiation by approximately 10-12%	[8, 9]
NT-4/5	TrkB	Similar function to BDNF in supporting neurons	Limited data, but presumed similar TrkB-related suppression	16% absolute reduction in neuronal loss.	[9, 69]

PI3K-Akt: Phosphoinositide 3-kinase–Protein kinase B; RAS-MEK-ERK: Rat sarcoma–Mitogen-activated protein kinase kinase–Extracellular signal-regulated kinase; PLCγ: Phospholipase C gamma.

Physiological role of neurotrophins in arsenic-induced neurotoxicity

Neurotrophins, such as BDNF, are essential for preserving synaptic plasticity, neuronal survival, and cognitive processes [68]. These growth factors exert their effects primarily via stimulation of Trk receptors, particularly TrkB, initiating multiple intracellular signaling cascades vital for neuronal health. For better understanding, the roles of various neurotrophins in arsenic-related neuronal damage are summarized in table 2, which provides a

comparative summary of their functions, disrupted signaling pathways, and neuroprotective potential. However, exposure to arsenic significantly disrupts neurotrophin signaling pathways, contributing to neurodegeneration and cognitive impairments. Arsenic exposure impairs the activation of TrkB receptors by inhibiting their phosphorylation, leading to the suppression of key downstream cascades like PI3K-AKT and RAS-MEK-ERK (Rat sarcoma–Mitogen-activated protein kinase kinase–Extracellular signal-regulated kinase). These pathways are crucial for regulating transcription of neuroprotective genes via the activation of the CREB at the BDNF promoter region [69] [fig. 5]. Illustrates the impact of arsenic on these signaling mechanisms, highlighting how arsenic inhibits TrkB activation, resulting in reduced BDNF expression and subsequent neuronal damage. Additionally, arsenic-induced disruption of the PLCγ (Phospholipase C gamma) pathway interferes with intracellular calcium levels and the activation of CaMK (Calcium/calmodulin-dependent protein kinase), further exacerbating neuronal dysfunction. The inhibition of these pathways compromises synaptic plasticity and neuronal survival, as illustrated in the diagram.

In a study performed by Pandey *et al.*, focusing on the role of E2 (Estrogen) and neurotrophins, particularly BDNF, in mediating these effects. Adult rats were exposed to varying doses of arsenic (1x and 10x), with male and ovariectomized female rats used as models for E2 deficiency. Behavioral assessments included passive avoidance and Y-maze tests to measure learning and memory. Results indicated that male rats experienced significant neuronal loss and cognitive decline compared to females, particularly at higher arsenic doses. E2 deficiency in females accelerated neuronal apoptosis and impaired cognitive function, while E2 treatment mitigated these effects, demonstrating the neuroprotective effects of neurotrophins in arsenic induced neurotoxicity [70]. These findings highlight the sex-specific modulation of neurotrophin pathways, with E2 acting as a key enhancer of BDNF expression via ERα-CREB (Estrogen receptor-α) signaling. Female brains may be more resilient to arsenic-induced neurotoxicity due to this hormonal regulation. This aligns with evidence that estrogen enhances synaptic plasticity, TrkB signaling, and mitochondrial function. However, ovariectomized or postmenopausal models lacking estrogen show a sharper decline in BDNF and more severe cognitive deficits. Future studies should explore gender-specific dosing and hormonal co-therapies in arsenic neurotoxicity management.

Similarly, in another study Mehta *et al.*, examined the physiological function of neurotrophins in arsenic-induced neurotoxicity, specifically looking at how RES (Resveratrol) and As_2O_3 (Arsenic Trioxide) interact to affect neurobehavioral functions and neurochemical alterations in female mice's hippocampal regions. Adult mice were exposed to As_2O_3 at doses of 2 and 4 mg/kg BW as well as 40 mg/kg BW in combination with RES over a 45-day period. The findings indicated that arsenic exposure resulted in increased anxiety, decreased locomotion, and cognitive impairments, which were associated with reduced ERα expression and lowered levels of BDNF and NMDAR 2B (N-methyl-D-aspartate receptor subtype 2B) in hippocampal tissues. Notably, RES supplementation restored cognitive functions and reversed the downregulation of neurotrophins, suggesting its potential as a protective compound against arsenic toxicity [10].

