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Role of Phytocompounds En Route Blood-brain Barrier in Cerebral Ischemia

Debjani Nath[1*], Nasima Khanam[1] and Ashutosh Ghosh[1]

[1]Department of Zoology, University of Kalyani, Kalyani, Nadia, West Bengal, Pin 741235, India.

Authors' contributions

This work was carried out in collaboration among all authors. Author DN designed the study. Author NK wrote the first draft of the manuscript. Authors NK and AG managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Cerebral ischemia is a condition that occurs when the blood vessels in the brain are occluded. Subsequent pathophysiological changes include critical structural and functional damage to the blood-brain barrier. Since remedies for restoring the blood-brain barrier are lacking, alternative methods are important. This study aims to discuss the potential role of phytochemicals in ameliorating blood-brain barrier inflammation and hyperpermeability.
Methodology: This literature review is based on information available in open source databases for the scientific community.
Results: Phytochemicals offer a large resource for neuroprotective cure. Different categories of phytochemical compounds have provided safer and accessible means of medication. A number of phytochemicals have demonstrated antioxidant and anti-inflammatory properties. The respective mechanisms of action have also been discovered for many. Phytochemicals generally inhibit the classic inflammatory signalling molecules, in addition to other pathways. Phytochemicals also strengthen the tight junctional complexes in the blood-brain barrier. Thus phytochemicals substantially improve the affected blood-brain barrier after cerebral ischemia.
Conclusion: Phytochemicals possess useful properties directed towards the healing of the blood-brain barrier in cerebral ischemia and further research may elevate phytochemicals as approved therapeutics.

**Corresponding author: E-mail: nath_debjani@yahoo.co.in;*

Keywords: Cerebral ischemia; blood-brain barrier; inflammation; oxidative stress; phytochemicals.

1. INTRODUCTION

Cerebral ischemia is a grave malady arising consequential to insufficient or restricted flow of blood in the cerebral arteries. Stroke due to cerebral ischemia has emerged as one of the fatal brain disorders of times. The condition occurs when a thrombus or embolus or hypoperfusion develops in a blood vessel blocking blood flow. The ischemic region of the brain becomes depleted of oxygen and nutrients causing considerable damage to brain cells. The ischemic core retains less than 20% of the blood supply, while the surrounding area is the ischemic penumbra which sustains a minor injury. This condition evokes a massive immune response in the brain tissue. The resulting inflammation and oxidative stress complicates the injury and leads to loss of integrity of the blood-brain barrier (BBB). One of the prominent features of cerebral ischemia is the destruction of the BBB. The loss of integrity of BBB has a tremendous impact on the pathophysiology of ischemia. However, measures to cope with this deteriorating BBB, are lacking. In recent times, phytochemicals have shown encouraging results in the treatment of impaired BBB. Phytochemicals are plant derivatives that have medicinal properties. This review is an attempt to provide a comprehensive picture of BBB damage in cerebral ischemia and prospective utilization of phytochemicals for remedial purposes.

2. CEREBRAL ISCHEMIA

Cerebral ischemia is a disorder that involves the damage of brain tissue. This damage to brain tissue is permanent and produces severe complications which may lead to death. Brain ischemia leads to extensive damage to grey matter and white matter. Cerebral ischemia is of three types -Global ischemia, Focal ischemia and transient ischemic attack (TIA). Global ischemia occurs when a wide area of brain tissue is affected and focal ischemia occurs when the attack is confined to a small part of the brain. TIA is called mini-stroke which lasts for a few minutes and does not cause permanent damage to the brain. But TIA is the warning sign of global or focal ischemia. Reperfusion of brain endothelial cells is connected to some risks for example cerebellar oedema, haemorrhage, vascular injury and death of nerve cell. Cerebral ischemia-reperfusion injury causes significant damage to brain functioning. The ischemic-reperfusion further generates an inflammatory response in the area concerned. The ischemic cascade initiates intricate mechanisms that lead to the alteration of metabolic and cellular characteristics of the affected brain cells. The infiltration of neutrophil and activation of residual glial cells from blood to ischemic cerebral parenchyma are crucial for inflammation. Activation of genes of pro-inflammatory mediators such as chemokines, adhesion molecules, cytokines and inflammatory enzymes is mediated by activated Signal transducer and activator of transcription (STAT3) and nuclear factor-κB (NF-κB) [1]. Acute neuroinflammation beginning within hours of the ischemic insult and the oxidative stress that follows, cause most of the brain injury including neuronal damage, and cerebral edema, cognitive impairments and faulty neuronal signalling which may lead to permanent brain damage [2]. The equilibrium of ionic gradients across the membrane is disrupted. This results in the accumulation of sodium, calcium in the brain tissue, reduction of pH, change in membrane potential, change in mitochondrial function and activation of calcium-dependent enzymatic reactions which includes enzymes that break the DNA. In the ischemic brain, free radicals such as hydrogen peroxide are produced in high amount. This causes peroxidation of lipid of brain cell membrane which triggers apoptosis of the cell. Pathophysiology of brain damage after cerebral ischemia involves complex mechanisms. pro-inflammatory mediators damage microglia, axons, nerves, capillaries are caused by and this is called “secondary brain damage“ after brain ischemia [3]. The effects of cerebral ischemia range from mild to severe, from transient reperfusion arrhythmias to the development of fatalities. The extent of injury varies depending on the part of the brain, duration and circumference of the ischemic area, presence of risk factors like hypercholesterolemia, hypertension, diabetes or advanced age which further aggravates the deleterious effects [4].

