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# Potential role of IGF-1/GLP-1 signaling activation in intracerebral hemorrhage

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ABSTRACT

IGF-1 and GLP-1 receptors are essential in all tissues, facilitating defense by upregulating anabolic processes. They are abundantly distributed throughout the central nervous system, promoting neuronal proliferation, survival, and differentiation. IGF-1/GLP-1 is a growth factor that stimulates neurons' development, reorganization, myelination, and survival. In primary and secondary brain injury, the IGF-1/GLP-1 receptors are impaired, resulting in further neuro complications such as cerebral tissue degradation, neuroinflammation, oxidative stress, and atrophy. Intracerebral hemorrhage (ICH) is a severe condition caused by a stroke for which there is currently no effective treatment. While some pre-clinical studies and medications are being developed as symptomatic therapies in clinical trials, there are specific pharmacological implications for improving post-operative conditions in patients with intensive treatment. Identifying the underlying molecular process and recognizing the worsening situation can assist researchers in developing effective therapeutic solutions to prevent post-hemorrhagic symptoms and the associated neural dysfunctions. As a result, in the current review, we have addressed the manifestations of the disease that are aggravated by the downregulation of IGF-1 and GLP-1 receptors, which can lead to ICH or other neurodegenerative disorders. Our review summarizes that IGF-1/GLP-1 activators may be useful for treating ICH and its related neurodegeneration.

## 1. Introduction

Intracerebral hemorrhage is characterized as a traumatic, sudden onset of severe headache, impaired level of consciousness, or critical neurological deficiency that results in blood accumulation within the brain (Siddiqui et al., 2021; Syme et al., 2005). The incidence rate of ICH is 24.6 per 100,000 individuals and is linked with a high mortality rate (Poon et al., 2016). Females over the age of 80 had significantly higher numbers across all time points and showed a sustained and increasing gap in 2017 (Krishnamurthi et al., 2020). Using the 45–54 year age group of intracerebral hemorrhage patients as a reference, incidence ratios increased from 0.10 for people under 45 years to 9.6 for people over 85 years (Van Asch et al., 2010) (see Fig. 1).

Intraventricular hemorrhage with hydrocephalus, hematoma (HMT) enlargement, seizures, perihematomal edema, venous thromboembolic events, nausea, pneumonia, increased blood pressure, and high glycemic index are all possible causes of death from ICH (Bhattathiri et al., 2006; Steiner et al., 2006). The Lobar hemorrhage causes severe cortical dysfunction, resulting in aphasia, irregular vision, cognitive disability, anisocoria (unequal pupils), seizures/coma, and hemianopia (An et al., 2017). Headache is more common in patients with severe hematomas and is frequently associated with head enlargement and hydrocephalus (Aguilar and Brott, 2011; Wallmark et al., 2014). Eclampsia, opioid misuse, increased systolic BP, trauma, arteriovenous malformation, smoking, low cholesterol, diabetes, and increased alcohol consumption are the leading causes of ICH (Kurth et al., 2003). It could also be due to increased blood flow in the brain, aneurysm burst, altered homeostasis, or vein flow obstruction (Celikbilek et al., 2013; Go et al., 2014; O'donnell et al., 2010).

ICH has the highest stroke mortality rate, with less than 40% of ICH patients attempting to recover stably and safely (Meretoja et al., 2012; Irwin et al., 2011). ICH, in general, affects the basal ganglia, cerebral hemispheres, cerebellum, thalamus, and brainstem (mainly pons) (Qureshi et al., 2001). Mature hematomas are brownish due to two essential haemoglobin (Hb) pigments, haematoidine and haemosiderin. ICH results in massive swelling and brain injuries resulting from pus produced by thrombin and other coagulation end products (Chakrabarty and Shivane, 2008) (see Fig. 2).

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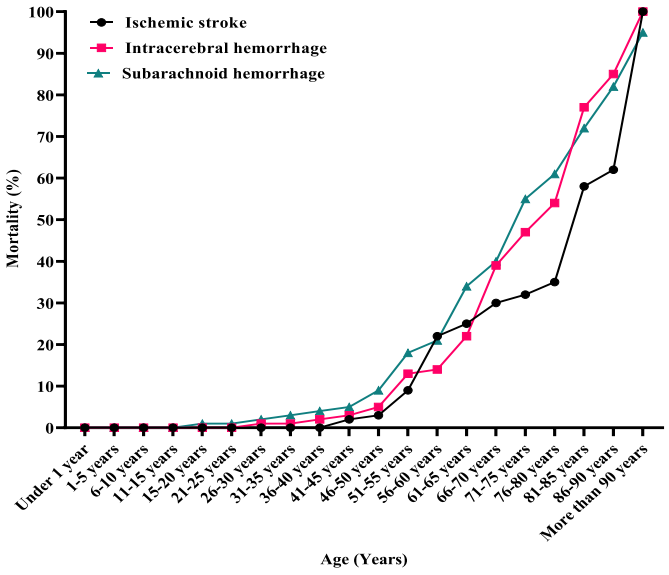


**Fig. 1.** Age-wise mortality incidences in brain hemorrhages.

Fig. 3 describes the etiopathological hallmarks responsible for primary brain injury, and Fig. 4 represents the consequences of secondary brain injury due to intracerebral hemorrhage.

Hematomas damage neurons and the early inflammation caused by hematoma plasma proteins is commonly referred to as secondary brain injury (Rajdev and Mehan, 2019; Rajdev et al., 2020). Clotting and the activation of complement cascades cause disruptions of the blood-brain barrier (BBB), resulting in cytotoxicity and edoema. The late onset of edoema is caused by Hb toxicity and the production of free radicals (Fewel et al., 2003). The accumulation of amyloid-beta (A) proteins on the inside surface of arterioles, capillaries, and cortical leptomeningeal arteries cause CAA (Siddiqui et al., 2019). Neurovascular complications include cortical infarction, fibrinoid necrosis, aligned blistering of the vessel walls (double-barrel effect), stenotic lumina, micro-aneurysms, and micro-haemorrhoids (Sahni and Weinberger, 2007). Reactive oxygen species (ROS) are produced in mitochondria as a byproduct of cellular metabolism and oxidative stress (OS) (Chen et al., 2011). A free radical reaction forms lipid peroxide byproducts such as 4-hydroxy--trans-2-non-enal and malondialdehyde (Han et al., 2008; Aronowski and Hall, 2005; Sook et al., 2006). Since BBB can easily traverse HEt detection, it is used to measure in vivo oxygen-free radical production (Swanson, 2006; Ma et al., 2014). The formation of superoxide ion radicals is caused by mitochondrial leakage of one to four percent of all electrons in the electron transport chain, neutralized by antioxidant enzymes (Tang et al., 2005). Mitochondrial failure occurs in hemorrhagic conditions, producing a substantial rise in ROS production (Bedard et al., 2015; Chan and Chan, 2014). This review focuses on multiple approaches and associated therapeutic interventions for early ICH complications and post-hemorrhagic symptoms based on available hypotheses and dogmas. Consequently, we focused our review on these two targets to highlight their neuroprotective contributions to cellular processes and brain functioning.