Emerging biomarkers for early detection of arsenic toxicity

Beyond BDNF and NGF, additional biomarkers are being explored to detect early-stage arsenic-induced neurotoxicity. These include serum and CSF (Cerebrospinal fluid) levels of BDNF, which may serve as non-invasive indicators of neuronal stress [73]. Altered levels of NFL (Neurofilament light chain), S100β (S100 Calcium-binding protein beta), GFAP (Glial fibrillary acidic protein), and oxidative stress markers like 8-OHdG8 (Hydroxy-2-deoxyguanosine) have also been observed in arsenic-exposed subjects. Integration of such biomarkers with miRNA profiles may offer a multiparametric approach for early diagnosis, disease monitoring, and therapeutic response prediction [74].

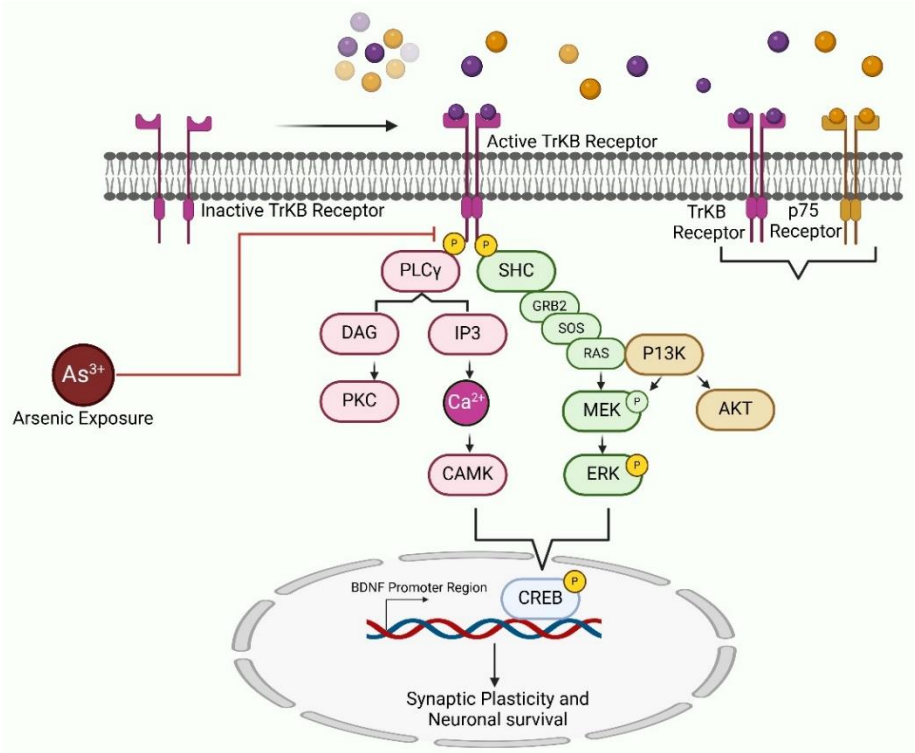

Fig. 5: Mechanisms of arsenic-induced neurotoxicity showing the disruption of neurotrophin signaling pathways. Arsenic exposure inhibits TrkB receptor activation, suppressing downstream pathways such as PI3K-AKT, RAS-MEK-ERK, and PLCγ-CaMK, ultimately leading to decreased CREB activation and BDNF transcription. This cascade of events contributes to synaptic dysfunction and neuronal apoptosis. PLCγ: phospholipase C gamma; CaMK: Ca^{2+}/calmodulin-dependent protein kinase; CREB: Cyclic AMP-Responsive Element-Binding Protein; PI3K-AKT: Phosphoinositide 3-kinase–Protein kinase; RAS-MEK-ERK: Rat sarcoma–Mitogen-activated protein kinase kinase–Extracellular signal-regulated kinase

