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REVIEW ARTICLE

Neuroinflammation: The Role of Anthocyanins as Neuroprotectants

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Abstract: Neuroinflammation is a trigger for several neurodegenerative and neuropsychiatric disorders. Exposure to noxious external stimuli induces homeostatic disturbances resulting in morphological changes in microglia, their activation, and elaboration of pro-inflammatory mediators. This leads to neuroinflammation with the progressive loss of neurons. Nutraceuticals such as anthocyanins are a class of brightly colored bioactive compounds present in fruits and vegetables with purported health benefits. They interfere with the activation of several signaling cascades that have a prominent role in preventing neuroinflammation. More importantly, anthocyanins can cross the blood-brain barrier and are safe. Hence, the current review focuses on the bioavailability of anthocyanins, clinical and *in vitro* evidence on their role in impeding the activation of transcription factors, modulating the immune milieu within the central nervous system, preventing the activation of microglia, and averting neuroinflammation.

Keywords: Anthocyanins, microglia, oxidative stress, signaling pathways, neuroinflammation, bioavailability.

1. INTRODUCTION

Brain disorders are leading contributors to the global burden of diseases. The incidence of neurodegenerative and neuropsychiatric disorders is fast escalating, creating loss of productivity and inciting immense economic burden. The cost involved in monitoring and managing patients with neurodegenerative disorders is rated to be twice the estimated cost spent on cancer. Neurological disorders are the second largest cause of mortality and have been progressively increasing over the years [1]. Recurrent exposure to environmental pollutants, chemicals, microbial products, and deranged lifestyles can cause homeostatic alterations affecting the vigorous defense of the physiological system.

The brain is a complex organ containing different cells and performing various functions. The integrity of glia and neurons could be overtly disturbed, triggering a series of events leading to the activation of transcription factors and expression of their products, apparently manifesting as inflammation. Besides, when inflammation exists in the central nervous system (CNS), stroke, brain trauma, meningitis, Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS) can ensue [2, 3]. Unrestrained neuroinflammation builds up cytotoxic mediators such as proinflammatory cytokines, oxidative markers, and inflammatory agents that can damage neurons in discrete brain regions resulting in AD, PD, and MS [4].

Apart from neurological disorders, neuroinflammation also plays a crucial role in the development of neuropsychiatric conditions such as schizophrenia and mood disorders. Neuroinflammation impairs brain function by altering the blood-brain barrier's permeability, allowing the passage of pro-inflammatory mediators and peripheral immune cells. Patients afflicted with anxiety and mood disorders show a substantial elevation in inflammatory cytokines [5]. Inflammation promotes the release of glutamate from microglia and oxidizes tetrahydrobiopterin, a cofactor needed for the formation of monoamines. Moreover, the overt expression of inflammatory cytokines can alter the neurocircuits in various brain regions manifesting the symptoms of anxiety and mood disorders [6]. In schizophrenic patients, the migration of peripheral immune cells causes neuroinflammation and deterioration of brain function [7]. In bipolar disorders, evidence of neuronal damage due to microglial activation [8] and elevation in inflammatory mediators such as nuclear factor-κB, tumor necrosis factor-alpha (TNF-a), inducible nitric oxide synthase, IL-1β, and IL-1 receptor was reported in postmortem studies of patients afflicted with mood disorders [9]. In major depressive disorder, an unusually higher level of inflammatory cytokines has been observed in some patients. Cytokines can cause alterations in the hypothalamic-pituitary-adrenal axis and the functioning of the glucocorticoid receptors. The activity of GR is also altered through several cytokine-mediated signaling pathways [5]. Moreover, inflammation can augment the release of oxidative markers, which can cause microglial activation. In addition, in schizophrenia and mood disorders, an apparent change in the plasticity of neurons of the gray and white matter occurs [10]. Thus, immunocyte infiltration, activation of immune signaling cascades, and pro-inflammatory cytokines cause neuroinflammation and cell destruction [3].

Nutraceuticals are foods consumed in the diet, and their benefits have been investigated in the dietary management of

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diseases. The consumption of secondary plant metabolites such as anthocyanins is proven to have anti-inflammatory action [11]. Anthocyanins have phenolic moieties in their structure and are oxidized forms of flavonoids. Structurally, anthocyanins are oxygenated versions of the flavylium (2-phenylchromenylium) moiety, like flavonoids in structure. The functional unit of anthocyanins is anthocyanidin which is devoid of the sugar moiety. Anthocyanin glycosides are coupled to sugar moieties. The color, stability, and chemical nature of anthocyanins can be altered depending upon the pH of the media to which it is exposed. Quinoidal bases, chalcone pseudobase, carbinol pseudobases, and the flavylium cation are the four molecular forms in which anthocyanins subsist. The colored and most stable flavylium cationic form appears at low pH. The color depends on the groups attached to their basic structure, with the hydroxyl group producing a bluish tinge and methoxy groups producing a red color [12, 13]. Blueberries, blackberries, strawberries, raspberries, elderberries, cranberry, bilberry, cherries, red wine, black grapes, and black currants are rich sources of anthocyanins. Some examples of anthocyanins include cyanidin, malvidin, delphinidin, peonidin, pelargonidin, and petunidin [14].