3. BLOOD-BRAIN BARRIER

In the brain, the microvessels are lined by brain microvascular endothelial cells (BMECs) that form the luminal face of BBB. BMECs have two transporters-efflux and influx transporter. Efflux transporters prevent the entry of many substances and metabolic enzymes in brain parenchyma. Thus, the homeostasis of the brain is maintained. The elements, essential nutrients

and factors are delivered to the brain from the blood by the influx transporters to support the nutrition of the brain. The passage of some ions through the paracellular barrier is blocked by the tight junctions present in adjacent BMEC's surface [5]. Blood vessels present between vein and arteries, 7.5 micrometres in diameter, are called microvessels. The diameter of microvessels is sufficient for squeezing red blood cells through these vessels. Blood is circulated by microvessels in the brain. Within the brain of humans, 100 billion capillaries are present which are 600km in length and 20 square meters in surface area. 10 micrometre of every brain cell gets blood by the foreground and two background microvessels [6]. The volume of the cortical brain (about 2%) and a wide space in other regions of the brain is occupied by these microvessels [7]. About 30% of the surface of BMEC is covered by pericytes (Fig.1). A basement membrane is present which surrounds the pericytes and BMECs and covers the abluminal (brain-side) surface of BMEC. Astrocytes are one of the important glial cells of the brain. Abluminal surface of the basement membrane is covered more than 90% by foot processes of astrocytes. An interaction between neurons and astrocytes cell complex is required for the formation of the neurovascular unit. The entry of phytochemicals into brain parenchyma from the blood requires the distribution of phytochemicals through a BMEC (transcellular) or between BMECs (paracellular). In a normal brain, the blood-brain barrier is intact. When the blood-brain barrier is intact; the distribution of phytochemicals between BMECs (paracellular) cannot be applied. In opened or leaky BBB, phytochemicals can be distributed between BMECs (paracellular).

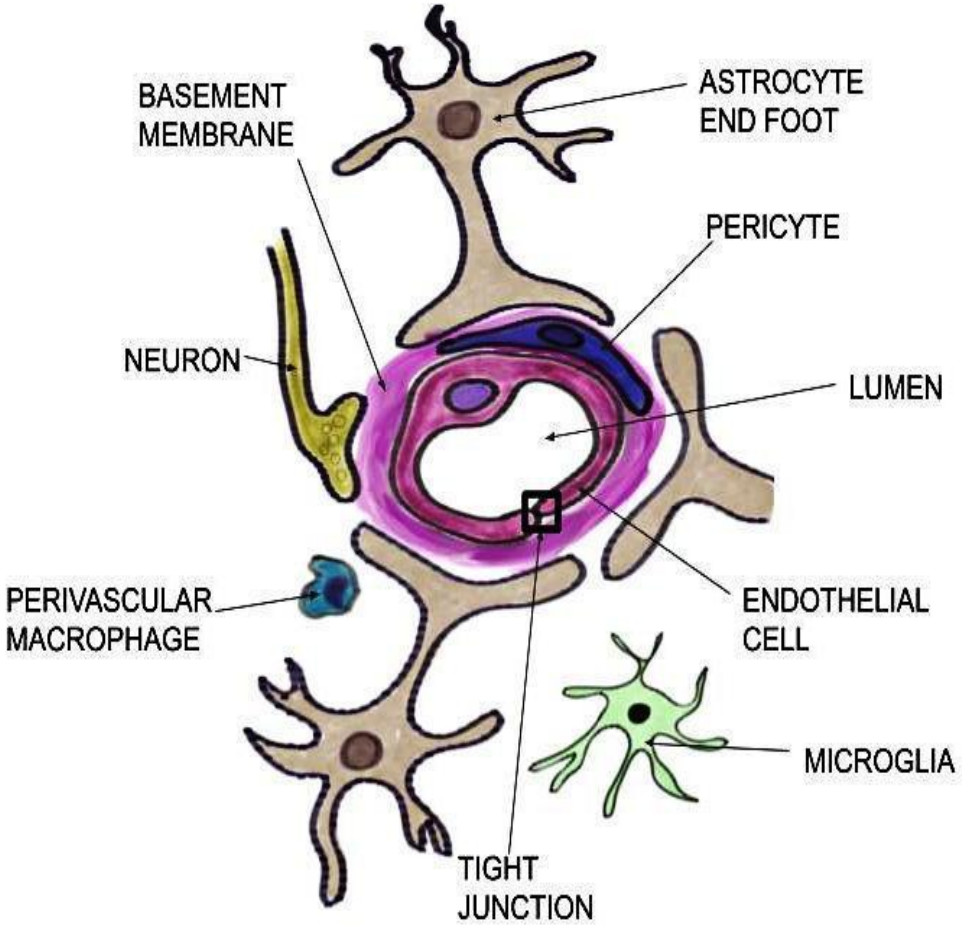

Fig.1. Blood-Brain Barrier

4. ALTERATIONS OF THE BLOOD-BRAIN BARRIER

In cerebral ischemia, BBB becomes breached or leaky i.e., the space between adjacent BMECs surface is increased. This condition of BBB is found in traumatic brain injury (TBI), cancer (at the blood–tumor barrier), multiple sclerosis, Alzheimer's disease, encephalitis, infections, liver failure and other less common conditions.

4.1 Changes in BBB Structure

After cerebral ischemia, there is a loss of structural and functional integrity of BBB. The cytoskeleton is disorganized as actin polymerizes and myosin chain increases. This results in the build-up of stress fibres in endothelial cells [8]. Tight junction (TJ) proteins are degraded and TJs get redistributed [9]. Astrocytes, one of the prominent cell types of BBB, get swollen at the end foot [10]. Pericyte coverage is decreased in the BBB [11]. The overall state of BBB altered forming leaky BBB with hyperpermeability.

4.2 Oxidative Stress and Blood-Brain Barrier

In the ischemic brain, reactive oxygen species (ROS) and other free radicals/oxidants cause oxidative stress. NADPH oxidase (NOX) appears to be the dominant source of ROS. The NOX family of enzymes include NOX1, NOX2, NOX3, NOX4, NOX5, DUOX1, and DUOX2. NOX2 (gp91phox-containing NOX) generates the toxic superoxide (O2●-) radicals and ROS in leukocytes and glial and vascular endothelial cells. Genetic depletion of gp91phox, which is the catalytic subunit of NOX2, has proven to provide neuroprotection [12]. Breakdown of BBB in the ischemic brain has been ameliorated in gp91phox-deficient mice. This may be attributed to decreased induction of MMP-9 and reduced loss of TJ proteins (occludin) since superoxide anion reportedly induces rearrangement or degradation of endothelial TJ [13]. Hydrogen peroxide forming NOX4 isoform and absence of copper/zinc- superoxide dismutase-1 (SOD1) also contributes to the development of cerebral ischemia.