Therapeutic implications and future perspectives

Rationale for the development of small molecules targeting neurotrophin receptors

Neurotrophins have less-than-ideal pharmacological characteristics, such as low stability, probably low oral bioavailability, restricted penetration of the BBB (Blood-brain barrier), and restricted parenchymal diffusion in the CNS [75]. Adverse consequences are also more likely due to the extremely pleiotropic actions of neurotrophins, which are produced by activating their multi-receptor signaling complexes [76]. These effects include worsening of some types of brain damage and upregulation of pain transmission [77]. The lack of knowledge regarding the integration of neurotrophin signaling processes with underlying disease mechanisms presents another difficulty in the therapeutic use of neurotrophin proteins. There are three stages to consider when developing neurotrophin-based treatment approaches [78]. Neurotrophin proteins have been administered by a variety of peripheral and central nervous system pathways during "phase one" in the intervention of AD, ALS (Amyotrophic lateral sclerosis), PD, diabetic neuropathy, and hereditary neuropathy [71]. Neurotrophins are thought to have protective effects against a range of critical mechanisms, including excitotoxicity, oxidative damage, and hypoxia-ischemia, and they may also aid in regeneration [79]. Neurotrophin proteins are delivered in the vicinity of specific neurons by gene therapy or cell transplant techniques in "phase two," which is a response to the hypothesis that lack of effectiveness is primarily caused by restricted bioavailability at target neurons. Many issues with administering neurotrophin proteins still exist, despite increasingly sophisticated delivery methods [80]. Targeting certain neurotrophin receptors with small molecule ligands that have advantageous medicinal qualities to either enhance beneficial activities or inhibit particular pathological pathways is known as "phase three" of neurotrophin-based therapeutic development [81]. One of the most promising small molecules under investigation is LM11A-31-a, a non-peptide ligand targeting the p75NTR (p75 neurotrophin receptor). Preclinical studies in AD models have shown that LM11A-31 can prevent synaptic loss, reduce tau phosphorylation, and improve cognitive performance, without activating pain pathways typically associated with NGF. This molecule successfully crossed the BBB and showed neuroprotective activity in both *in vitro* and *in vivo* settings. A Phase 2a clinical trial (NCT03069014) evaluating LM11A-31 in mild-to-moderate AD patients demonstrated favorable safety and tolerability, although cognitive endpoints showed modest benefits, suggesting further trials are needed to establish efficacy [82]. The p75NTR has become a particularly intriguing target for brain damage and degeneration. According to recent research, p75NTR expression is elevated in several clinical contexts and may be involved in controlling cell survival in neurodegenerative diseases, spinal cord injuries, and CNS axonal damage [80].

The therapeutic potential of neurotrophins is limited by poor BBB permeability and rapid enzymatic degradation. Recent advances in nanotechnology and exosome-based delivery systems offer promising solutions [83]. Nanoparticles conjugated with targeting ligands can deliver BDNF/NGF across the BBB with sustained release, while engineered exosomes derived from mesenchymal stem cells provide a biocompatible platform with low immunogenicity and high CNS targeting efficiency [84]. Hybrid strategies combining neurotrophins with antioxidants or miRNAs may further enhance therapeutic impact. However, these approaches require optimization of dose, targeting, and safety profiles in large-animal and human models [85].