Anthocyanins are proposed to alleviate the symptoms associated with several neurodegenerative and neuropsychiatric disorders. They are perceived to act on inflammatory signaling cascades, expression of pro-inflammatory cytokines, and chemokines [15]. Neuroinflammation is triggered by the release of several pro-inflammatory cytokines, while neurotoxic compounds activate glia leading to neurodegeneration. Damaged and dying neurons increase cytokine formation further, exacerbating neuroinflammation. Microglia, predominant cells of the innate immune system, are maintained in a quiescent state, and the presence of healthy neurons regulates microglial activation. Exposure to stimulatory signals causes a morphologic transition from the ramified to an amoeboid form. The phenotypic M1 form produces pro-inflammatory mediators and immune-regulatory cytokines that trigger neuronal damage [16, 17].

Anthocyanins suppress microglial overactivation, a hallmark of neuroinflammation. In addition, they restrain the transcription or post-transcriptional activity of several pro-inflammatory genes [18]. Hence, our review focuses on the potential of anthocyanins in repressing neuroinflammation, their impact on several signaling pathways, and their plausible role as neuroprotective agents.

2. BIOAVAILABILITY OF ANTHOCYANINS

As anthocyanins have nutritive utility, their pharmacokinetics can crucially impact their response. Parent anthocyanins have limited bioavailability [19-21], and their absorption, as well as metabolism, could be affected by the type of sugar attached [21, 22], physicochemical factors, and the presence of microbiota [23-25].

Their chemical structure might impact the bioavailability of anthocyanins. Anthocyanins exhibit a diverse nature depending on the number of hydroxyl or methoxyl groups attached to the basic flavylium cation (2-phenylbenzopyrylium) and its ability to accept glycosyl moieties such as D-glucose, D-galactose, D-rhamnose, and D-arabinose. The efficacy of anthocyanins increases when the 3',4'-ortho positions on the B-ring of the anthocyanin chromophore are occupied with dihydroxyl groups. Also, the attachment of a hydroxyl group on the third position of ring C can enhance their efficacy [26]. Anthocyanidin glycosylation, or acylation, alters their polarity, with glycosylation favoring hydrophilicity and acylation enhancing hydrophobicity. However, as hydroxylation increases their polarity, the paracellular movement into the cell could be affected [27, 28].

Anthocyanins should be absorbed in appreciable amounts to achieve the desired response at a target site. Several factors could affect their absorption, such as the pH, dose of anthocyanins, and food-anthocyanin interactions. Anthocyanin pigments are sensitive to pH changes, and stable flavylium cation prevails at pH 1–3 (Fig. **1**). At alkaline pH, due to structural rearrangements, the pseudobase carbinol dominates [29]. Initially, anthocyanins are likely to be transformed in the oral cavity [30]. An *ex vivo* analysis revealed that 30% cyanidin-3-glucoside (C3G) is converted into chalcones by salivary content [30]. In another human study, deglycosylated anthocyanins appear in the oral cavity along with protocatechuic acid, a C3G metabolite. Phase-II products were also found in saliva [31]. Thus, the pH of the oral cavity (~6.8), the involvement of microorganisms, salivary proteins, and the quick transit onwards minimize the time they remain in the oral cavity affecting absorption [29, 30, 32].

Animal models have shown that anthocyanins are rapidly absorbed and appear in blood within 5-20 minutes, albeit in low concentrations. Oral administration of anthocyanins for short periods results in the systemic circulation of the parent anthocyanins; nevertheless, when used for long periods, saturation occurs [33]. The presence of native anthocyanins in plasma plausibly reflects their absorption from the stomach [29, 34, 35]. Although the flavylium cation is stable at low pH, the ability to undergo passive diffusion may be reduced. Carriers like bilitranslocase could facilitate the transport of anthocyanins from the lumen to the gastric mucosa epithelial layer [36]. Animal and human studies show that anthocyanins are substrates for bilitranslocase, a membrane-bound carrier present in the gastric mucosa epithelium. The small intestine is another location for parent anthocyanin absorption [13]. In human subjects, absorption is facilitated through active transporters such as sodium-dependent glucose transporter or passive diffusion [36]. Methylated anthocyanin derivatives are mainly produced in the upper gastrointestinal tract and may be low in the large intestine [37]. In humans, anthocyanins can also be hydrolyzed by β-hydroxylase lactase phlorizin hydrolase (LPH) present in the small intestine mucosal brush border accompanied by O-methylation, O-glucuronidation, or O-sulfonylation [14]. Similarly, in animals, black raspberry anthocyanins were absorbed in the intestine to the extent of 7.5 % [38].

