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NAVIGATING THE AFTERMATH OF HYPOXIC-ISCHEMIC ENCEPHALOPATHY (HIE): A REVIEW ON PATHOPHYSIOLOGICAL CASCADES, METABOLIC DYSFUNCTION, AND EMERGING NEUROPROTECTIVE STRATEGIES

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ABSTRACT

Hypoxic-ischemic encephalopathy (HIE) is a neonatal brain injury caused by a lack of oxygen during the prenatal, intrapartum, or postnatal period. It is a major cause of long-term neurological disorders in children. The clinical manifestations range from mild behavioral abnormalities to severe seizures, motor dysfunction, cerebral palsy, and permanent brain damage. Despite recent advances in antenatal diagnosis and improvements in hospital-based neonatal care, the incidence of perinatal asphyxia remains high. The underlying pathophysiological mechanisms are not yet fully understood, and effective therapeutic options remain limited. Therefore, the present review summarizes the established pathophysiological mechanisms of perinatal asphyxia and discusses current therapeutic strategies aimed at reducing disease severity and preventing disease progression at an early stage. Furthermore, it highlights the mechanisms of action of existing drugs and identifies emerging molecular targets that may facilitate the development of more effective therapeutic interventions.

KEYWORDS: Hypoxic-ischemic encephalopathy (HIE); Pathophysiological Cascades; Metabolic Dysfunction; Mitochondria Dysfunction; Neuroprotective Strategy

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE), is a type of neonatal brain injury that occurs due to inadequate oxygen supply to the brain during the prenatal, intrapartum, or postnatal period. Globally, the incidence of HIE is estimated to be 1.5–2.5 cases per 1,000 live births [1]. The mortality and morbidity associated with HIE can reach up to 60% by the age of two years. The condition affects neurological function, with clinical manifestations ranging from mild behavioral abnormalities to severe seizures, cerebral palsy, cognitive impairment, and permanent neurological disability [2].

Despite significant advances in obstetric and neonatal care aimed at preventing hypoxic-ischemic events, the incidence of HIE remains a major global health concern. The complex pathophysiological mechanisms underlying HIE are not yet fully understood, limiting the development of effective therapeutic interventions [3]. Consequently, current neonatal research focuses on elucidating the molecular and cellular mechanisms involved in the different phases of HIE and developing neuroprotective therapeutic strategies that can be administered as early interventions to minimize neuronal injury and improve neurological outcomes.

METHOD OF LITERATURE SEARCH

A comprehensive literature review was conducted by retrieving articles from indexed databases, including PubMed, Scopus, EMBASE, and Web of Science, using predefined keyword searches. Priority was given to original research articles, systematic reviews, and meta-analyses published within the last ten years. Duplicate publications, animal studies, short communications, case reports, letters to the editor, commentaries, and articles published in languages other than English were excluded.

The retrieved articles were screened for duplication, relevance, and scientific quality. Following a rigorous screening process, 28 articles were selected for full-text review. The Medical Subject Headings (MeSH) terms used in the literature search included *hypoxic-ischemic encephalopathy*, *biomarkers*, *oxidative stress*,

pathophysiology, *metabolic dysfunction*, *amino acid dysregulation*, *neuroprotective therapeutic targets*, and *HIE outcomes*. The study selection process is illustrated in the PRISMA flow diagram (Figure 1).