## 2. Regulation of IGF-1 signaling in the brain

Insulin-like growth factor-1 (IGF-1) is a synthesized polypeptide hormone in the liver. It is found in the olfactory bulb, granule cell layers, cerebellar cortex, dentate gyrus, choroid plexus, hippocampus, amygdala, thalamus, and substantia nigra. Pituitary growth hormone (GH) regulates IGF-1 secretion in the systemic circulation (Laron, 2001; Bentov and Werner, 2006). IGF-1 levels in white matter and cerebrospinal fluid (CSF) are low (Ghazi Sherbaf et al., 2018). Neurons produce IGF-1 under normal physiological conditions, whereas astrocytes produce these trophic factors following local injury. IGF-1 remains bound to high-affinity binding proteins (IGFBPs) in blood circulation. The IGF-1 receptor signaling cascade also includes activation of the MAPK, PI3K, and AKT pathways (Madathil and Saatman, 2015; Ashpole et al., 2015). It promotes neural tissue growth and development by increasing anabolic processes. Fig. 5 illustrates the signaling cascades of the

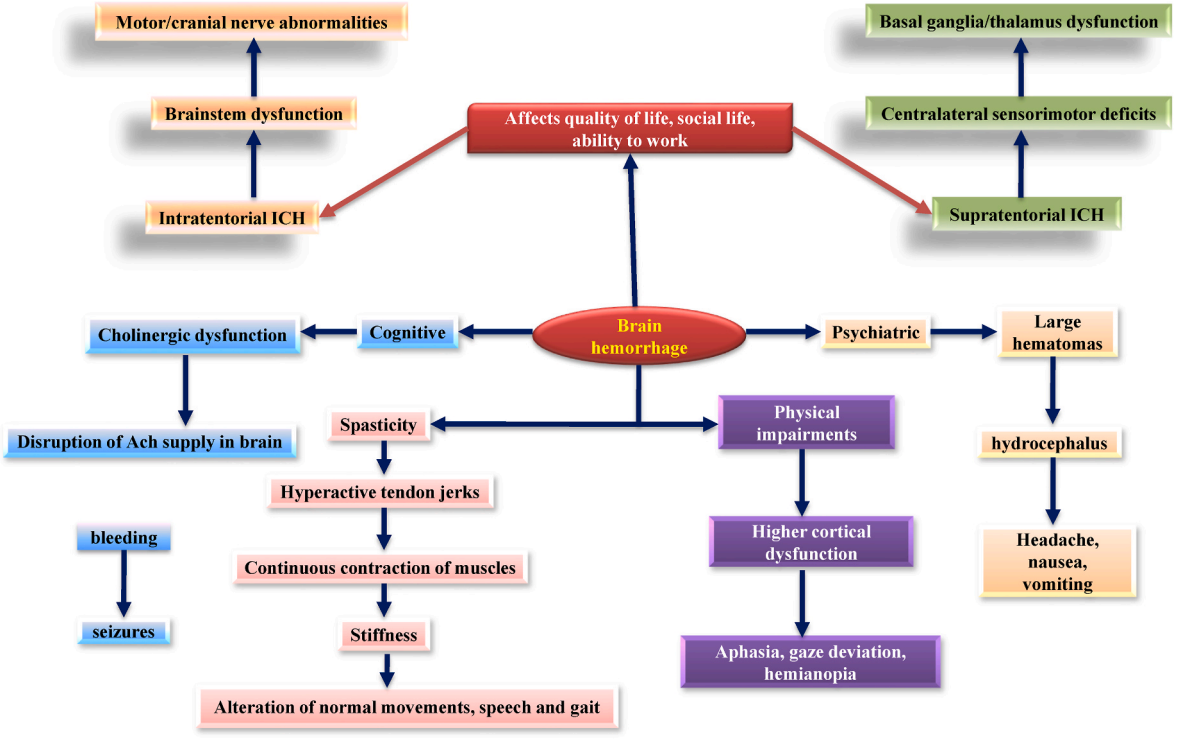