The food matrix affects anthocyanin absorption, although the effect of food has not been thoroughly established. However, one experiment on human subjects indicates that pelargonidin absorption declined by half when consumed with milk [39]. Another study found that consuming food containing pectin delays the absorption of C3G and delphinidin-3-glucoside [40].

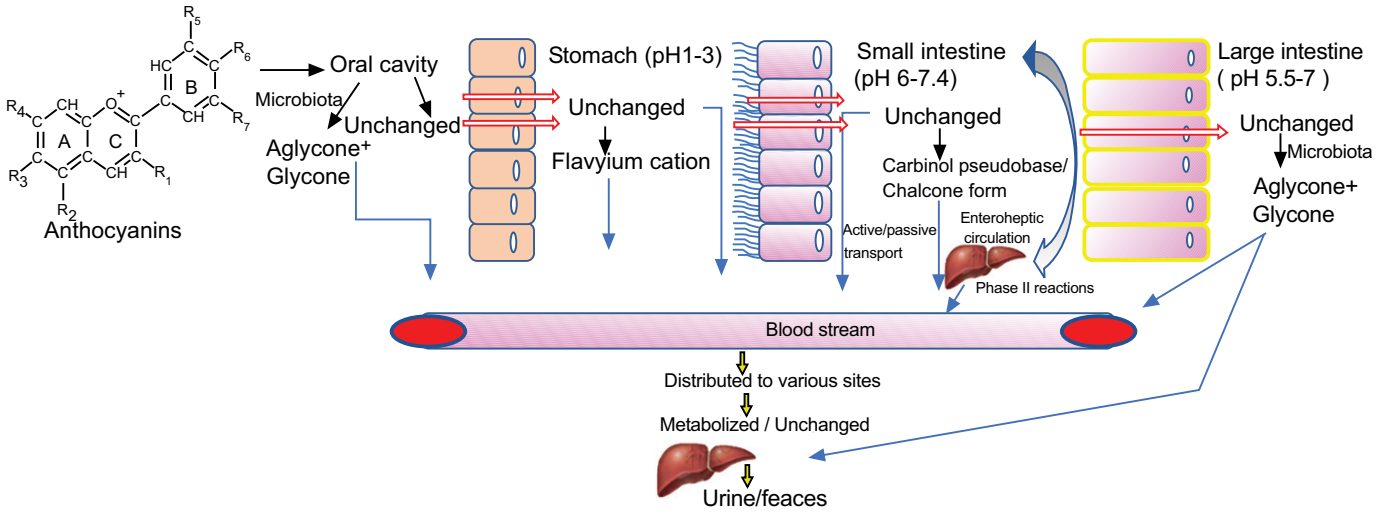

Fig. (1). Bioaccessibility of anthocyanins and their passage across several barriers. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

3. INFLUENCE OF MICROBIOTA

Anthocyanin monoglucosides and diglucosides could be potential targets for microorganisms [41]. Prevalent microbiota in the oral cavity elaborate ß-glucosidases, cause deglycosylation of complex glycosylated forms and improve their absorption [42]. A study detected ß-glycosidase activity in the oral cavity resulting in the hydrolysis of black raspberry anthocyanins [31].

Anthocyanin-rich extracts pass from the oral cavity to the upper gastrointestinal tract; however, higher concentrations were found in the distal intestine, cecum, and colon due to poor absorption [13]. Anthocyanins that fail to undergo metabolism and absorption in the proximal intestine might be processed in the colon. Around 85% of blueberry anthocyanins have been detected in the colon [13, 14, 43]. The gut microbial community includes commensals and symbiotic organisms that work in various capacities to modulate gastrointestinal homeostasis. Evidence indicates that the gut microbiome plays a significant role in anthocyanin biotransformation [41, 44]. Microbiota improves the absorption of anthocyanins by splitting the glycosidic linkage, cleaving the heterocyclic ring, converting the A-ring into phloroglucinol derivatives, and the B-ring to benzoic acid derivatives [45]. *Bifidobacterium* and *Lactobacillus* species contain enzymes like β-glucosidase that catalyzes the metabolism of polyphenolic compounds [46]. For example, protocatechuic acid, a metabolite produced by the gut microbiota through the oxidation of C3G, has beneficial effects on plagues [47]. Besides, after consuming anthocyanin-rich fruits, microbial diversity increased in the gastrointestinal tract with the colonization of *Bifidobacterium* and *Lactobacillus* species [48]. 8-week dietary intake of 300 g fresh berries (70.7 mg anthocyanins) increased the microbial population of Lachnospiraceae and Ruminococcaceae [49]. Boto-Ordonez *et al.* [50] demonstrated that the administration of dealcoholized red wine to nine participants for 20 days increased fecal levels of *Bifidobacterium, Enterococcus,* and *Eggerthella lenta* species.