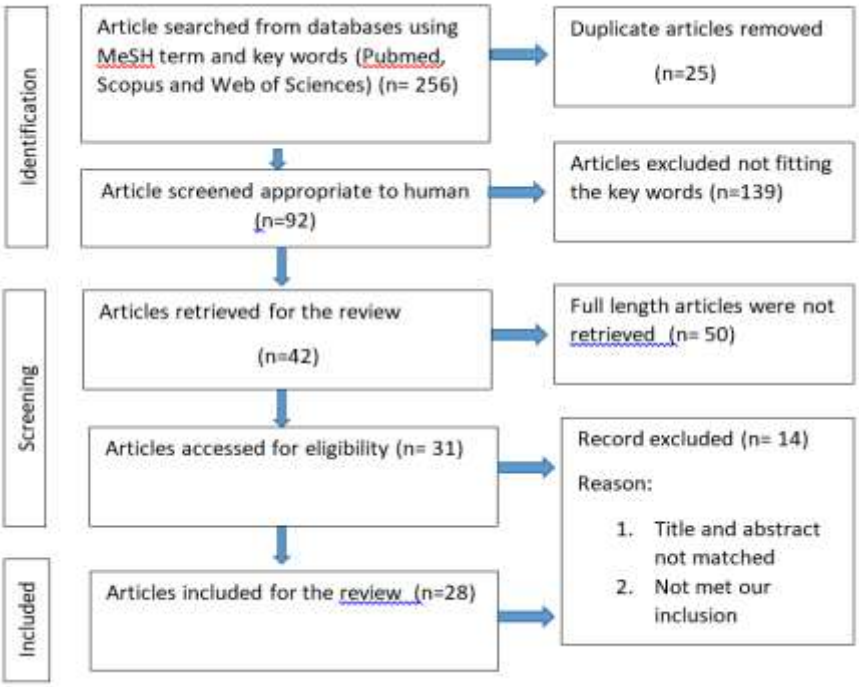

Figure 1: Article screening from Literature search and selection strategy for review (a PRISMA flow chart).

Pathophysiology of HIE

The pathophysiology of hypoxia is still in a debatable condition. It is a complex process where multiple stages involved following an initial hypoxia phase, quiescent phase, delayed phase, and progressive phase. In the initial hypoxia phase, oxygen supply reduced, which affected the blood flow to the tissue leading to impaired cellular respiration and depletion of cellular ATP generation. As a result, the cell undergoes anaerobic metabolism and cause lactice acid accumulation, intracellular acidosis, block ion pumps, depolarize the membrane and cellular edema. These events develop cyto-toxicity, oxidative stress and cellular injury.

Quiescent phase or Latent phase represents a partial metabolic recovery following reperfusion and reoxygenation. This phase lasts for hours. In this phase cellular energy level normalize temporarily and some physiological function appears to be improved. Major disturbances persist due to mitochondrial dysfunction, inflammatory signalling and apoptotic pathway which leads to further injury (secondary phase) in the cell.

The delayed phase or secondary phase lasts hours to days after initial insult and is marked by delayed cellular damage. This phase involves excessive ROS & NO generation, calcium influx, glutamate-mediated cytotoxicity, inflammation and activation of programmed cell death. It is a critical phase for therapeutic intervention.

The progressive or tertiary phase develops days to weeks after hypoxia and is associated with chronic inflammation, impaired repair mechanism, neurodegeneration and altered neurodevelopment and leading to permanent cellular damage and organ damage.

In the initial phase of hypoxia, ATP synthesis reduces and lactic acidosis occurs [3]. Disruption of the neuronal cell membrane results in a massive influx of calcium into the cell, which activates NMDA (N-methyle D-aspartate) receptors through excitotoxic neurotransmitters such as glutamate and aspartate [4]. Primary energy failure at initial stage of hypoxia insult can be controlled by very few therapeutic strategies, melatonin is one of them.

Physiological hypoxia is essential for embryonic growth and development. In the normal fetus, the partial pressure of oxygen ranges from 25–30 mm Hg, increasing to about 75–85 mm Hg after birth, as soon after delivery, newborns are exposed to room air. However, neonates may sometimes experience episodes of hypoxia and hyperoxia, leading to oxidative stress, which can cause cellular damage and impair brain development [2].

Fetal antioxidant defense systems develop and strengthen during the final weeks of pregnancy, enabling them to cope with the physiological oxidative stress that occurs at birth. [3,4]. As a result, preterm infants struggle more to adjust to the PaO2 rise during birth [5]. Because preterm neonates lack antioxidant defense mechanisms, they are more susceptible to OS, which can have short- to long-term negative effects, especially on the retina, lung, brain, and gut [6]. Free radicals damage the brain because of its high energy and oxygen requirements [7]. However, the brain has a high polyunsaturated omega-3 fatty acids, particularly in the membranes of neurons, which makes it more vulnerable to OS [8].