**Fig. 2.** Clinical presentation during the progression of brain hemorrhage.

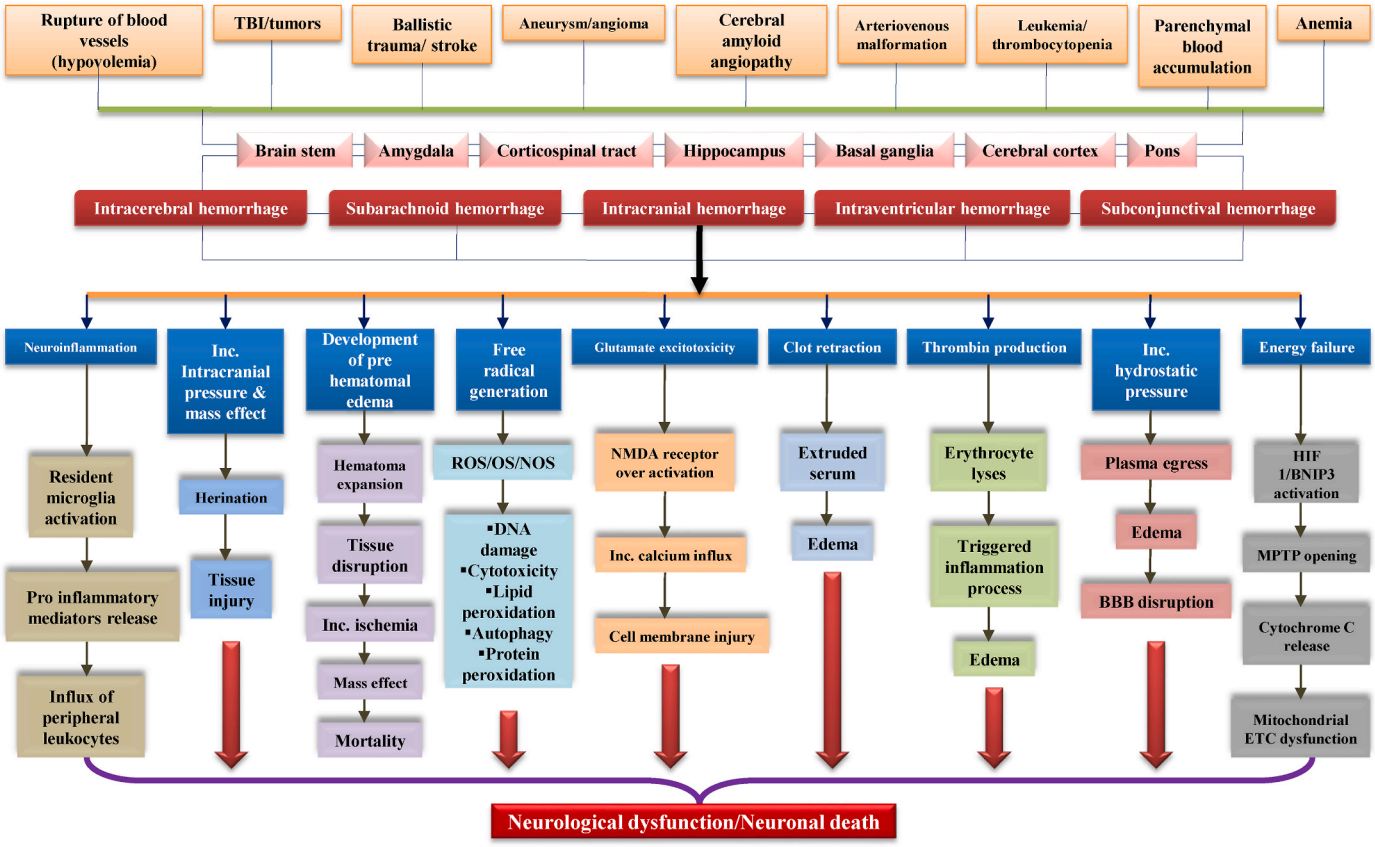


**Fig. 3.** Etiopathological hallmarks responsible for primary brain injury. Various etiopathological causes, such as trauma, stroke, aneurysm, etc., have affected different brain regions. Dysfunction in major brain areas leads to neuronal cell death, which further causes free radical generation, energy failure, hematoma development, etc. Primary brain injury occurs with the final activation of these cascades in the body.

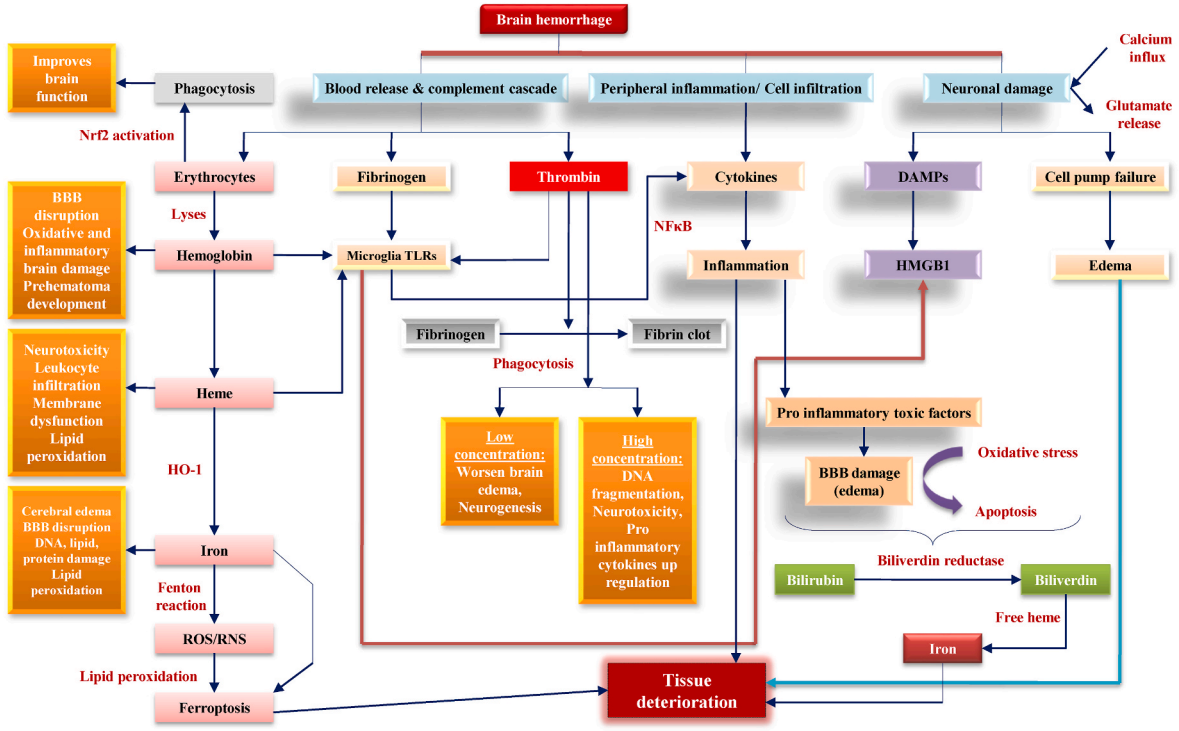


**Fig. 4.** Consequences of secondary brain injury due to intracerebral hemorrhage. Another signaling cascade starts in the brain with the onset of primary brain injury, referred to as secondary brain injury. Additional neuro complications occur in the body throughout this phase, such as Nrf2 activation, fibrinogen, and thrombin, further contributing to neuroinflammation, edema, and microglia activation. Finally, these factors cause more severe tissue damage.