Anthocyanins distribute in the liver, heart, and kidney [51, 52]. Also, parent anthocyanins and aglycones were detected in various brain regions such as the cortex, cerebellum, hippocampus, and striatum [13, 53].

4. BIO-ACCESSIBILITY IN THE BRAIN

Anthocyanins annul inflammation, counter oxidative stress induced by various external agents, and improve brain function. However, there is skepticism about the transit of anthocyanins across highly selective barriers such as the blood-brain barrier. Analyzing the concentration of anthocyanins in several brain regions confirms their transportation across the blood-brain barrier.

Several studies have assessed the transit of C3G across the blood-brain barrier. C3G isolated from mulberry fruits (*Morus alba L.)* was administered orally to rats in a dose of 50 mg/kg. Chen *et al.* have reported that a single dose of C3G was detected in rat brain 15 min after oral administration and achieved a high concentration within 45 min. The level in the brain declined steadily and was undetected four h after administration, indicating that anthocyanins traverse through the blood-brain barrier [54].

Ke *et al.* [55] have demonstrated that C3G (30 mg/kg, intraperitoneal) got distributed in mice brain tissue within 15 min of treatment. A peak concentration of 3.5 nmol/g was observed within one h; however, C3G was not detected six h after administration. Anthocyanins were detected in the brain of rats fed with a diet enriched with blackberry (*Rubus fruticosus L.*) for 15 days. Brain levels of C3G (0.21 nmol/g of tissue) were higher compared with the plasma (0.15 nmol/ml), demonstrating the ability of C3G to cross the blood-brain barrier [13].

Another study reported that the intravenous administration of C3G to rats in a dose of 668 nmol for 20 min led to its distribution into the brain rapidly, achieving a concentration of 2.21-44.11pmol/g in 20 min [56].

Gutierres *et al.* [57] suggested that treatment with purified grape skin anthocyanins (200 mg/kg) for one week reduced anticholinesterase levels in isolated rat synaptosomes of the cerebral cortex. Anthocyanins (100 μM) have also decreased the binding of [3^H] flunitrazepam to the GABAA receptor-benzodiazepine site by 43 %, suggesting that they cross the blood-brain barrier.

Anthocyanins were detected in the cerebellum, cortex, midbrain, and diencephalon of pigs fed with a diet fortified with 2% (w/w) freeze-dried powdered Jersey blueberry (V*accinium corymbosum L. cv. 'Jersey*') for eight weeks. About fifteen anthocyanins exist in Jersey blueberry, the most common being the glucosides, galactosides, and arabinosides of malvidin and petunidin delphinidin-3-glucoside, and C3G. In the cortex, malvidin-3-glucoside was detected in a concentration of 279 fmol/g of tissue and at a concentration of 432 fmol/g of tissue in the midbrain/diencephalon after 18 hours of ingestion [58].

A diet of lyophilized, powdered blueberries (2% w/w) with an anthocyanin content of 267.2 μg/g fed to rats resulted in the detection of anthocyanin content in the hippocampus and the cortex up to 0.45 nmol/g and 0.46 nmol/g, respectively [59].

Their hydrophilic existence restricts the transportation of anthocyanins through the blood-brain barrier. In addition, the aggregation of hydroxyl groups on the B-ring of the anthocyanin moiety increases their hydrophilicity and can restrict their absorption [60]. Thus, to achieve the desired neuroprotective effect, the selection of more lipophilic anthocyanins may be crucial [60].

5. METABOLISM AND EXCRETION OF ANTHOCYANINS

Anthocyanins undergo biotransformation in the liver followed by their clearance through bile or kidneys [61]. Ludwig [37] *et at.* have identified pH-mediated cleavage of cyanidin in the small intestine to catechuic acid, which is transformed into ferulic and isoferulic acid. The degradation of the B-ring of raspberry anthocyanins leads to the formation of 3,4 dihydrobenzoic acid (protocatechuic acid) and 4-hydroxybenzoic acid, while degradation of the A-ring produces phloroglucinaldehyde [37]. UDP glucuronosyltransferase, catechol-O-methyl transferase, and sulfotransferases catalyze the glucuronidation, methylation, and sulphation of anthocyanins in the intestine, kidneys, and liver. The metabolic pathway of C3G has been outlined in Fig. (**2**).

The microbiota-mediated cleavage of the B-ring of raspberry anthocyanins produces hydroxycinnamates [62]. Microbial biotransformation opens the anthocyanin ring, facilitates deglycosylation and scission. Malvidin-3-O-glucoside undergoes microbial metabolism forming syringic acid, which then undergoes enzyme-mediated demethylation of the B-ring forming gallic acid.