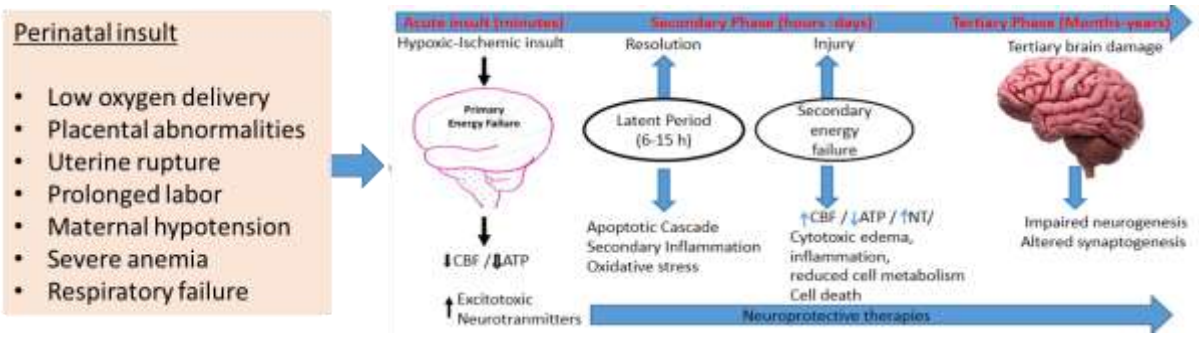

Figure 2: Pathophysiology of brain injury due to Hypoxia.

Oxidative stress and metabolic dysfunction in HIE

During abnormal oxidative reactions, various transition metals such as Fe_2^+ or Cu^+ accumulated in brain cell which generates reactive oxygen species (ROS), nitric oxide (NO) which affects the central nervous system (CNS) development [9-12]. Hence, Oxidative stress as induced by hypoxia/ischemia damages the cellular structure and function in the brain, which lead to neuroinflammation, mitochondria dysfunction, and altered redox state of neurons [13]. Mitochondria dysfunction reduces the ATP production in the cell. Lactic acidosis (lacticaemia) and impaired ionic transport within cells, along with increased intracellular calcium influx, activate neuronal nitric oxide synthase (nNOS), which produces nitric oxide (NO•); this contributes to secondary energy failure and delayed neuronal cell death [14,15]. Changes in the neuronal membranes release high level of glutamate, which activates N-methyl-d-aspartate (NMDA) receptors. Similarly, lipases, proteases, and endonuclease activated by calcium [16]. Inflammation, mitochondrial dysfunction, and increased levels of superoxide ($O_2•^-$) enhance ROS generation, which subsequently oxidize biomolecules like DNA, lipids, proteins, and other cellular components, cellular apoptosis (**Fig. 1**) [17]. This review summarizes the effects of fluctuating oxygen levels—such as hypoxia/ischemia followed by reoxygenation—on the developing brain, particularly in relation to free radical production and bioenergetic failure, which impair cell proliferation, differentiation, and migration. The major free radicals are hydroxyl (•OH), superoxide ($O_2•^-$), hydrogen peroxide (H_2O_2), nitric oxide (NO•), nitrogen dioxide ($NO_2•$), peroxyl (ROO•), lipid peroxyl (LOO•), hypochlorous acid (HOCl), nitrous acid (HNO_2), peroxynitrite ($ONOO^-$) and others [18]. These reactive oxygen and nitrogen species (ROS/RNS) contribute to oxidative stress. Superoxide radicals and hydrogen peroxide are generated at 11 distinct sites in mammalian mitochondria associated with substrate catabolism, electron transport, and oxidative phosphorylation. Of these, six sites are located in Complex I ($NADH/NAD^+$), while five are found in Complex III, functioning at the redox potential of the ubiquinol/ubiquinone (QH_2/Q) pair. Variations in substrate availability and the redox state of these mitochondrial sites influence both normal physiological and pathological processes. Studies have shown that approximately 0.15% of the daily oxygen (O_2) consumed is converted into superoxide anions ($O_2•^-$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH).

Hypoxia condition reduces antioxidant defense mechanisms, which affects the tissue of liver and brain as well as disrupt the redox homeostasis in the brain, leads to cell death [19]. Intrauterine hypoxic condition is one of the several reasons for the development of hypoxia and brain injury at birth, immunodeficient Preterm infants, low / immature antioxidant defence mechanism, newborns with high level of free iron [20].