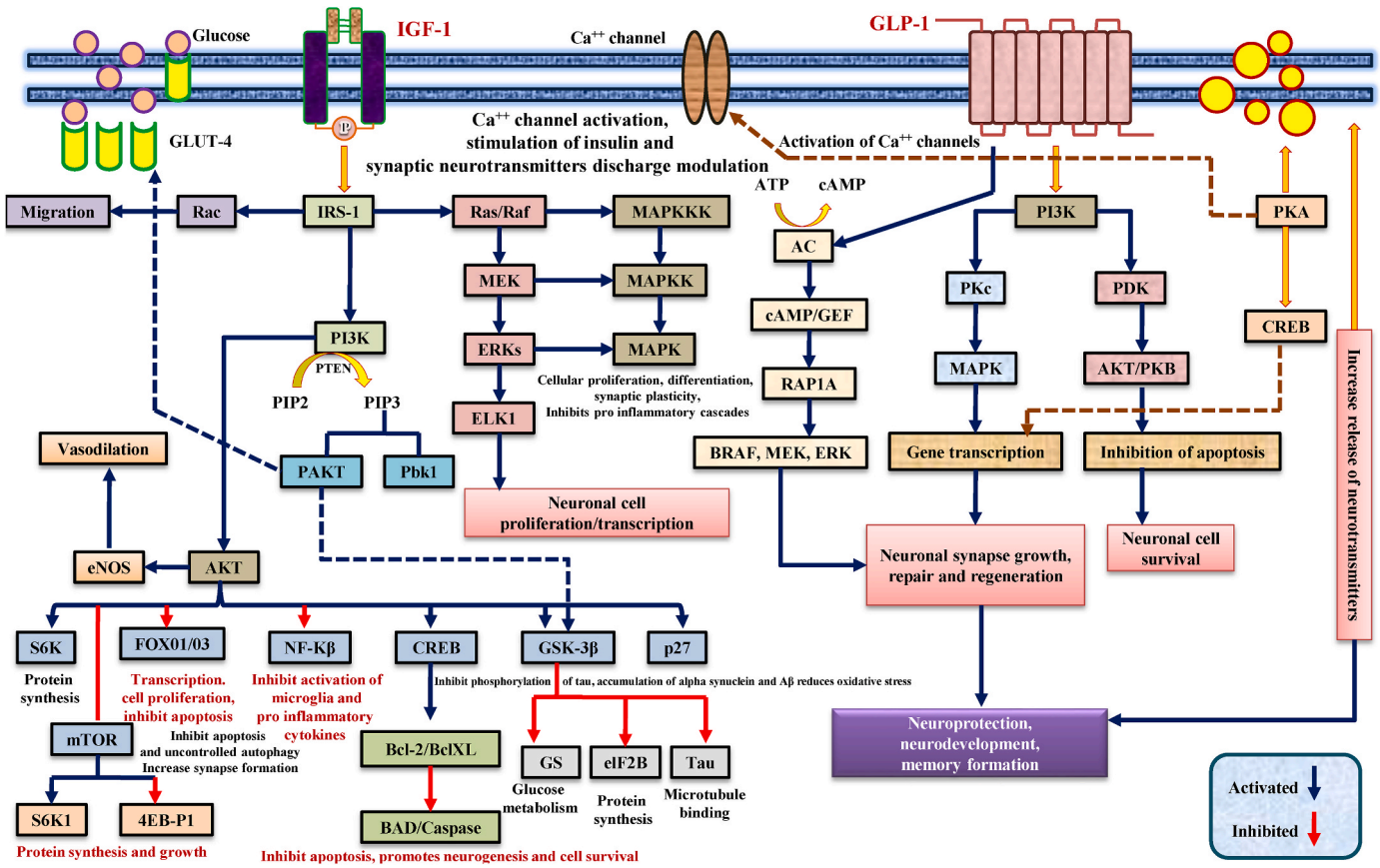


**Fig. 5.** Involvement of IGF-1/GLP-1 receptor signaling in various neurocomplications. The IGF-1 signal transduction on the growth axis mainly involves activating two signal transduction chains. The PI3K activation pathway and the MAPK activation pathway transmit mitotic and metabolic signals to the cell nucleus, activating IGF-1 secretion, inducing cell proliferation, differentiation, and inhibiting cell apoptosis. On the other hand, GLP-1R signaling facilitates β-cell glucose metabolism through PI3K-dependent activation of PKC and PDK. The GLP-1 receptor coupled with GLP-1R activates adenyl cyclase when it binds to GLP-1, increasing the cAMP's intracellular level. CAMP-mediated signaling promotes the RAP1A pathway, which, in turn, induces translational activation of BRAF, MEK, ERK, and thus promotes gene transcription, leading to neuroprotection.

**Abbreviations:** IGF-1 = insulin like growth factor-1; GLP-1 = Glucagon like peptide-1; Ras = Rat sarcoma; Raf = Rapidly Accelerated Fibrosarcoma; IRS-1 = insulin receptor substrate-1; PIP2=Phosphatidylinositol 4,5-bisphosphate; PIP3 = phosphatidylinositol (3,4,5)-trisphosphate; PDK = 3-Phosphoinositide-dependent kinase; PI3k = 3-Phosphoinositide-dependent kinase 1; PKA = protein kinase A; PKB = protein kinase B; Akt = Ak strain transforming; mTOR = mammalian target of rapamycin; ROS = reactive oxygen species; GSK3-β = Glycogen synthase kinase 3-beta; MAPK = mitogen-activated protein kinase; MEK = Mitogen-activated protein kinase kinase; ERK = extracellular signal-regulated protein kinase; CREB = cAMP-response element binding protein; NF-kB = nuclear factor kappa-light-chain-enhancer of activated B cells; BCl-2=B-cell lymphoma 2; Bax = Bcl-2 Associated X-protein; Caspase = cysteine-dependent aspartate-directed proteases; AC = adenylyl cyclase; cAMP = cyclic Adenosine MonoPhosphate; GLUT4 = glucose transporter 4; ATP = Adenosine triphosphate; NOS = nitric oxide synthase.

IGF-1/GLP-1 receptors. IGF-1 signaling becomes irregular with age, resulting in age-related alterations in experimental animals. The synthesis of glucose and the migration of GLUT-4 to the neuronal cell membrane were also correlated with the PI3K AKT-mediated IGF-1 signaling to promote glucose absorption into neurons (Holly and Perks, 2006; Muller et al., 2012).

The IGF-1 receptor (IGF-1R) is a membrane-bound tyrosine kinase receptor that regulates the pharmacological activities of IGF-1. When IGF-1 bind to its receptor, it autophosphorylates at several tyrosine sites, phosphorylating the IRS-1 protein sequentially. These phosphorylated tyrosine sites function as docking sites for various intracellular signaling proteins. The complex signaling pathways such as PI3K, MAPK, and AKT are thus activated. IRS-1 binds to PI3K, phosphorylation occurs, and PIP-2 converts to PIP-3, which recruits other proteins to the plasma membrane, including PDK-1 and AKT (Li et al., 2009; Puche and Castilla--Cortázar, 2012). It also binds to two protein kinases, AKT and PDK-1, resulting in AKT initiation and promoting cell growth, maturation, and survival via intracellular protein interactions. AKT phosphorylation regulates the mammalian target of rapamycin (mTOR), enhanced protein synthesis, ribosome development, and pro-apoptotic BAD protein inhibition (Huang et al., 2012). Furthermore, when the PI3K-AKT signal activates the IGF-1R, the GSK-3 inhibitory protein is phosphorylated, resulting in increased glycogen accumulation in neurons (Kreft and Jetz, 2007; Yin et al.,). FOXO-1 has also been inactivated, preventing direct transcription of pro-apoptotic FOXO genes (Junnila et al., 2013). As a result, it was found that PI3K signaling inhibits the pro-apoptotic system through different mechanisms. The olfactory lobe, cerebellum, and hippocampus showed the highest levels of postnatal IGF-1 expression, which then declined after neuronal proliferation (Wrigley et al., 2017). IGF-1 has been shown to stimulate all neural cells (glial cells, astrocytes, neurons, and oligodendrocytes), increase mitochondrial function, and encourage proliferation and differentiation of oligodendrocytes and myelin development survival, and maturation. This mechanism has been confirmed by cultural studies (in-vitro/in-vivo) and experiments with transgenic mice (Chesik et al., 2008; Spielman et al., 2014).