Anthocyanin excretion in urine in the unmetabolized form is low and often below detection limits. In C3G administered rats, urinary metabolites included protocatechuic acid and hippuric acids. In feces, C3G, ferulic acid, protocatechuic acid, methylated and glucuronidated metabolites were identified. Of the total C3G administered, approximately 6.62% and 2.53% were excreted in urine and feces, respectively [54]. Human subjects treated with isotopically labeled ^{13}C-C3G contained protocatechuic acid in urine along with benzoic acid and glycine-coupled hippuric acid [63].

In older women treated with 189 g blueberries (690 mg anthocyanins) or 12 g elderberry extract (720 mg anthocyanins), analysis of their urine samples detected only two prominent peaks, corresponding to cyanidin-3-sambubioside and cyanidin-3-glucoside. Also, methylated and glucuronide forms were identified. However, in blueberry-treated older women, different anthocyanin peaks were not observed. The presence of 3′, 4′-dihydroxyl groups on anthocyanin ring B increased their probability of methylation at 3′-O-position resulting in a five-to-tenfold lower anthocyanin level. Except for two older women, the flavylium anthocyanin cation was plausibly more defiant towards conjugation with glucuronides [64].

In another study, the consumption of blueberry extract (~ 439 mg of anthocyanins) showed poor urinary excretion of parent anthocyanins (0.02%) over 9 hours. Besides, minor fractions of hippuric acid, homovanillic acid, vanillic acid, and p-coumaric acid were detected in urine [22]. Also, glucuronide and sulfate conjugated forms were identified in human urine [14, 63, 65].

6. MOLECULAR SITES OF ACTION: NUCLEAR FACTOR KAPPA B SIGNALING AND OXIDATIVE MARKERS

Anthocyanins derived from various sources respond to several types of external stimuli by targeting cell surface receptors, acting on second messengers, interfering with signal transduction, and regulating the release of transcription factors. They avert lipopolysaccharide (LPS) mediated foray of immune cells into the hippocampus and interfere with the activation of microglia [66]. The expression of NF-κB serves as a cellular marker of injury in the central nervous system (CNS) (Fig. **3**) [67, 68]. Thus, anthocyanins have a role in preventing the transcription and expression of inflammatory cytokines/mediators such as TNF-α, IL1β, IL-6, prostaglandin E2 (PGE2), and nitrite. Also, in an environment of prevailing neuroinflammation, transcription factors such as NF-κB and activator protein 1 (AP-1) activate the expression of inducible nitric oxide synthase (iNOS), which increases the output of nitric oxide (NO) and neurotoxic peroxynitrite ($ONOO^-$). Enormous levels of reactive oxygen species (ROS) induce oxidative stress perturbing the internal environment and disrupting the electron transport chain. Disturbance in the redox balance can trigger the activation of several signaling pathways and the release of pro-inflammatory cytokines. Moreover, genes for COX-2, iNOS, TNF-α, IL-1β, and IL-6 have promoter regions containing the κB binding sites. At the transcriptional level, the actuation of the COX-2 promoter occurs when its *cis*-acting elements are coupled with NF-κB, Nuclear Factor of Activated T-cells (NFAT), cAMP Response Element-Binding protein (CREB), and c/EBPβ (CCAATenhancer-binding protein). Activation of COX-2 genes leads to the overt expression of PG [69]. LPS-induced inflammation of the cerebral vasculature is primarily attributed to the release of COX-2 and PGE_2 [70].