Under such conditions, oxidative and nitrosative stress may arise, triggering pathways that intensify the initial tissue damage, including activation of pro-inflammatory transcription factors (NF-κB) and pro-apoptotic pathways (Bcl-2, caspase-3) [21]. Excessive accumulation of ROS, NO, and RNS, along with disrupted redox balance, contributes to damage in the sensorimotor cortex. [22]. Damage also extends to the basal ganglia, thalamus, and brainstem [22]. The accumulation of ROS and RNS critically involved in hippocampal long-term potentiation (LTP) [23]. Oxidative stress is also involved in the pathophysiology of the blood–brain barrier (BBB). The BBB consists of microvessels formed by endothelial cells where, the permeability increases due to the activation of matrix metalloproteinases (MMPs) in endothelial cells, astrocytes, microglia, neurons, and leukocytes, and leading to degradation of the extracellular matrix. Secondary neuronal injury caused due to Inflammation, along with OS, cytotoxicity, and edema [24]. TNF-α induces NO and promote BBB permeability by altering the NO-dependent pathway such as ONO [25]. Thus protein-bound iron biomarkers and prostaglandins are considered to be indicators of oxidative stress level in prognosis of disease. [26]

Neuroprotective therapeutic strategy in HIE:

Neonatal oxidative stress is addressed by several therapeutic strategies, which include, free radical inhibition, mitochondrial therapy, amino acid antagonists, stem cell therapy, therapeutic hypothermia, etc.

Allopurinol is an inhibitor of xanthine oxidase, reduces the production of free radicals by decreasing the level of S-100B protein in blood. [27] It acts as a free radical scavenger in HIE treatment. Deferoxamine acts as iron chelator, binds to free iron and chelates non-bound protein iron (NBPI). In animal models, it reduces the severity

of brain injury and improves cerebral metabolism. Erythropoietin (EPO) acts as cyto-protective, anti-oxidant and 4nti-inflammatory by upregulating anti-apoptotic genes and pathways like STAT 5 and ERK signaling. It reduces inflammation, oxygen driven free radicals and decreases protease activation [28].

Melatonin (N-acetyl 5 methoxy tryptamine) is a neuroprotective agent, functionally regulates circadian and endocrine rhythm, and antiinflammation and has analgesic, anxiolytic, and antioxidant activity [9]. It upregulates glutathione reductase and glutathione peroxidases and simultaneously down-regulate lipoxygenases and NOS [10]. In animal models, the efficacy rate is higher and beneficial in sepsis neonates. In the case of preeclampsia, melatonin level was found to be reduced in the blood. The pharmacokinetics of 5 & 15 mg/kg/24 h melatonin with cooling at 2 & 26 h after hypoxia was observed by Robertson et al. and reported that the melatonin levels in plasma were 15-30 mg/l and increased the neuroprotection [15].

Superoxide dismutase is a scavenging enzyme, helpful in reducing brain injury. SOD encapsulated with biodegradable poly nanoparticles has been shown neuroprotective in rat models of cerebral reperfusion injury [17].

N-acetylserotonin (NAC) acts as a free radical scavenger, which enhances glutathione levels, and reduces inflammatory cytokines. In rat models, it has been observed to be hypoxic-ischemic brain injury in neonatal rats. Daily NAC 50 mg/kg administration in rats in combination with hypothermia has been shown to increase myelin expression and long-term neuromotor outcome [17].

Small molecule inhibitors, and activators, which target mitochondrion tetra- and triphenylphosphonium (TPP) are gradually becoming feasible as adjunct therapies [11]. In animal model, Coenzyme Q10 reduces the production of ROS through mitochondrial complex. Efficacy of Coenzyme Q10 in neonatal hypoxic-ischemic brain injury is in the exploratory stage [26]. Mitoquinone (MitoQ) is an antioxidant to treats mitochondrial damage, inhibits lipid peroxidation, reduction of superoxide production, and further ROS generation [27]. In the rat model, MitoQ has shown a protective effect. Fission and fusion of mitochondria reduces ATP production and generates ROS and leads to cellular apoptosis [29-32]. **Table 1** explains the therapeutic targets, drug candidates, primary site of drug either in gene or protein and the mechanism of action.

Table 1: Therapeutic targets and corresponding candidate drugs and agent are listed in the table.