Excess nitric oxide, NO levels in cerebral ischemia can react with O2●- to form toxic peroxynitrite which nitrosylates proteins, disrupting protein functionality. NO also induces S-nitrosylation of the MMPs, disrupting the "cysteine switch" in cerebral ischemia. Thus, oxidative stress plays a leading role in the pathogenesis of ischemic stroke and breakdown of BBB [14].

4.3 Neuroinflammation and Blood-Brain Barrier Damage

Pro- and anti-inflammatory cytokines are expressed rapidly in the brain after ischemic stroke [15]. The leading agents of BBB disruption after ischemic stroke are interleukin-1 (IL-1), IL-6, IL-10, tumor necrosis factor (TNF), interferon (IFN) and transforming growth factor (TGF). IL-1 and TNF appear to exacerbate cerebral injury whereas IL-10, IFN and TGF are neuroprotective (Fig. 2).

Monocytes/macrophages and activated lymphocytes are recruited by Monocyte chemoattractant protein-1, MCP-1 into the brain after injury. These chemokines facilitate BBB breakdown by rearranging the distribution of TJ proteins.

4.4 Adhesion Molecules and BBB

Adhesion molecules are critical when leukocytes infiltrate into the ischemic brain by invading the BBB. P-selectin and E-selectin are involved in the breakdown of BBB and leukocyte transmigration. In cerebral ischemia, hypoxia and proinflammatory cytokines (IL-1β; TNF-α) upregulate ICAM-1, which recruits activated leukocytes in the central nervous system (CNS) [16]. Members of the integrin β2 family also bind to the Ig superfamily (via leukocyte function-associated antigen-1, LFA-1 and Mac-1), consequently aiding neutrophil adhesion and trafficking across BBB [17]. These events result in the breakdown of the protective barrier, namely BBB.

4.5 Matrix Metalloproteinases and BBB

Matrix Metalloproteinases, MMPs, mainly MMP-9 and MMP-2 have been implicated in the destruction of structural integrity in BBB during the early stages of cerebral ischemia. Evidence suggests that MMP-2 degrades the proteins occludin and claudin-5 of tight junctions [18]. However, MMPs exert beneficial roles in the repair stages of stroke.

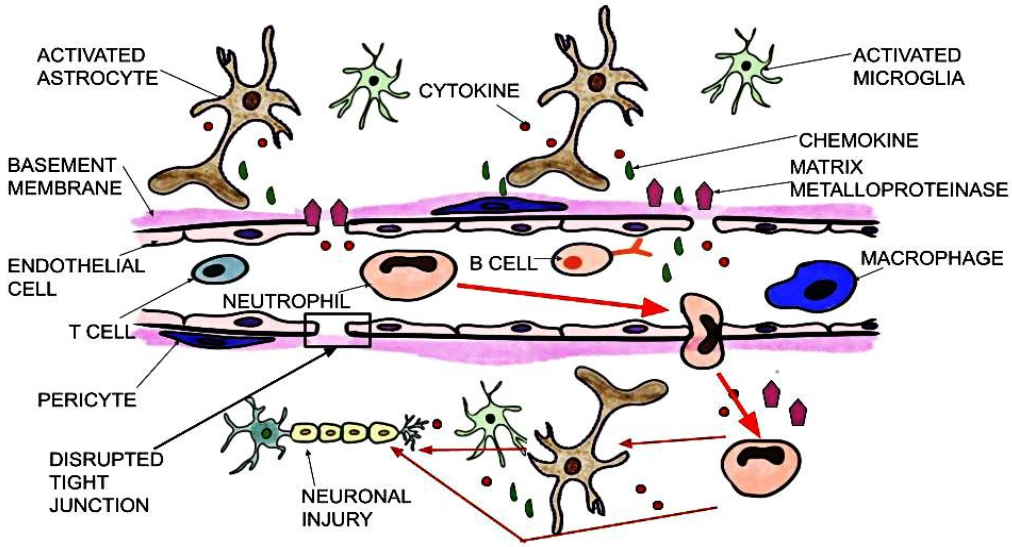

Fig. 2. Neuroinflammation in BBB in Cerebral Ischemia

Treatment procedures of ischemic stroke usually focus on the dissolution of the clot and diminishing the neuroinflammation via recanalization of obstructed arteries with intervention or thrombolysis therapies. However, the efficacy of these processes is determined by the narrow window of time that ensures minimal brain damage. Thrombolytic therapies for acute ischemic stroke encompasses intra-arterial thrombolysis, intravenous thrombolysis using alteplase or tenecteplase and ultrasound enhanced thrombolysis [19]. But the limitations of these strategies have left opportunities for non-conventional therapeutic approaches to develop. Natural products have also exhibited neuroprotective effects. Anti-inflammatory and antioxidant features are also present in some phytochemicals. Small phytochemicals can cross the BBB and interact within the brain. These interactions influence the already disrupted brain homeostasis and help stabilize the disarrayed BBB.

5. ROLE OF PHYTOCHEMICALS IN BBB

Phytochemicals refer to the wide range of bioactive components of plant extracts that play an active role in disease resistance in plants and protection against herbivory. Phytochemicals are non-nutritive chemical compounds from plants. Since ancient times phytochemicals in plant extracts have found their way into the medicinal practices of different cultures and some of them have persisted to date. Phytochemicals possess properties that are beneficial to human health and confer disease protection. The traditional knowledge has, in recent years, been under scientific investigation and the chemistry of phytochemicals is being unravelled.

Phytochemicals may be primary or secondary metabolites of plants. They are broadly classified into phenolics, terpenoids, steroids and alkaloids [20]. Different phytochemicals have shown useful characteristics like anti-inflammatory activity, free radical-scavenging activity, hormesis, neuroprotective effects [21,22] etc. These natural chemicals exhibit low toxicity and high efficiency. Phytochemicals in whole food are generally non-toxic. Most phytochemicals exhibit a hormetic curve, to put it plainly, they can be toxic at higher concentrations but are essentially harmless in the amounts ordinarily consumed. Plant extracts are easily available and can be processed effectively. A number of phytochemicals have also been shown to counter BBB damage by reducing inflammation and hyperpermeability. A short account of potential phytochemicals which can attenuate BBB damage during cerebral ischemia has been summarized below (Fig.3).