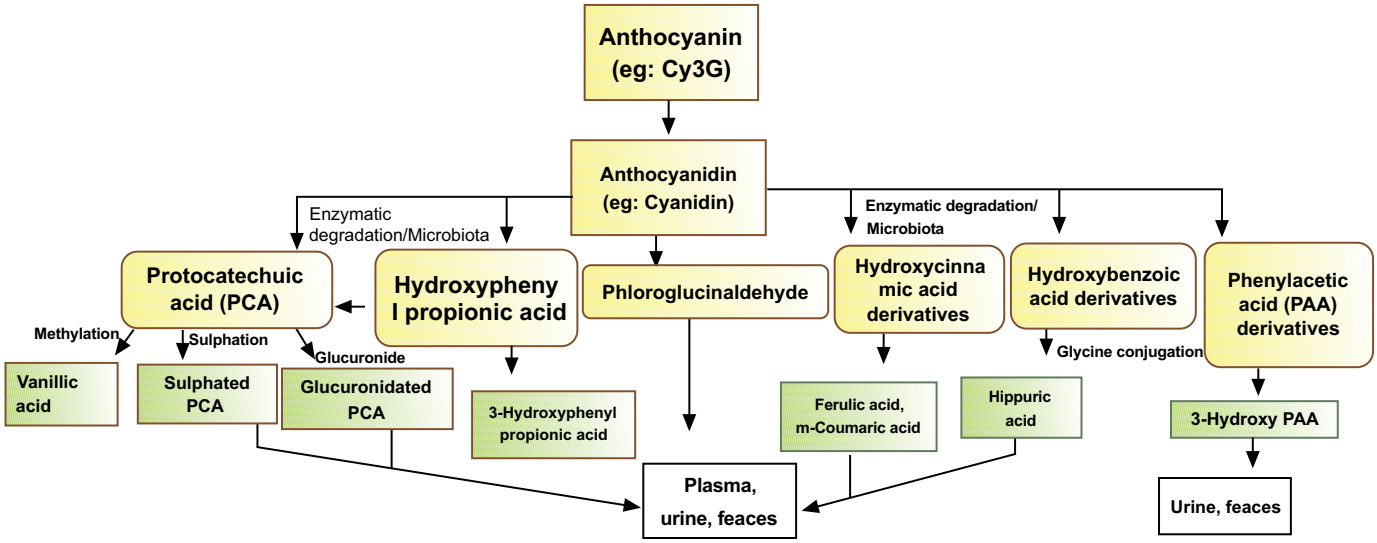

Fig. (2). Metabolism and metabolites formed from anthocyanins. Cy3G: Cyanidin-3-glucoside. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

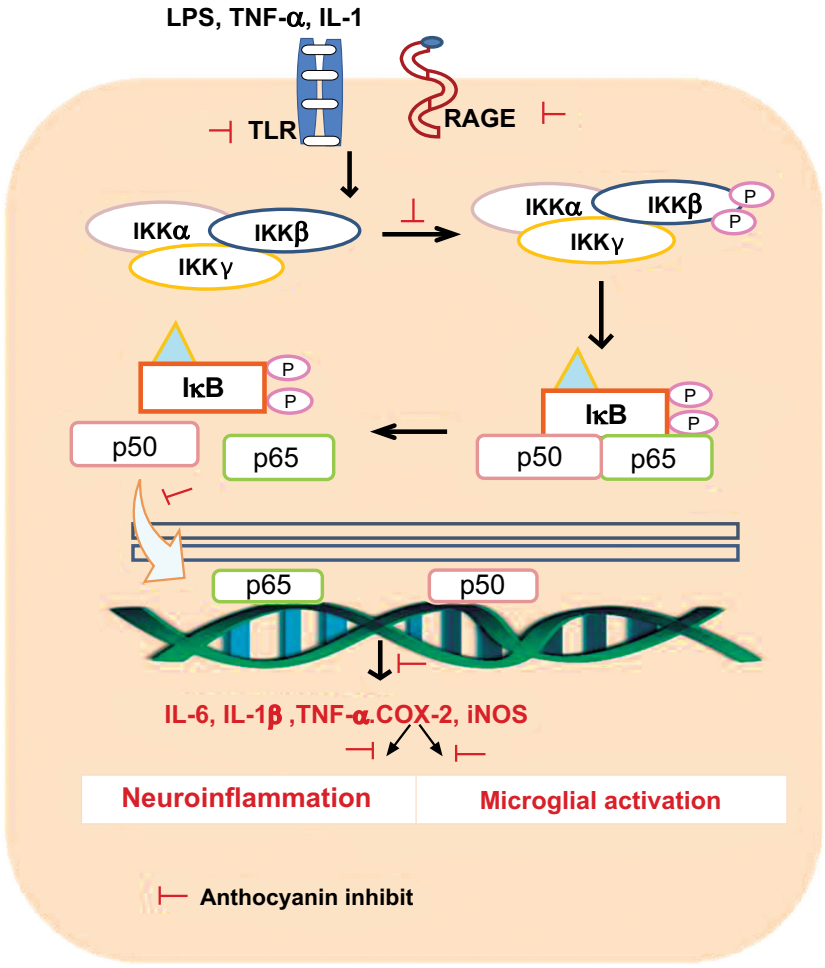

Fig. (3). Anthocyanins and their impact on NFkB signaling. Anthocyanins exert their action on various sites of the NFkB pathway. The activation of Toll-like receptors (TLR), and RAGE (Receptor for advanced glycation end products) is blocked. Also, anthocyanins suppress IKK kinase, prevent the activation of p65, interfere with the nuclear translocation of NF-κB and the expression of pro-inflammatory factors that are responsible for neuroinflammation. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