Therapeutic target	Candidate drug/agent	Primary gene/protein target	Mechanism of action
Inflammasome inhibition	Mcc950	Nlrp3	● inhibitor of NLRP3 ● Prevents activation of caspase-1 ● Reduces IL-1beta and IL-18 production ● Enhances neuronal survival
Nlrp3-related pyroptosis	Colchicine (indirect), olt1177	Nlrp3	● Inhibition of microtubule polymerization ● NLRP3 inflammasome suppression and Microglial modulation ● Anticytokine effects ● Blood-brain barrier protection ● Downstream neuroprotection
Hif pathway stabilization	Roxadustat, dmog	Hif1a(via phd inhibition)	● Stabilization of HIF-1α and HIF-2β ● Increases transcription of glycolytic enzyme and glucose transporters ● Enhance angiogenesis and epo expression
Nrf2 antioxidant pathway	Dimethyl fumarate, sulforaphane	Nfe2l2(nrf2)	● Activation of nrf2 antioxidant pathway ● Direct inhibition of inflammatory signalling NF-k beta, reduces grey and white matter injury ● Reduces glial activation in severe hypoxia-ischemia SFN-NRF 2 activation, ● Activates Glutathione synthesis to counter ROS ● Increased expression of heme oxygenase-1
Tlr4 signaling	Tak-242 (resatorvid)	Tlr4	● TLR4 inhibitor ● Inhibits nf-kbactivation, mapk pathways, irf3 activation ● Reduced neuroinflammation by reducing TNF alpha, IL -1 beta, IL6, NOS and COX-2 ● Reducing caspase 3activation
Erythropoietin signaling	Erythropoietin (epo)epor		● JAK STAT % pathway, uregulated BCL 2, BCL XL and reduce bax, caspase-3) ● Preserves mitochondrial integrity by PI3K-AKT pathway ● MAPK/ERKpathway(supports neuronal

			differentiation and repair)
Ppar-ϒ modulation	Pioglitazone, Rosiglitazone	Pparg	● Activate the ppar-γ(nuclear receptor) ● Inhibits NF-Kb and AP-1 ● Reduces TNF alpha, IL1beta and IL6, COX-2, NOS ● Reduces rosand lipid peroxidation, caspase-3 activation, bax and enhances vascular protection
Melatonergic signaling	Melatonin	Mtnr1a/mtnr1b	● Directly scavenges ROS and RNS ● Enhances SOD, catalase and glutathione peroxidase and Prevents mptp opening ● Reduces pro-apoptotic proteins: Bax, caspase-3&9 ● Increases anti- apoptotic protein:Bcl-2 and Inhibits NF-Kb signalling ● Reduced TNF alpha, IL-1b, IL-6
NMDAreceptor blokade	Magnesium sulfate,xenon	Grin1/s	● Reduce NMDA receptor antagonism, calcium Influx and Exitotoxic neuronal injury ● Inhibits voltage gated calcium channel-prevents calcium mediated mitochondrial dysfunction, moderate ● Antiapoptotic and anti-inflammatory
AMPA/kainate antagonism	Topiramate	Gria1-4(ampar subunits)	● Blocks AMPA /kainate glutamate receptors, reducing excitotoxicity and preventing calcium-mediated neuronal injury ● Increases gaba-mediated chloride ion influx, stabilizing neuronal membranes ● Reduction of oxidative stress ● Blocks voltage-gated sodium and calcium channels, which helps stabilize neuronal membranes and Anti -inflammatory
Xanthine oxidase inhibition	Allopurinol	Xdh(xo)	● Inhibits xanthine oxidase, reducing the production of ROS and limiting oxidative stress ● Decreasing ROS levels ● Anti-inflammatory ● Reducing oxidative stress, allopurinol may help preserve mitochondrial function and energy production, preventing secondary neuronal injury
Microglia /mmp modulation	Minocycline	Mmp9(downregulation)	● Suppresses microglial activation, reducing the release of tumor necrosis factor-alpha (TNF-alpha), IL-1 beta (IL-1β), and nitric oxide ● Inhibits neuro-inflammation ● Reduction of oxidative stress ● Inhibition of mmp-9, stabilize bbb ● Reduction of glutamate induced exitotoxicity ● Prevention of secondary energy failure
Cb receptors	Cannabidiol(cbd)	Cnr1/cnr2	● Anti-inflammatory -by acting on immune cells and reducing the production of pro-inflammatory cytokines viz; IL-1**β,** TNF-**α**, and IL-**6** ● Antioxidant properties, directly scavenging ros and reducing lipid peroxidation ● Enhances the activity of SOD ● Decreases glutamate release and modulates glutamatergic signaling, reducing **excitotoxicity** ● **Agonist of the 5-HT la receptor**, a serotonin receptor involved in neuroprotection.