5.1 Phenols

Phenolic compounds are the most widely distributed secondary metabolite in the plant kingdom. Comprising at least one hydroxyl group (-OH) is directly bonded to an aromatic hydrocarbon group, phenols play an important role in plant defence. Due to their antioxidant properties phenols are effective against free

radical-mediated inflammation of BBB. Antioxidant activity in protecting BBB generally includes the upregulation of Nuclear factor erythroid 2-related factor 2, Nrf2 which decreases proinflammatory cytokines and upregulates proteins of tight and adherens junctions [23]. Repair of cell junctions and stabilization of F-actins regulate leaky BBB and restore the natural permeability of BBB. Polyphenols like resveratrol, curcumin, baicalein, salvianolic acid A, fisetin, hyperoside, IMM-H004 have antioxidant properties.

Although phenolic phytocompounds can be effective against oxidative stress, they can also become a double-edged sword. The multiple phenolic -OH groups in phytocompounds, in an environment where the pH and redox factors are unfavourable, may promote pro-oxidant activity to a greater extent. Thus, the duality must be cautiously considered when formulating doses [24].

5.1.1 Resveratrol

Resveratrol [5-[(E)-2-(4-hydroxyphenyl)-ethenyl] benzene-1,3-diol)], a non-flavonoid polyphenol obtained from red grapes has reportedly exhibited neuroprotective properties in cerebral ischemia. Resveratrol is active against NO (nitric oxide) mediated oxidative stress and inflammation. Resveratrol, as an anti-inflammatory and antioxidant also modulates transcription factors to reduce NO, IL-1ß, IL-6, TNF-a, MCP-1; C-reactive protein, IL-12p40 and IL-23 (a phenotype of T cells) [25]. Resveratrol is also immunomodulatory in action as it stimulates the polarization of microglia to the anti-inflammatory M2 phenotype (via PGC-1α) [26]. Resveratrol significantly prevents lymphocytes, matrix metalloproteinases and IL-17A from crossing the disrupted BBB and enhances tight junctions thus recovering BBB integrity [27].

Resveratrol has a weak toxicity profile and is safe for animals; humans can consume up to 5000mg safely [28].

5.1.2 Curcumin

Curcumin [(1E,6E)-1,7-Bis(4-hydroxy-3-metho xyphenyl)hepta-1,6-diene-3,5-dione], obtained from *Curcuma longa*, is a common dietary supplement. It is an antioxidant and anti-inflammatory chemical with neuroprotective functions. Curcumin can downregulate nuclear factor kappa-light-chain-enhancer of activated B cells, NF-κB and in turn, inhibits NADPH oxidase. It can also inhibit the expression of Bax, Bcl-2, caspase 3, and caspase 9, inhibiting apoptosis and proinflammatory cytokines (TNF-a, IL-1ß, and IL-1a) and inducible nitric oxide synthase, iNOS. Curcumin is known to reduce ROS induced Cox-2 expression and increase the expression of antioxidative enzymes like catalase, HO-1 and SOD-2 [29,30]. In addition, curcumin helps maintain TJ integrity [31].

Curcumin has both pro-mutagenic and anti-mutagenic properties with an oral LD 50 (median lethal dose) value greater than 2000mg/kg body weight per day for rats and mice. The toxic effects of curcumin in low doses are negligible and has been recognized as safe by USFDA [32].

5.1.3 Baicalein

Baicalein (5,6,7-trihydroxyflavone) is a flavone obtained from *Scutellaria baicalensis*. Baicalein lowers NF-κB expression by preventing IκBa phosphorylation and nuclear translocation of NF-κB/p65, and other proinflammatory cytokines (IL-6, IL-18, and TNF-a) [33]. Baicalein as an antioxidant inhibits proapoptotic caspase-3 and increases the Bcl-2/Bax ratio [34].

5.1.4 Genistein

Genistein (5,7-Dihydroxy-3-(4-hydroxyphenyl) chromen-4-one), an isoflavone, displays anti-inflammatory action via ERK and MAPK signalling in microglial cells [35]. Genistein is a well-known inhibitor of protein tyrosine kinases [36]. Under unfavourable conditions, occludin of TJ undergoes phosphorylation. However, genistein attenuates this phosphorylation and prevents TJ disassembly. Genistein also prevents oxidative stress-related TJ disruption. During oxidative stress, c-Src kinase phosphorylates tyrosine of TJ proteins (ZO-1 and occludin) and adherens junction protein (E-cadherin), but genistein suppresses oxidative stress stimulated c-Src kinase activation [37].

5.1.5 Quercetin

Quercetin is a naturally occurring flavonoid found in many grains, vegetables and fruits. Quercetin is associated with the regulation of enzymes (tyrosine kinase, PI-3 kinase, NF-κB, PKC and the MAPK family) whose downstream signalling proteins influence the assembly and integrity of TJ proteins [36]. Quercetin suppresses PKCδ to

regulate TJ proteins like occludin, ZO-2 and claudin-1 and -4 [38]. This maintains TJ integrity and in turn, helps to maintain the integrity of the BBB.

However, quercetin has a lower blood-brain barrier penetration ability. The long half-life of quercetin metabolites may be problematic and higher doses may lead to nephrotoxicity [39].

5.1.6 Kaempferol

Kaempferol (3,4′,5,7-tetrahydroxyflavone), a flavone compound, is also effective in combating inflammation, oxidative stress and leaky BBB. Kaempferol abates the activation of microglia [40] and attenuates BBB leakage. Kaempferol is shown to inhibit the expression of MMPs (especially MMP3) maintaining the integrity of BBB in cerebral ischemia [41]. Kaempferol increases the expression of TJ proteins ZO-1,-1, occludin and claudin [42].

Kaempferol has low oral bioavailability and low doses are relatively safe for animals [43].