## 3. Regulation of GLP-1 signaling in the brain

GLP-1 is an endogenous hormone (insulinotropic) that maintains a glucose-insulin balance. Intestinal endocrine L-cells primarily secrete it to initiate glucose-dependent insulin secretion, glucagon secretion blockage, food intake, and gastric clearance (Supeno et al., 2013). GLP-1

is a hormone with trophic effects on neurogenesis, proliferation, and differentiation (Mehan et al., 2022). It also reduces cell death in neurons, beta-cell islets, and fibroblasts (Brooker et al., 2000). The GLP-1 receptor (GLP-1R), a seven-transmembrane GPCR that activates adenyl cyclase (AC), resulting in the production of cyclic adenosine monophosphate, facilitates the physiological function of GLP-1 (cAMP). cAMP stimulates phosphokinase A (PKA), which phosphorylates and inhibits several downstream proteins and anti-apoptotic factors.GLP-1R is found in various tissues, including pancreatic islet cells, blood vessels, lungs, heart, kidneys, neurons, and lymphocytes. They are also expressed on presynaptic neurons, cell bodies, and dendrites (Daftary and Gore, 2005; Lunetta et al., 2012).

GLP-1 is considered down-regulated in ICH and responds via the PI3K and MAPK pathways (Cancedda et al., 2004). GLP-1 is metabolized by DPP-4 in 2–3 min, lowering peripheral glucose levels. DPP-4 (serine protease) explicitly removes dipeptides from the amino terminals of proteins containing proline/alanine residues, inhibiting their function. DPP-4 is a soluble protein that circulates in the blood, penetrates brain tissue, and infiltrates the pancreas and liver (Baggio and Drucker, 2007). GLP-1 analogues such as exendin-4, exendin-XR, liraglutide, albiglutide, dulaglutide, and lixisenatide are DPP-4 insensitive. They can cross the BBB in the same way as GLP-1 (except for albiglutide) and may also bind to GLP-1R (Doyle and Egan, 2001). GLP-1 analogues are neurotrophic, neuroprotective, and memory-enhancing (Brubaker and Drucker, 2004; Li et al., 2005). Exendin-4 has been shown to provide neuroprotection in the SAOS rat model by decreasing the brain region that deteriorated after stroke injury. In experimental rats, intracerebroventricular (ICV) GLP-1 injection was associated with improved memory and recognition and significant neuroprotective effects (Baggio and Drucker, 2007; Hölscher, 2012). GLP-1 has been studied as a potential treatment for neurodegenerative disorders such as Alzheimer's (AD) (During et al., 2003; Cardona-Gomez et al., 2000) and Huntington's disease (HD) (Torres-Aleman, 2010). GLP-1 stimulates cell formation, maturation, growth, and differentiation while inhibiting apoptosis (Li et al., 2005). GLP-1 has been shown to promote neuritis development in cultured neuronal cells and protect against excitotoxicity and oxidative injury (Campbell and Drucker, 2013). Another study found that mice with higher GLP-1 receptor expression in the hippocampus had better cognitive spatial abilities and neurological performance (Perry and Greig, 2004; Perry and Greig, 2005). Several studies on the IGF-1/GLP-1 receptor have been conducted, and significant findings from trials on drugs acting on these receptors are included in this review in Table 1.

## 4. Dysregulation of IGF-1 and GLP-1 signaling during ICH

Although IGF-1 and GLP-1 have a primary role in metabolic

**Table 1**
Clinically available IGF-1/GLP-1 receptor modulators in various dysfunctions.

| S. No. | Target modulators | Target involved | Key findings | Therapeutic indications | Current status | Reference |
|---|---|---|---|---|---|---|
| **01.** | Demethylasterriquinone B1 (activator) | IGF-1R | •Release of newly bound AβOs into the extracellular medium | •The neuroprotective potential of astrocytes was sensitive to chronic AO exposure. | •Physiological protection against synaptotoxic AβOs | Pitt et al. (2017) |
| **02.** | Insulin (human) recombinant expressed in yeast (activator) | Endogenous peptide agonist | ↓ amino acid (AA)-regulated mTORC1-directed signaling | •GSK3 regulates mTORC1 activity by phosphorylating the mTOR-associated scaffold protein raptor on Ser (859) | •↓ phosphorylation of mTOR substrates | Stretton et al. (2015) |
| **03.** | Direct IGF injection (activator) | IGF1R | ↑ prostate cancer cell line PC3 | • IGF-1-mediated increased migration of PC3 cells via activated MET | • MET tyrosine kinase is essential in the genesis of solid tumors | Varkaris et al. (2013) |
| **04.** | Somatomedin C (activator) | IGF1R | •Potent activator of the AKT signaling pathway | ↑ systemic body growth and growth-promoting effects | NA | Varkaris et al. (2013) |
| **05.** | PQ 104 (inhibitor) | IGF-1R | ↑ RPTPβ, AKT Ser473 phosphorylation and VSMC proliferation ↓ IGF-I | •A novel mechanism for coordinate regulation of IGFBP-2 and IGF-1 | •The thermoregulatory role for both IGF-1R and neuronal insulin receptors | (Shen et al., 2012; Sanchez-Alavez et al., 2011) |
| **06.** | Picropodophyllotoxin (inhibitor) | Selective IGF1R | ↓ MAPK phosphorylation | •PPP treated mice grew smaller tumors | ↓ RMS tumor proliferation by cyclolignan PPP | Tarnowski et al. (2017) |
| **07.** | Rapamycin (inhibitor) | mTOR and IGF-1R | ↓ cell growth and survival | ↓ mammalian target of rapamycin (mTOR) signaling | •Combining the mTOR inhibitor and an IGF-1R antibody/inhibitor | Wan et al. (2007) |
| **08.** | Metformin and diazoxide (activator) | IGF-1/Insulin | ↓ insulin/IGF-1 system is beneficial in cancer-bearing animals | •DR could be used as a supportive treatment during cancer treatment | • Their anti-neoplastic potential in humans, such as DR, is still under investigation | (Klement and Fink, 2016) |
| **09.** | BMS 536924 (inhibitor) | Dual IR/IGF1R | ↑ LAT1 activity via NKCC1 depletion or deletion | ↓ intracellular $Na^+$ concentration by NKCC1 depletion | •NKCC1 suppresses mTORC1 by inhibiting its key activating signaling pathways | Demian et al. (2019) |
| **10.** | Tirzepatide (activator) | GIP and GLP-1 receptor | ↓ HbA1c (Dose-dependent) | ↑ GIP and GLP-1 receptor signaling in vitro showed glucose-dependent insulin secretion | •Combining GIP and GLP-1 receptor stimulation could lead to a new type 2 diabetes treatment option. | Frias et al. (2018) |
| **11.** | Exenatide (activator) | GLP-1 receptor | ↓ endogenous (hepatic) glucose production | ↓ postprandial hyperglycemia in type 2 diabetes | ↑ energy expenditure and weight loss by neural and metabolic regulation | Cervera et al. (2008) |
| **12.** | Liraglutide (activator) | GLP-1 receptor | ↑ GLP1 receptor, glucose concentrations leading to insulin release | •Improve glycaemic control in adults with type 2 diabetes . | ↓ risk of a heart attack, stroke, or death in adults | (Drucker et al., 2010) |
| **13.** | Lixisenatide (activator) | GLP-1 receptor | ↑ cAMP levels in the brain, neurogenesis in the brain | ↑ neurogenesis and cognition and memory formation in the adult brain | • Used along with diet and exercise to treat type 2 diabetes | (Hunter and Hölscher, 2012) |
| **14.** | Albiglutide (activator) | GLP-1 receptor | ↑ glucose-dependent insulin secretion ↓inappropriately elevated glucagon secretion | ↓ gastric emptying, food intake, blood glucose level | •Used with a diet and exercise program to control blood sugar levels in adults with type 2 diabetes | Rosenstock et al. (2009) |