Igf signaling	Igf-1	Igf1r	● activates thePI3K/AKT pathway,reduces oxidative stress. ● The MAPK/ERK activated and thus neuroprotective ● Anti-inflammatory Supports myelination and neurodevelopment ● Restoration of cerebral blood flow via angiogenesis ● Neurogenesis-proliferation and differentiation of neural stem cells
G-csf signaling	G-csf	Csf3r	● Neurogenesis and neuroprotection ● Anti-inflammatory, Anti-apoptotic and Stem cell mobilization
Sirtuin activation	Resveratrol	Sirt1	● Reduces oxidative stress by scavenging reactive oxygen species (ROS) and reactive nitrogen species (RNS), ● Activates nuclear factor erythroid 2-related factor 2 (NRF 2) Superoxide dismutase (sod), catalase, and glutathione peroxidase. ● Anti-inflammatory effects (nf-κb) pathway, ● Reduces tnf-α, il-6, and il-1β ● Inhibits caspase activation- antiapoptotic ● Activator of sirtuin 1 (sirt1), a nad+-dependent deacetylase involved in cellular stress responses. ● Improves mitochondrial function Promotes cerebral blood flow by no production Neurogenesis and synaptic plasticity
Apelinergic pathway	Apelin analogs	Aplnr	● Acting via the APJ receptor (aplnr) ● Anti apoptotic ● Suppresses the neuroinflammation ● Inhibits the NLRP 3 inflammasome ● Antioxidant and mitochondrial protection and blood brain barrier protection
Ghrelin pathway	Ghrelin	Ghsr	● Neuroprotection via GHS-r1 alpha, AKT signaling by suppressing inflammation and inhibiting NF-Kb signaling ● Antiapoptotic via activating P13/AKT pathway ● Antioxidant and mitochondrial protection ● Reduces neurotoxicity ● Suppress NLRP 3 inflammasome activation ● Neurogenesis and synaptic plasticity
Annexin a1 pathway	Ac2-26 peptide	Fpr2/alx	● Activation of FRP 2/ALX ● Switches inflammation from proinflammatory to a resolution phase ● Suppresses the microglial activation ● Reduce the release of TNF alpha, IL1b,IL1b IL6,NOS ● Helps in Inhibition of NF -Kb and MAPK sgnalling, Blood brain barrier - integrity, ● Reduces the activation of caspase-3 ● Reduces the oxidative and nitrosative stress ● Enhances efferocytosis ● Supports neurorepair and neuroplasticity
Matrix preservation	Minocycline Doxycycline	Mmps(esp.mmp 9)	● microglial inhibition ● Has significant anti-inflammatory and immunomodulatory properties, ● Downregulates IL1b, TNF- alpha, IL6 and nf-kb signaling ● Inhibit MMP-2 and MMP-9 thus protects blood brain barrier ● Anti- apoptotic Antioxidant and mitochondrial

			protection ● Reduces the production of free radicles such as NO, ROS ● Indirectly induce glutamate -induced injury