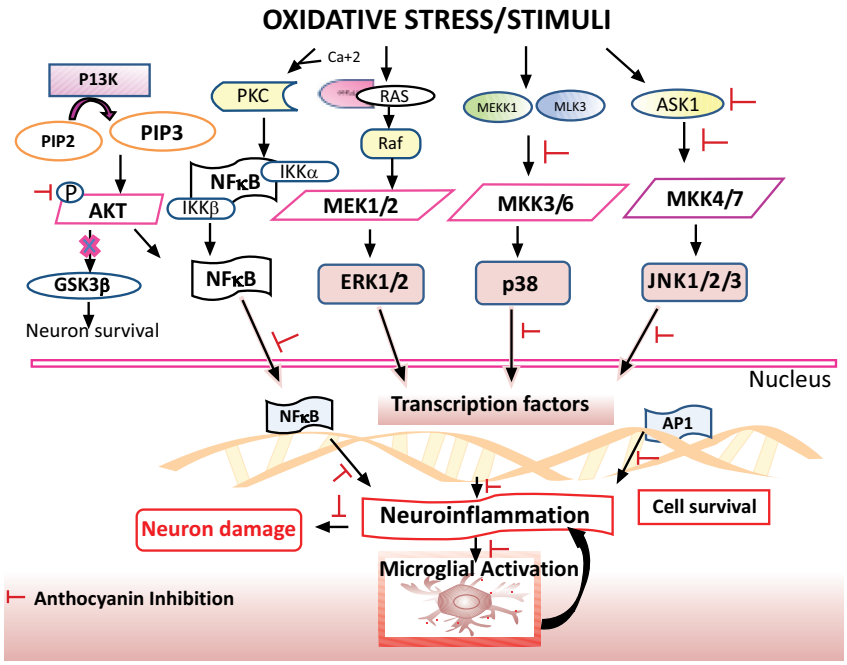

Fig. (4). Role of anthocyanins in alleviating oxidative stress-mediated neuroinflammation. Anthocyanins target ASK1 and prevent activation of the MAPK (Mitogen-activated protein kinases), JNK (c-Jun N-terminal kinases), and ERK (extracellular signal-regulated kinase) pathways. Activation of AP-1 and NFκB is attenuated. In addition, anthocyanins also affect the activation of PI3K/Akt pathway and prevent the activation of NFκB. **Abbreviations:** ASK1: Apoptosis signal regulating kinase 1; AP-1: Activator protein-1; Mitogen-activated protein kinases kinase (MEKK, MKK3, MKK4, MKK7; NFκB: Nuclear factor-kappa B; PIP2: phosphatidylinositol-4,5-bisphosphate; PIP3: phosphatidylinositol-3,4,5-bisphosphate PI3K: phosphatidylinositol 3-kinase; Akt: Protein kinase B; GSK2B: Glycogen synthase kinase 3 beta. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

Anthocyanins play a pivotal role in inhibiting IkB kinase (IKK), thereby impeding NF-κB translocation, a critical point in the inflammatory signal transduction process (Fig. **4**). The polyphenol-rich fraction of blueberry extract (PC18) prepared from the juice of wild blueberry (*Vaccinium angustifolium*) contains glycosylated anthocyanins such as malvidin, delphinidin, cyanidin, petunidin, and peonidin. Pretreatment of BV2 cells (mouse, C57BL/6, brain, microglial cells) with PC18 (in a concentration of 25-100 μg/ml) 16 h before LPS exposure produced significant benefit. PC18 suppressed nuclear translocation of NF-κB, the expression of both iNOS and COX-2 genes in BV2 cells (mouse, C57BL/6, brain, microglial cells). Luciferase reporter assays are used to study the activation or repression of a target gene; hence, gene expression of iNOS and COX-2 was analyzed using iNOS and COX-2 luciferase reporter assay. LPS exposure to transiently transfected BV2 cells resulted in a significant increase in iNOS and COX-2 promoter activity. PC18 dose-dependently (25-100 μg/ml) reduced iNOS and COX-2 promoter activity, ultimately decreasing the formation of COX-2 and iNOS proteins [71]. In a concentration of 100 μg/ml, the expression of COX-2 protein was reduced by 50 %, and iNOS protein expression declined by 20 %. PC18 interferes with the formation of these proteins but was incapable of interrupting the activity of preformed COX-2 and iNOS proteins. Thus, blueberry polyphenols attenuate the activation of pro-inflammatory genes and the expression of cytokines [71].

Seed coats of black and yellow soybeans are consumed as functional foods, but black soya beans (*Glycine max* (L.) Merr.) are used more extensively. Black soya beans are reported to have anti-inflammatory and anti-proliferative action. On extraction, the seed coats of black soya bean contained 72 % C3G, 20 % delphinidin-3-glucoside, and 6 % petunidin-3-glucoside. LPS-exposed BV2 cells exhibited a marked increase in nuclear NF-κB p65 levels. Pretreatment of BV2 cells an hour before LPS exposure with black soya bean anthocyanins (concentration of 0.5 μg/ml) decreased the levels of nuclear NF-κB p65 interference with nuclear translocation. Also, LPS mediated degradation of IκB-α, an inhibitor of NF-κB, was significantly averted with black soybean anthocyanins [72]. In addition, black soya bean seed coat extract attenuates TNF-α, IL-1β mRNA, and protein levels in BV2 microglial cells. Also, the expression of pro-inflammatory mediators like NO and PGE_2 was suppressed. Black soybean anthocyanins prevent nuclear translocation of NF-κB p65, phosphorylation of several signaling kinases such as c-Jun amino-terminal kinase (JNK), p38 MAPK, and Akt. By blocking Akt phosphorylation, black soybean anthocyanins prevented the activation of NF-κB.