5.2 Terpenes

Terpenes are derived from five-carbon isoprene units. Terpenes are mainly antioxidants and thus are potentially beneficial for BBB restoration after damage. These compounds increase the activity of glutathione peroxidase and SOD and inhibit iNOS and COX-2 which lowers the levels of malondialdehyde, lactate dehydrogenase, ROS, proinflammatory cytokines and proapoptotic caspases and genes [44].

Some prominent terpenes which are helpful for dysfunctional BBB include parthenolide (a sesquiterpene lactone from *Tanacetum parthenium*), borneol (Trimethylbicyclo [2.2.1] heptan-2-ol, a terpene derivative), madecassic acid (triterpenoid from *Centella asiatica*) and panaxatriol (ginsenosides) saponins.

5.2.1 Bacoside

Bacosides are the main component of *Bacopa monnieri*. These are triterpenoid saponins of dammarane-type containing jujubogenin or pseudojujubogenin as their aglycone units. The nootropic and neuroprotective activity of bacosides are reported. Bacoside A is the main bacoside, it is a mixture of four saponins: bacoside A3, bacopaside II, jujubogenin isomer of bacopasaponin C (bacopaside X) and bacopasaponin C [45] Bacoside A has antioxidant, neuroprotective and anti-inflammatory activity. BacosidesA stabilizes the mitochondrial membrane of brain cells. Research shows that bacoside-A increases the level of mitochondrial enzymes and decrease the level of lipid peroxide, cholesterol [46]. Bacoside A maintains ionic balance in the cells of the brain after exposure of rats to cigarette [47]. Investigations have found that ebelin lactone derived from bacoside penetrates BBB [48]. Another bacoside, Bacopaside I has a neuroprotective activity. Amount of ATP of brain and activity of $Na^{+}K^{+}$ ATPase, antioxidant enzymes and $Ca^{2+}Mg^{2+}$ATPase are increased after oral administration of bacopaside I. Bacopaside I reduces brain malondialdehyde amount [49].

Bacoside, as plant extracts, have been in use since ancient times. With LD 50 value 17g/kg (alcoholic extract) and 5g/kg (aqueous extract) in rats, it is relatively non-toxic [50]. It has been confirmed as safe for humans.

5.2.2 Linalool

Linalool (3,7-dimethyl-1,6-octadien-3-ol), is a monoterpenol found in many essential oils. During ischemia, Linalool prevents oxidative stress-induced cortical neuronal death by it's antioxidant and anti-inflammatory effects [51].

5.2.3 Gallic Acid

Gallic acid (3,4,5-Trihydroxybenzoic acid) is a phenolic compound that downregulates inflammatory factors (TNF-α, IL-1β/6), chemokines (CCL-2, ICAM-1, TIMP-1), COX-2 and NO by blocking NF-κB and MAPK signalling pathways [52].

5.2.4 Oleanolic acid

Oleanolic acid (3b-hydroxyolean-12-en-28-oic acid) is a plant secondary metabolite of the terpenoid family. It is predominantly found in fruits, herbs, medicinal plants and olive oil such as *Calendula officinalis, Olea Uropaea* and *Viscum album*. It has anti-inflammatory and antioxidant activity. It has been found that oleanolic acid improves motor performance and slows disease progression after cerebral ischemia and other neurodegenerative disorder [53,54].

5.2.5 Ursolic acid

Ursolic acid (3b-hydroxy-urs-12-ene-28-oic acid) is chemically a pentacyclic triterpenoid. Ursolic

acid (UA) has anti-inflammatory effects. UA inhibits the activation of microglial and astrocyte and reduces the levels of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 in brain inflammation in mice affected with cognitive deficits [55]. Research proved that UA can be an important drug against cerebral ischemia [56,57].

5.3 Alkaloids

Alkaloids are natural plant heterocyclic compounds containing nitrogen. Alkaloids are neuroprotective chemicals and help seal leaky BBB by increasing the expression of cell-cell junctional proteins. Terpenes also inhibit the NF-κB pathway.

5.3.1 Berberine

Berberine (derived from *Berberis sp)* reduces oxidative stress in cerebral ischemia by scavenging free radicals species [58]. Berberine also contributes to the stability of TJs. The probable cause is the inhibition of nuclear translocation of NF-κB p65 subunit which inhibits the inflammatory pathway of NF-κB [59], though ample research is necessary.

LD 50 value of Berberine sulfate is 25mg/kg in mice. Even though berberine has promising characteristics, it causes gastric lesions in animals and reportedly has toxics effects on dopaminergic neurons [60]. Further investigations are required to fully analyze the potential use of berberine in BBB.

5.3.2 Vinpocetine

Vinpocetine, an alkaloid derivative from plants, has also shown anti-inflammatory effects in ischemia. Vinpocetine inhibits NF-κB activation by preventing phosphorylation and degradation of IκBα. Vinpocetine also reduces pro-inflammatory cytokines like TNF-α, IL-6, MCP-1, ICAM-1, VCAM-1, and CRP in blood plasma in the later stages of stroke [61].

5.4 Other Phytochemicals

D-allose (carbohydrate), sesamin (lignan) and ruscogenin (sterol) exhibit analogous functions. They also facilitate the restoration of the disrupted BBB [44].

5.4.1 Cyanidin

Cyanidin (2-(3,4-Dihydroxyphenyl)chromenylium-3,5,7-triol) is a natural organic compound. It is a particular type of anthocyanidin (glycoside version called anthocyanins). Tart cherries contain a natural pigment which is anthocyanins. Beans, fruits, vegetables, and other edible plant materials contain anthocyanin. Anti-inflammatory and antioxidant activity of anthocyanins, including cyanidin-3-O-glycosides (CG), are reported [62]. Anthocyanin has neuroprotective activity against focal cerebral ischemia.