Neuroprotection against Aβ-induced degeneration

Although reducing Aβ accumulation is a viable strategy for preventing AD neurodegeneration, new research suggests that reducing Aβ alone may not be enough therapy [86]. It has been shown that Aβ depletion *in vitro* is hazardous, and it may have vital physiological functions in controlling excitatory transmission and cognition [87]. Furthermore, Aβ-based treatments are unlikely to enhance the function or plasticity of damaged neurons and won't target the non-Aβ pathways that underlie the development of the illness [88]. While dual-target strategies aiming to reduce Aβ burden and enhance neurotrophin signaling appear synergistic in theory, the practicality is complex. For instance, Aβ-targeting therapies (e. g., aducanumab) reduce amyloid plaques but do not reverse synaptic damage, while neurotrophins like BDNF may restore synaptic function without reducing plaque load. Thus, combinatorial strategies must carefully balance timing, dosage, and patient selection [89]. Additionally, overexpression of neurotrophins or indiscriminate p75NTR modulation may lead to off-target effects, including altered pain sensitivity, unintended activation of pro-apoptotic pathways, or glial cell hyperactivation [90]. There are several ways in which small medicines that target p75NTR may alter the pathophysiological processes underlying AD. The RAGE receptor, which binds advanced glycation end products, cell surface APP, p75NTR, the α7nicotinic acetylcholine receptor, and BBP-1 (Branchpoint binding protein), a GPCR (G protein-coupled receptor). The distributional similarities between p75NTR and neurons that are susceptible to degeneration in AD, such as those in the entorhinal cortex, neocortex, hippocampus, and basal forebrain, indicate that p75NTR may mediate Aβ toxicity, making it an especially interesting target for preventing Aβ's harmful effects. On the other hand, p75NTR expression seems to be elevated in AD tissue in the entorhinal cortex, neocortex, and hippocampus, with neurons expressing more p75NTR seemingly being relatively immune to neurodegenerative features. Based on research showing that Aβ raises p75NTR levels in neuronal cultures and that downregulating p75NTR expression increases susceptibility to Aβ, it is plausible that Aβ may cause upregulation of p75NTR expression and that p75NTR signaling can promote protective signaling [91].

Neuroprotection against oxidative stress and excitotoxicity

Potential causes of AD and other neuropathological conditions for which neuroprotection is being sought include oxidative stress and excitotoxicity [92]. Degenerative signaling is triggered by oxidative stress, which also activates stress kinases like JNK [93]. It has been demonstrated that, depending on the model used, neurotrophins either prevent or enhance oxidative stress-induced mortality [94]. Responses to neurotrophins are determined by several factors, such as specific oxidative stress test settings and whether death happens by necrosis (which neurotrophins enhance) or apoptosis (which neurotrophins inhibit). Through the p75NTR connection, NGF has been demonstrated to stop cell death in an excitotoxicity paradigm [95].

Despite promising preclinical findings, translation to clinical success has been limited. For example, recombinant NGF in Phase I/II trials for peripheral neuropathy showed modest efficacy but significant adverse effects such as injection site pain and hyperalgesia [96]. Similarly, BDNF gene therapy has faced challenges related to vector safety, delivery precision, and immune activation. Small molecules like LM22A-4 (a TrkB agonist) have shown benefits in animal models of Rett syndrome and Huntington's disease, but human trials are currently lacking [97].

Furthermore, off-target effects remain a key concern, particularly with p75NTR modulators, which can interact with signaling pathways like RhoA (Ras homolog family member A), JNK, and NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells), potentially causing pro-inflammatory or pro-apoptotic effects in non-neuronal tissues [98]. Therefore, targeted delivery systems and highly selective modulators are essential for minimizing systemic toxicity and optimizing therapeutic outcomes.

CONCLUSION

Arsenic-induced neurotoxicity remains a serious global health concern, contributing to cognitive deficits, neurodevelopmental disorders, and neurodegeneration. Its pathological effects are primarily driven by oxidative stress, mitochondrial dysfunction, neuroinflammation, apoptosis, and impaired neurotransmission. However, arsenic disrupts Trk receptor activation, impairing essential pathways such as PI3K-Akt, RAS-MEK-ERK, and PLCγ-CaMK, which leads to reduced BDNF expression, increased oxidative stress, inflammation, and apoptosis, accelerating neurodegeneration. Neurotrophins such as BDNF and NGF offer significant neuroprotective potential, but their therapeutic application faces

challenges due to poor bioavailability and delivery barriers. Emerging approaches, including small-molecule mimetics and targeted delivery systems, hold promise. Future research should focus on optimizing these strategies and identifying early biomarkers to enable timely intervention and improve clinical outcomes.

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CONFLICT OF INTERESTS

Declared none

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