functions, they are also involved in mitogenic activities and cell differentiation. In several in-vivo and in-vitro experiments, IGF-1 and GLP-1 serve as neuroprotective agents. In ICH, IGF-1/GLP-1 administration facilitates axonal regeneration, improves functional recovery, and improves neuronal transmission. IGF-1/GLP-1 ICV injection significantly reduced neuronal loss in impaired areas due to bleeding following experimental hypoxic ischemia and temporary forebrain ischemia. The neuroprotective and anti-inflammatory properties of IGF-1/GLP-1 suggest that these agents effectively treat patients with stroke conditions. IGF-1/GLP-1 analogues provided significant neuroprotective effects in ischemic/hypoxic conditions (Li et al., 2009).

Several preclinical studies have shown that IGF-1/GLP-1 signaling effectively protects neurons from oxidative stress and reduces inflammatory responses in ischemia and strokes. As a result, it is concluded that IGF-1/GLP-1 is downregulated by a different pathway during hemorrhagic conditions, resulting in neurodegeneration, apoptosis, and necrosis, all of which contribute to neuro complications. Consequently, administering exogenous drugs by targeting such receptors may provide neuroprotective effects.

## 5. Drug therapy available for the management of intracerebral hemorrhage

Despite significant advances in pre-clinical research, few treatment approaches are effective in clinical trials to manage intracerebral hemorrhage. Most targeted molecular pathways include reducing excitotoxicity and calcium influx, restoring mitochondrial alterations, activating multiple intracellular enzymes, and decreasing free radical formation, nitric oxide production, inflammation necrosis, and apoptosis. However, the ICH has also been compatible with existing standard healthcare facilities in some cases. ICH management is usually supportive to avoid further brain damage and related illnesses. Due to the limited range of treatment options available to ICH patients, effective monitoring is required to enhance protective effects against these complications. There may not be a range of immediate and effective treatments for ICH. However, several studies have shown that certain drugs of different categories remarkably influence the disease through numerous experiments and data, as discussed below.

Table 2 provides an overview of currently available treatment options for the management of intracerebral hemorrhage.

### 5.1. Minocycline (MNC)

It is a tetracycline group antibiotic that enters the central nervous system quickly. Several studies have found that MNC has significant neuroprotective effects, including preventing apoptosis and reducing matrix metalloproteinase activity via inflammation inhibition. In ICH rat models, MNC administration reduced cerebral edoema and inflammation while maintaining BBB porosity (Zhao et al., 2011; Shi et al., 2011). The neuroprotective effect of MNC was insignificant in the first three to 4 h following hemorrhage (Szymanska et al., 2006). It is a treatment option for ICH and is currently being evaluated in a clinical trial (CT) for its efficacy (MACH; NCT01805895; 2018) (A pilot study of minocycline in intracerebral hemorrhage patients (MACH); Taken from: https://clinicaltrials.gov/ct2/show/NCT01805895; Accessed on January 7, 2020).

### 5.2. Albumin (ABM)

In ICH and ischemic stroke, ABM has several neuroprotective effects. ABM therapy improved BBB integrity and neurological functions (Belayev et al., 2005, 2007). Despite the impact of ABM in clinical trials for acute ischemic stroke (ALIAS), the potential effects of ABM in ICH are currently being investigated (ACHIEVE, NCT00990509), which has examined the main results of ABM in ICH patients. The severity of the BBB disruption and the intensity identified in pre-and post-MRI imaging

**Table 2**
Overview of clinically available treatment options for the management of intracerebral hemorrhage.

| S. No. | Drug | Therapeutic interventions | Mechanism of action | Clinical status | Reference |
|---|---|---|---|---|---|
| **01.** | Magnesium sulfate | ↑ recovery of vital magnesium-dependent cell functions<br>• Prevents the death of ischaemic neurons | ↓ cerebral oxygen metabolism, the synaptic inhibitor | phase II: potent, phase III: in process | Saver et al. (2004) |
| **02.** | Uric acid | ↓ ischemia-induced tyrosine nitration<br>• Protects the brain in a model of transient focal ischemia in rats | • Free radical scavenger | phase II: potent, phase III: in process | (Romanos et al., 2007; Amaro et al., 2007, 2010) |
| **03.** | Dapsone | • Neuroprotective effect in brain ischemia | • Anti-inflammatory, antioxidant | clinical pilot trial: potent, phase III: in process | (Rıos et al., 2004; Kaur et al., 2013) |
| **04.** | Cromolyn | ↑ CNS damage in models of ischemic and hemorrhagic stroke by amplifying the inflammatory responses | • Mastocyte stabilization, reduction in BBB leakage | phase III: in process | (Strbian et al., 2006, 2007) |
| **05.** | Ebselen | ↓ lipid peroxidation and iNOS protein expression in the cerebral cortex | • Antioxidant | phase III: in process | Sui et al. (2005) |
| **06.** | Statin | ↑ cholesterol independent vasoprotective effects | • Antioxidant, HMG-CoA reductase inhibitors | phase IV: in process | Prinz et al. (2008) |
| **07.** | Cyclosporin A | • Potent inhibitor of mPTP formation | • Anti-inflammatory, anti-excitotoxic | phase II: in process | Leger et al. (2011) |
| **08.** | Clomethiazole | • Neuroprotective in both global and focal ischemia | • Sedative, muscle relaxant, anticonvulsant, a neuroprotective agent | non-functional | (Sydserff et al., 2000; Chaulk et al., 2003; Lyden et al., 2002) |
| **09.** | Selfotel | ↓ early post-ischemic brain injury in transit focal ischemia | • Neuroprotective agent | Phase III: non-functional | Davis et al. (2000) |
| **10.** | Aptiganel | • Provides shield to cerebral<br>• Gray matter and white matter from ischemic injury prevent the degeneration of myelin and axons | • Neuroprotective agent in focal brain ischemia. | Phase III: non-functional | (Schabitz et al., 2000; Albers et al., 2001) |
| **11.** | Fanapanel | ↓ infarct size in a transient middle cerebral artery occlusion in ischemic stroke | • Neuroprotective agent in cerebral ischemia | non-functional | Walters et al. (2005) |