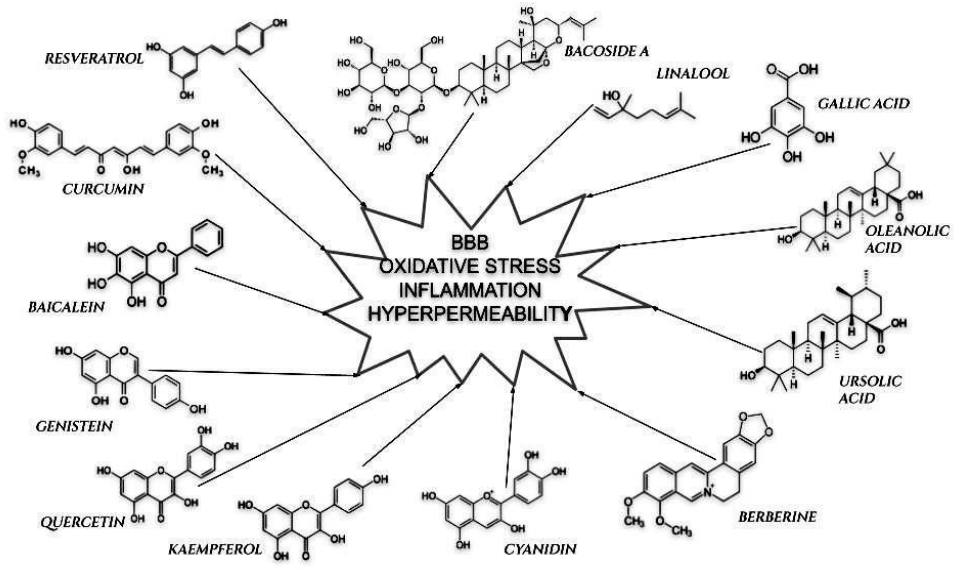

Fig. 3. Potential phytochemicals in alleviating BBB damage

6. CONCLUSION

Cerebral ischemia is a cerebrovascular disease affecting cerebral blood flow. The pathophysiology of the BBB is adversely affected leading to inflammation and hyperpermeability. The leaky BBB may sometimes act as a double-edged sword, allowing the entry of therapeutic drugs into the brain parenchyma as well as facilitating the entry of harmful substances which further aggravate the injury. Thus, it is preliminary that the integrity of the BBB is maintained alongside the target therapies. In view of this, many natural phytochemicals have demonstrated the capacity to cross the BBB and confer neuroprotection. The antioxidant and anti-inflammatory functions and their respective mechanisms have been delineated in quite a few phytochemicals, even though extensive research is warranted. The *in vitro* studies have shown promising results boosting further investigations. Although the bioavailability of phytochemicals may in some cases be ambiguous, nonetheless the curative effect is adequate. Elaborate studies are required to uncover each and every aspect of phytochemical interactions *in vivo* for the restoration of blood-brain barrier in cerebral ischemia. Bioavailability, competent transport systems for phytochemicals, presence of receptor and transporter proteins and most importantly the ability to cross BBB in sufficient amount are yet to be scrutinized thoroughly. Despite this, the prevailing course is favourable. Present studies have established that phytochemicals are efficient in protecting the BBB against oxidative stress, inflammation, apoptotic pathways and hyperpermeability. These investigations have paved the path for advancing the strategies of administration and formulations of the phytocompounds for restoring BBB. Following the current trends, phytochemicals may emerge as the next therapeutic agents for indisposed BBB and cerebral ischemia.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Lu Y, Chu C, Liang Fen W, Kuang X, Liu K, Zhang H, et al. Neuroprotective effect of kaempferol glycosides against brain injury and neuroinflammation by inhibiting the activation of NF-κB and STAT3 in transient focal stroke. Plos One. 2013;8(2): e55839.
2. Ahad MA, Kumaran KR, Ning T, Mansor NI, Effendy MA, Damodaran T, et al. Insights into the neuropathology of cerebral ischemia and its mechanisms. Reviews in the Neurosciences. 2020;31(5):521-38.
3. Del Zoppo GJ. The neurovascular unit in the setting of stroke. Journal of internal medicine. 2010;267(2):156-71.
4. Collard CD, Gelman S. Pathophysiology, clinical manifestations, and prevention of ischemia-reperfusion injury. The Journal of the American Society of Anesthesiologists. 2001;94(6):1133-8.
5. Sanovich E, Bartus RT, Friden PM, Dean RL, Le HQ, Brightman MW. Pathway across blood-brain barrier opened by the bradykinin agonist. RMP-7. Brain research. 1995;705(1-2):125-35.
6. Boström M, Hellström Erkenstam N, Kaluza D, Jakobsson L, Kalm M, Blomgren K. The hippocampal neurovascular niche during normal development and after irradiation to the juvenile mouse brain. International Journal of Radiation Biology. 2014;90(9):778-89.
7. Ohno K, Pettigrew KD, Rapoport SI. Lower limits of cerebrovascular permeability to nonelectrolytes in the conscious rat. American Journal of Physiology-Heart and Circulatory Physiology. 1978;235(3):H299-307.
8. Shi Y, Zhang L, Pu H, Mao L, Hu X, Jiang X, et al. Rapid endothelial cytoskeletal reorganization enables early blood–brain barrier disruption and long-term ischaemic reperfusion brain injury. Nature communications. 2016;7(1):1-8.
9. Rosenberg GA, Yang Y. Vasogenic edema due to tight junction disruption by matrix metalloproteinases in cerebral ischemia. Neurosurgical focus. 2007;22(5):1-9.
10. Xiang J, Tang Y, Li C, Su EJ, Lawrence DA, Keep RF. Mechanisms underlying astrocyte endfeet swelling in stroke. Brain Edema XVI. 2016:19-22.
11. Cai W, Liu H, Zhao J, Chen LY, Chen J, Lu Z, Hu X. Pericytes in brain injury and repair after ischemic stroke. Translational Stroke Research. 2017;8(2):107-21.