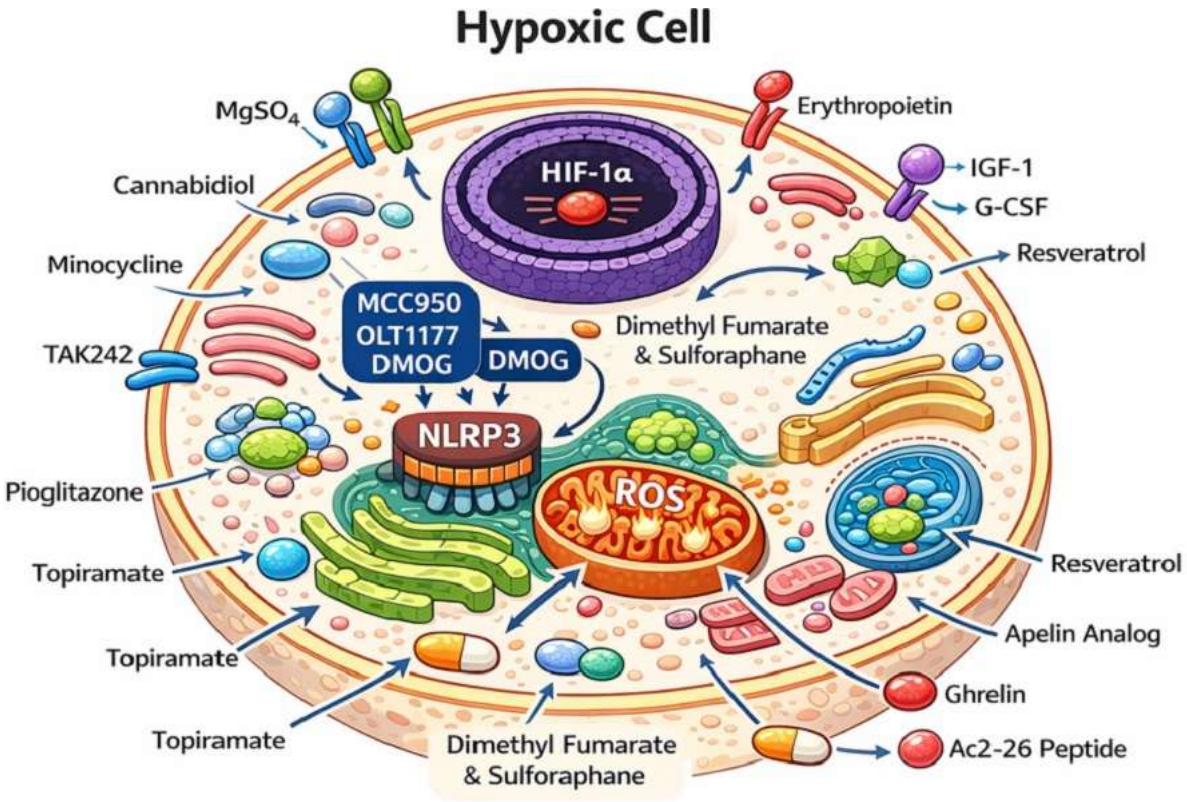

Figure 3: Therapeutic target sites in hypoxia cell (Based on the literature search, refer Table 1).
The Table 1 and figure 3 explains the cellular response to hypoxia, and highlighting the central role of Hypoxia-inducible factor 1-alpha (HIF-1α) in regulating adaptive mechanisms. Under low oxygen conditions, mitochondria generate excessive Reactive oxygen species (ROS), leading to oxidative stress and activation of the NLRP3 inflammasome, which promotes inflammation and cellular damage. Various therapeutic agents as mentioned in the table 1 showing the target sites for reduction of ROS production, inhibiting inflammasome activation, or enhancing protective signaling pathways, thereby improving cell survival under hypoxic conditions. Agents like DMOG acts by enhancing HIF-1α activity, promoting gene expression which supports cell survival, angiogenesis, and metabolic adaptation. The major target of hypoxia condition in a cell is the mitochondria, where ROS generation is excessive. Antioxidant compounds such as resveratrol, cannabidiol, and dimethyl fumarate act to reduce ROS generation and limit oxidative stress, to protect other cellular components. ROS activates NLRP3 inflammasome, which triggers inflammation. Specific inhibitors like MCC950 and OLT1177 directly block inflammasome activation, while agents like TAK242 suppress the inflammatory signaling pathways. Therapeutic agents like erythropoietin, IGF-1, and G-CSF bind to membrane receptors, activating pro-survival and anti-apoptotic signaling cascades. Peptides like ghrelin and apelin modulates inflammation and cellular metabolism.

CONCLUSION

The study narrated extensively with a major focus on causal factors of hypoxia and Anti oxidative stress defence mechanism and therapeutic targets. Under causal factors, Preeclampsia, changes in intrauterine hypoxic condition to normoxic condition at birth, mitochndrial dysfunction and Nitric oxide generation are the major causal factors for the development of brain injury.

Acknowledgement: Nil

Author contribution: Article conceptualization, designing and drafting was done by BP, first draft was done by RRD, full article reviewed by BP, RRD, SP, NM, RKG, SSB and BN

Statements and declarations: Not Applicable

Ethical consideration: Not applicable

Consent to participate: Not Applicable

Consent for Publication: Not applicable

Declaration of Conflict of Interest: Authors have nothing to declare in conflict of interest.

Funding: Not Applicable

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