**Abbreviations:** IGF-1 = insulin like growth factor-1; GLP-1 = Glucagon like peptide-1; GIP = Gastric inhibitory polypeptide; IGF-1R = Insulin like growth factor-1 receptor; IR=Insulin receptor; AβO = amyloid-beta oligomers; mTOR = mammalian target of rapamycin; Akt = Ak strain transforming; GSK3-β = Glycogen synthase kinase 3-beta; MET = Mesenchymal Epithelial Transition; RMS = Rhabdomyosarcoma; VSMC = vascular smooth muscle; LAT1 = Large Amino Acid Transporter 1; iNOS = Inducible nitric oxide synthase; BBB = blood brain barrier; HMG-CoA = β-Hydroxy β-methylglutaryl-Coenzyme A; mTORC1 = mTOR Complex 1.

was the key findings of this investigational study (Ginsberg et al., 2011; Rekik et al., 2012).

### 5.3. Monocytes/macrophages (MCs/MPs)

Monocytes/macrophages (MCs/MPs) have also been shown to repair brain and brain tissue (Sanberg et al., 2010; Sica and Mantovani, 2012). MCs have a neuroprotective effect on the blood cells of the spinal cord. It is divided into M1 and M2 subunits. M1 cells produce pro-inflammatory cytokines, while M2 cells participate in tissue regeneration, angiogenesis, and the inflammatory process (Kigerl et al., 2009; Shechter et al., 2009). M1 was subsequently proven to cause neuronal death, while M2 prevented neuron apoptosis. As a result, MCs revived activity and reduced hematoma size (Hu et al., 2012). Similarly, restoring neurons in brains damaged by lipopolysaccharide due to MC penetration displayed a phenotype associated with cell repair (Jeong et al., 2013).

Mesenchymal stem/stromal cells have been shown to exhibit anti-inflammatory genotypes in clinical settings (Eggenhofer and Hoogduijn, 2012; Walker et al., 2012). Due to various functional modulations, models such as UCB-BM-MNCs8 were replaced by MCs/MPs stroke models. Apoptosis occurs in stem cells replaced, resulting in anti-inflammatory responses and the development of macrophage-derived growth factors such as VEGF, IGF-1, GLP-1, platelet-derived growth factor (PDGF), and erythropoietin. As a result, we believe MCs/MPs are effective therapeutic agents for neural repair and immunoregulation (Lu et al., 2013; Chernykh et al., 2010).

### 5.4. Deferoxamine mesylate (DM)

Iron is essential in ICH-mediated secondary brain injury (Wagner et al., 2002). Autophagia, OS/HR formation, and excitotoxicity are caused by RBC hemolysis (Nakamura et al., 2004; Chen et al., 2010). In pig and rat models of ICH, DM (iron chelator) was protective against secondary brain damage (Okauchi et al., 2010; Selim, 2009). It possesses anti-phagocytic, anti-apoptotic, anti-inflammatory, and anti-oxidant properties. In particular, hemorrhagic models reduced Hb-induced neurotoxicity and enhanced post-ICH neural defense (Okauchi et al., 2010; Gu et al., 2009). In the Phase I clinical trial, the safety and dose-finding DM study were investigated in ICH patients. The safety and efficacy of various DM formulations have been tested to determine the maximum tolerated dose. A phase II clinical trial with a high amount of DM was also conducted (NCT01662895) (Ji et al., 2009).

### 5.5. Pioglitazone (PGZ)

Pioglitazone, a peroxisome proliferator-activated-gamma (PPAR gamma) agonist, plays a vital role in the modulation of inflammation and OS and enhances systemic phagocytosis reflux of the hematoma without affecting neighbouring brain cells, and thus may be a practical treatment approach for ICH (Cai et al., 2018; Swanson et al., 2011). In a blind, randomized placebo-controlled CT, the results of an investigation on the safety of PGZ for hematoma resolution in ICH (SHRINC) indicate that PGZ should be evaluated as a possible treatment for ICH in a subsequent phase II/III trial (Gonzales et al., 2020).

### 5.6. Direct oral anticoagulants (DOACs)

Oral anticoagulants include factor IIa or thrombin inhibitors (dabigatran) and factor Xa inhibitors (betrixaban, apixaban, rivaroxaban, edoxaban). Tix-5, a factor Xa inhibitor, was isolated from tick saliva, while hirudin, a DTI, was isolated from leech saliva (Gonzales et al., 2013; Tanaka-Azevedo et al., 2010). Dabigatran etexilate (Pradaxa), a drug in the DTI family, was the first DOAC-approved drug in the USFDA category. It was quickly followed by rivaroxaban (Xarelto) (approved in July 2011) and apixaban (Eliquis) (approved in December 2012). In contrast, the SFDA approved edoxaban in January 2015 (Savaysa). The FDA approved betrixaban, a new DOAC, in June 2017 (Skelley et al., 2018). DOACs have replaced warfarin as a safer option due to a 50–60% lower ICH risk. DOACs are an appealing alternative to warfarin and other oral anticoagulants due to their ease of administration, rapid onset of action, short half-life, and more predictable pharmacokinetics (Gómez-Outes et al., 2015).

### 5.7. Clopidogrel and ticlopidine (TCP and CPD)

TCP and CPD are two common pro-drugs that must be metabolized and have been shown to improve platelet function. They are both members of the thienopyridine family (ADP receptor antagonists). Both drugs inhibited platelet accumulation and downregulated AC, resulting in fewer ADP platelet binding sites (Cattaneo, 2007). Thienopyridines have been used to treat platelet function defects, and research has shown that they are particularly antagonistic to P2Y12 (platelet receptor) and have no effect on P2Y1 (Cattaneo, 2007). Platelet agonists such as collagen, thromboxane A2 analogues, and thrombin prevent platelet aggregation (Cattaneo, 2011).