12. Walder CE. Green SP, Darbonne WC, Mathias J, Rae J, Dinauer MC, et al. Ischemic stroke injury is reduced in mice lacking a functional NADPH Oxidase. Stroke. 1997;28:2252-8.
13. Liu J, Jin X. Liu Kj. Matrix. metalloproteinase-2-mediated occludin degradation and caveolin-1-mediated claudin-5 redistribution contribution to blood-brain barrier damage in early ischemic stroke stage./Neurosci. 2012;29:3044-57.
14. Yang C, Hawkins KE, Doré S, Candelario-Jalil E. Neuroinflammatory mechanisms of blood-brain barrier damage in ischemic stroke. American Journal of Physiology-Cell Physiology. 2019;316(2):C135-53.
15. Lakhan SE, Kirchgessner A, Hofer M. Inflammatory mechanisms in ischemic stroke: Therapeutic approaches. Journal of Translational Medicine. 2009;7(1):1-1.
16. Wang Qing TX, Nan YM. The inflammatory response in stroke. J Neuroimmunol. 2007;184:53-68.
17. Tsai NW, Chang WN, Shaw CF, Jan CR, Huang CR, Chen SD, Chuang YC, Lee LH, Lu CH. The value of leukocyte adhesion molecules in patients after ischemic stroke. Journal of Neurology. 2009;256(8):1296-302.
18. Yang YI, Estrada EY, Thompson JF, Liu W, Rosenberg GA. Matrix metalloproteinase-mediated disruption of tight junction proteins in cerebral vessels is reversed by synthetic matrix metalloproteinase inhibitor in focal ischemia in rat. Journal of Cerebral Blood Flow & Metabolism. 2007;27(4):697-709.
19. Christophe BR, Mehta SH, Garton AL, Sisti J, Connolly Jr ES. Current and future perspectives on the treatment of cerebral ischemia. Expert opinion on pharmacotherapy. 2017;18(6):573-80.
20. Koche DE, Shirsat RU, Kawale MA. An overerview of major classes of phytochemicals: their types and role in disease prevention. Hislopia Journal. 2016;9:1-1.
21. Slavin JL, Lloyd B. Health benefits of fruits and vegetables. Advances in nutrition. 2012;3(4):506-16.
22. Bradbury KE, Appleby PN, Key TJ. Fruit, vegetable, and fiber intake in relation to cancer risk: Findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). The American journal of clinical nutrition. 2014;100(suppl_1):394S-8S.
23. Roth S, Singh V, Tiedt S, Schindler L, Huber G, Geerlof A, Antoine DJ, Anfray A, Orset C, Gauberti M, Fournier A. Brain-released alarmins and stress response synergize in accelerating atherosclerosis progression after stroke. Science Translational Medicine. 2018;10(432).
24. Castañeda-Arriaga R, Pérez-González A, Reina M, Alvarez-Idaboy JR, Galano A. Comprehensive investigation of the antioxidant and pro-oxidant effects of phenolic compounds: A double-edged sword in the context of oxidative stress?. The Journal of Physical Chemistry B. 2018;122(23):6198-214.
25. Wight RD, Tull CA, Deel MW, Stroope BL, Eubanks AG, Chavis JA, et al. Resveratrol effects on astrocyte function: relevance to neurodegenerative diseases. Biochemical and biophysical research communications. 2012;426(1):112-5.
26. Yang X, Xu S, Qian Y, Xiao Q. Resveratrol regulates microglia M1/M2 polarization via PGC-1α in conditions of neuroinflammatory injury. Brain, Behavior, and Immunity. 2017;64:162-72.
27. Saha A, Sarkar C, Singh SP, Zhang Z, Munasinghe J, Peng S, et al. The blood-brain barrier is disrupted in a mouse model of infantile neuronal ceroid lipofuscinosis: amelioration by resveratrol. Human Molecular Genetics. 2012;21(10):2233-44.
28. Boocock DJ, Patel KR, Faust GE, Normolle DP, Marczylo TH, Crowell JA, et al. Quantitation of trans-resveratrol and detection of its metabolites in human plasma and urine by high performance liquid chromatography. Journal of Chromatography B. 2007;848(2):182-7.
29. Sharma N, Nehru B. Curcumin affords neuroprotection and inhibits α-synuclein aggregation in lipopolysaccharide-induced Parkinson's disease model. Inflammopharmacology. 2018;26(2):349-60.
30. Xiao L, Ding M, Fernandez A, Zhao P, Jin L, Li X. Curcumin alleviates lumbar radiculopathy by reducing neuroinflammation, oxidative stress and nociceptive factors. European cells & Materials. 2017;33:279.
31. Lee B, Moon KM, Kim CY. Tight junction in the intestinal epithelium: its association with diseases and regulation by