TCP and CPD increase bleeding time through thrombin and shear-induced platelet aggregation. They may also have additional therapeutic effects that result in fibrinogen reduction, which may be associated with hemorrhagic recovery (reduction in plasma and blood viscosity), decreased erythrocyte aggregation, increased nitric oxide production PDTF disruption, and fibronectin synthesis blockage. TCP administration has been related to preventing both moderate and secondary phases of strokes. TCP (500 mg/day) was administered to patients with ischemic stroke and reduced the risk of stroke-related mortality by 12–15 percent (Jeremias and Brown, 2010).

## 6. Conclusion

ICH has a negative impact on public health and is becoming a significant social and economic burden. Concerns about higher occurrence and mortality rates in low and middle-income countries have been expressed. New therapeutic agents are urgently needed to protect and treat post-hemorrhagic complications. The etiopathological factors linked to ICH are concerning because they are poorly understood. Several studies on the downregulation of IGF-1/GLP-1 signaling in ICH have already been published.

Nonetheless, the review aimed to link the disease to a specific target in the system influenced by the diseased state. Furthermore, the core of this manuscript provides a detailed explanation of the disease and its pathophysiology. Moreover, we attempted to explain the connection between the IGF-1/GLP-1 signaling target and ICH. A range of information is available on clinical trials involving IGF-1 and GLP-1. However, it has been found that there is no specific treatment for ICH other than symptom relief; several medications have been discussed extensively in the review.

As a result of our findings, activation of IGF-1 and GLP-1 may be a potential therapeutic target when combined with existing drug therapy in brain hemorrhage patients with behavioural and neurochemical changes (Shandilya and Mehan, 2021). Antithrombotic agents, antiplatelet agents, thrombolytic agents, calcium channel blockers, AMPA antagonists, and other medications are safer options for hemorrhagic patients. Patients with deep hematomas, increased intracranial pressure, uncontrolled arterial hypertension, and seizures may benefit from healthcare attention. Clinical trials are also required to assess the efficacy of hemostatic treatment. There have also been no reports of specific therapies for improving post-ICH outcomes. To summarise, more detailed research is needed to investigate the role of IGF-1/GLP-1 signaling in brain hemorrhage and develop effective and safe drug therapy.

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## Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## Research involving human participants and/or animals

This article does not contain any studies with human participants or animals performed by any of the authors.

## CRediT authorship contribution statement

**Ehraz Mehmood Siddiqui:** involved in, Investigation, Writing – original draft, Writing – review & editing, All authors read and approved the manuscript and all data were generated in-house and that no paper mill was used. **Sidharth Mehan:** has contributed, Conceptualization, Resources, Supervision, Writing – review & editing, All authors read and approved the manuscript and all data were generated in-house and that no paper mill was used. **Sonalika Bhalla:** Writing – review & editing, involved in revision, scientific editing and literature search, All authors read and approved the manuscript and all data were generated in-house and that no paper mill was used. **Ambika Shandilya:** Writing – review & editing, involved in revision, scientific editing and literature search, All authors read and approved the manuscript and all data were generated in-house and that no paper mill was used.

## Declaration of competing interest

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## Abbreviations

| | |
|---|---|
| ICH | Intracerebral hemorrhage |
| IGF-1 | Insulin like growth factor-1 |
| GLP-1 | Glucagon like peptide-1 |
| IVH | Intraventricular hemorrhage |
| HMT | Hematoma |
| BBB | Blood brain barrier |
| RBCs | Red blood cells |
| Hb | Hemoglobin |
| CAA | Cerebral amyloidal angiopathy |
| Aβ | Amyloid beta |
| 8-OHdg | 8-hydroxy-2-deoxyguanosine |
| FOXO | Forkhead box transcription factors |
| HEt | Oxidized hydroethidine |
| MPTP | Mitochondrial permeability transition pore |
| CSF | Cerebrospinal fluid |
| GH | Growth hormone |
| IGFBPs | IGF-1 binding proteins |
| MAPK | Mitogen activated protein kinase |
| IRS-1/2 | Insulin receptor substrate-1/2 |
| PDK-1 | Phosphoinositide dependent protein kinase-1 |
| mTOR | Mammalian target of rapamycin |
| BAD | BCL2 associated agonist of cell death |
| GSK3b | Glycogen synthase 3 b |
| IGF-1R | Insulin like growth factor-1 receptor |
| GLUT4 | Glucose transporter type 4 |
| GLP-1R | Glucagon like peptide-1 receptor |
| GPCR | G protein-coupled receptor |
| AC | Adenyl cyclase |
| cAMP | Cyclic adenosine monophosphate |
| PKA | Protein kinase A |
| DPP-4 | Dipeptidyl peptidase 4 |
| AD | Alzheimer's disease |
| PD | Parkinson's disease |
| HD | Huntington's disease |
| Ca | Calcium |
| OS | Oxidative stress |
| NDD | Neurodegenerative diseases |
| NFT | Neuro fibrillary tangles |
| LB | Lewy bodies |
| DLB | Dementia with lewy bodies |
| MSA | Multiple system atrophy |
| a-syn | a-synuclein |
| ALS | Amyotrophic Lateral Sclerosis |
| SNP | Synucleinopathies |
| SN | Substantia nigra |
| RR | Relative risk |
| TBI | Traumatic brain injury |
| BDNF | Brain-derived neurotrophic factor |
| mHtt | Mutant huntingtin |
| DM | Diabetes mellitus |
| MMP | Matrix metalloproteinase |
| ABM | Albumin |
| CT | Clinical trial |
| MPs | Macrophages |
| MCs | Monocytes |
| PIC | Pro inflammatory cytokines |
| hUCB-MNCs | Human umbilical cord blood-derived mononuclear cells |
| LPS | Lipopolysaccharide |
| MSCs | Mesenchymal stem/stromal cells |
| UCB- BM-MNC | Sumbilical cord blood-bone marrow-mononuclear cells |
| MDGF | Macrophage derived growth factors |
| VEGF | Vascular endothelial growth factor |
| PDGF | Platelet derived growth factor |
| EPO | Erythropoietin |
| HR | Hydroxyl radical |
| MTD | Maximum tolerated dose |
| PGZ | Pioglitazone |
| PPARγ | Peroxisome proliferator activated receptor gamma |
| DOACs | Direct oral anticoagulants |
| DTI | Direct thrombin inhibitor |
| USFDA | United States Food and Drug Administration |
| PDTF | Platelet dependent tissue factor |
| SDDH | Sheng-Di-Da-Huang |
| IL-6 | Leukocyte interleukin 6 |
| MMPs | Matrix metalloproteinases |
| iNOS | Inducible nitric oxide synthase |
| COX-2 | Cyclooxygenase-2 |
| IL-1β | Interleukin-1 beta |
| TNF-α: | Tumor necrosis factor-alpha |

## Appendix A. Peer Review Overview and Supplementary data

A Peer Review Overview and (sometimes) Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.crneur.2022.100055.

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