phytochemicals. Journal of immunology research. 2018;2018.
32. Bhat A, Mahalakshmi AM, Ray B, Tuladhar S, Hediyal TA, Manthiannem E, et al. Benefits of curcumin in brain disorders. Bio Factors. 2019;45(5):666-89.
33. Yang S, Wang H, Yang Y, Wang R, Wang Y, Wu C, et al. Baicalein administered in the subacute phase ameliorates ischemia-reperfusion-induced brain injury by reducing neuroinflammation and neuronal damage. Biomedicine & Pharmacotherapy. 2019;117:109102.
34. Aryal P, Kim K, Park PH, Ham S, Cho J, Song K. Baicalein induces autophagic cell death through AMPK/ULK1 activation and downregulation of m TORC 1 complex components in human cancer cells. The FEBS Journal. 2014;281(20):4644-58.
35. Zhao Z, Fu J, Li S, Li Z. Neuroprotective effects of genistein in a SOD1-G93A transgenic mouse model of amyotrophic lateral sclerosis. Journal of Neuroimmune Pharmacology. 2019;14(4):688-96.
36. Suzuki T, Hara H. Role of flavonoids in intestinal tight junction regulation. The Journal of Nutritional Biochemistry. 2011;22(5):401-8
37. Rao RK, Basuroy S, Rao VU, Karnaky Jr KJ, Gupta A. Tyrosine phosphorylation and dissociation of occludin–ZO-1 and E-cadherin–β-catenin complexes from the cytoskeleton by oxidative stress. Biochemical Journal. 2002;368(2):471-81.
38. Suzuki T, Hara H. Quercetin enhances intestinal barrier function through the assembly of zonnula occludens-2, occludin, and claudin-1 and the expression of claudin-4 in Caco-2 cells. The Journal of nutrition. 2009;139(5):965-74.
39. Keddy PG, Dunlop K, Warford J, Samson ML, Jones QR, Rupasinghe HV, Robertson GS. Neuroprotective and anti-inflammatory effects of the flavonoid-enriched fraction AF4 in a mouse model of hypoxic-ischemic brain injury. PLoS One. 2012;7(12):e51324.
40. Li WH, Cheng X, Yang YL, Liu M, Zhang SS, Wang YH, et al. Kaempferol attenuates neuroinflammation and blood brain barrier dysfunction to improve neurological deficits in cerebral ischemia/reperfusion rats. Brain research. 2019;1722:146361.
41. Park SE, Sapkota K, Kim S, Kim H, Kim SJ. Kaempferol acts through mitogen-activated protein kinases and protein kinase B/AKT to elicit protection in a model of neuroinflammation in BV2 microglial cells. British Journal of Pharmacology. 2011;164(3):1008-25.
42. Suzuki T, Tanabe S, Hara H. Kaempferol enhances intestinal barrier function through the cytoskeletal association and expression of tight junction proteins in Caco-2 cells. The Journal of Nutrition. 2011;141(1):87-94.
43. M Calderon-Montano J, Burgos-Morón E, Pérez-Guerrero C, López-Lázaro M. A review on the dietary flavonoid kaempferol. Mini reviews in Medicinal Chemistry. 2011;11(4):298-344.
44. Welcome MO. Blood brain barrier inflammation and potential therapeutic role of phytochemicals. Pharma Nutrition. 2020;11:100177.
45. Deepak M, Sangli GK, Arun PC, Amit A. Quantitative determination of the major saponin mixture bacoside A in Bacopa monnieri by HPLC. Phytochemical Analysis: An International Journal of Plant Chemical and Biochemical Techniques. 2005;16(1):24-9.
46. Anbarasi K., Vani G., Devi C.S. Protective effect of bacoside A on cigarette smoking-induced brain mitochondrial dysfunction in rats. J. Environ. Pathol. Toxicol. Oncol. 2005;24(3):225–234.
47. Anbarasi K, Vani G, Balakrishna K, Devi CS. Effect of bacoside A on brain antioxidant status in cigarette smoke exposed rats. Life Sciences. 2006;78(12):1378-84.
48. Ramasamy S, Chin SP, Sukumaran SD, Buckle MJ, Kiew LV, Chung LY. In silico and in vitro analysis of bacoside A aglycones and its derivatives as the constituents responsible for the cognitive effects of Bacopa monnieri. PLoS One. 2015;10(5):e0126565.
49. Liu X, Yue R, Zhang J, Shan L, Wang R, Zhang W. Neuroprotective effects of bacopaside I in ischemic brain injury. Restorative Neurology and Neuroscience. 2013;31(2):109-23.
50. Al-Snafi AE. The pharmacology of Bacopa monniera. A review. International Journal of Pharma Sciences and Research. 2013;4(12):154-9.
51. Park H, Seol GH, Ryu S, Choi IY. Neuroprotective effects of (−)-linalool against oxygen-glucose deprivation-induced neuronal injury. Archives of pharmacal research. 2016;39(4):555-64.

52. Bai J, Zhang Y, Tang C, Hou Y, Ai X, Chen X, Zhang Y, Wang X, Meng X. Gallic acid: Pharmacological activities and molecular mechanisms involved in inflammation-related diseases. Biomedicine & Pharmacotherapy. 2021;133:110985.
53. Martín R, Carvalho-Tavares J, Hernández M, Arnes M, Ruiz-Gutierrez V, Nieto ML. Beneficial actions of oleanolic acid in an experimental model of multiple sclerosis: a potential therapeutic role. Biochemical Pharmacology. 2010;79(2):198-208.
54. Martín R, Hernández M, Córdova C, Nieto ML. Natural triterpenes modulate immune-inflammatory markers of experimental autoimmune encephalomyelitis: Therapeutic implications for multiple sclerosis. British Journal of Pharmacology. 2012;166(5): 1708-23.
55. Wang YJ, Lu J, Wu DM, Zheng ZH, Zheng YL, Wang XH, Ruan J, Sun X, Shan Q, Zhang ZF. Ursolic acid attenuates lipopolysaccharide-induced cognitive deficits in mouse brain through suppressing p38/NF-κB mediated inflammatory pathways. Neurobiology of Learning and Memory. 2011;96(2):156-65.
56. Wang Y, He Z, Deng S. Ursolic acid reduces the metalloprotease/anti-metalloprotease imbalance in cerebral ischemia and reperfusion injury. Drug Design, Development and Therapy. 2016;10:1663.
57. Li L, Zhang X, Cui L, Wang L, Liu H, Ji H, et al. Ursolic acid promotes the neuroprotection by activating Nrf2 pathway after cerebral ischemia in mice. Brain Research. 2013;1497:32-9.
58. Kim M, Shin MS, Lee JM, Cho HS, Kim CJ, Kim YJ, Choi HR, Jeon JW. Inhibitory effects of isoquinoline alkaloid berberine on ischemia-induced apoptosis via activation of phosphoinositide 3-kinase/protein kinase B signaling pathway. International Neurourology Journal. 2014;18(3):115.
59. Gu L, Li N, Gong J, Li Q, Zhu W, Li J. Berberine ameliorates intestinal epithelial tight-junction damage and down-regulates myosin light chain kinase pathways in a mouse model of endotoxinemia. Journal of Infectious Diseases. 2011;203(11):1602-12.
60. Belwal T, Nabavi SM, Nabavi SF, Dehpour AR, Shirooie S, editors. Naturally Occurring Chemicals against Alzheimer's Disease. Academic Press; 2020.
61. Zhang F, Yan C, Wei C, Yao Y, Ma X, Gong Z, et al. Vinpocetine inhibits NF-κB-dependent inflammation in acute ischemic stroke patients. Translational stroke research. 2018;9(2):174-84.
62. Wang H, Nair MG, Strasburg GM, Chang YC, Booren AM, Gray JI, et al. Antioxidant and antiinflammatory activities of anthocyanins and their aglycon, cyanidin, from tart cherries. Journal of natural products. 1999;62(2):294-6.

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