An *in vivo* study on aged rats fed with a blueberry (~ 394 mg/day of lyophilized blueberries) supplemented diet for four months has shown benefit with attenuation in the expression of NF-κB in the cerebellum, hippocampus, frontal cortex, basal forebrain, and striatum [73].

American elderberry (*Sambucus nigra* subsp. *Canadensis*) is rich in secondary metabolites and exhibits many health benefits. American elderberry extract with a total monomeric anthocyanin content of 103.9 μg/mL (as cyanidin-3-glucoside) effectively resolved the inflammatory response

induced by LPS and IFNγ in immortalized mouse microglial cells (BV2 cells). Exposure of BV2 cells to elderberry extract (0 to 400 μg/mL) was given an hour before stimulation with LPS, and the formation of ROS declined with 400 μg/mL of extract. Specifically, American elderberry extract prevents microglia activation, and interferes with the expression of iNOS, pro-inflammatory cytokines, and chemokines. Cyanidin 3-O-glucoside at a concentration of 6.25 μM reduced IFNγ-mediated increase in the formation of ROS up to 80 %. Elderberry extract suppresses the activation of microglial nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) [74], thereby reducing the formation of superoxide anions and averting the oxidation of proteins, lipids, and DNA. NOX can catalyze ROS formation by facilitating the electron transfer from NADPH to molecular oxygen. NOX enzymes are responsible for host defense, cellular signaling, metabolism, stress response, transcription, and translational regulation [75]. Concurrent findings were also observed in another study wherein pretreatment of BV2 cells with elderberry extract (12.5–200 μg/ml) suppressed microglial activation [76].

Red-colored fruits and vegetables such as strawberries and pomegranates contain callistephin (3-O-glycoside of pelargonidin) and are reported to have profound anti-inflammatory, antioxidant, and neuroprotective action. C8-4B mouse microglial cells treated with callistephin (100 μM) for 24 h protected against LPS/IFN-γ induced damage. C8-4B mouse microglial cells challenged with LPS/IFN-γ express high levels of COX-2 and iNOS, which are reduced by callistephin alone. The immune challenge of C8-4B mouse microglial cells with LPS/IFN-γ upregulated phosphorylated p38 and inflammatory apoptotic death. Callistephin prevented the phosphorylation of p38, downregulated caspase-3/7, and minimized apoptotic neuron damage [77].

In another *in vivo* study, an improvement in the antioxidant reserve of nonprotein thiols occurred when blueberry, crowberry, and elderberry juice (1:1:1) were fed to mice for a period of 42 h and 3-4 weeks. Diet enriched with blueberry, crowberry, and elderberry activates the promoter region of the enzyme γ-glutamyl cysteine ligase, facilitating the biosynthesis of glutathione, a thiol-rich antioxidant [78].

Black rice rich in cyanidin-3-O-β-D-glycoside, and its metabolite, protocatechuic acid, inhibit COX-2, TNF-α, (IL) 1β, and IL-6 in LPS-induced RAW 264.7 cells. They also inhibit the iNOS gene expression. The phosphorylation of IκB-α was obstructed, affecting the translocation of NF-κB to the nucleus, and interfering with the activation of MAPK, thereby exerting an anti-inflammatory action [79]. Protocatechuic acid also prevents microglial activation by enhancing SIRT1 (Silent information regulator 1) signaling, as SIRT1 deacetylates a subunit of NF-κB, thus interrupting NF-κB signaling [80].

The effects of anthocyanins observed *in vitro* have been supported by *in vivo* studies. Black soybean anthocyanins administered to mice for 14 days (24 mg/kg/day) repressed LPS-induced oxidative damage, neuroinflammation, and neurodegeneration. There is a decrease in the expression of neuroinflammatory and apoptotic mediators such as IL-1β, TNF-α, NF-$_k$B, poly ADP ribose polymerase (PARP-1), apoptosis regulator Bax, cytosolic cytochrome C, and cleaved caspase-3 occurred [81]. Moreover, black soybean anthocyanins effectively reduced the expression of p-JNK, a stress kinase capable of actuating glial cells, promoting the release of inflammatory mediators and apoptotic markers.

7. IMPACT OF ANTHOCYANINS ON MITOGEN-ACTIVATED PROTEIN KINASE (MAPK) SIGNALING

Anthocyanins counter neuroinflammation by preventing the activation of intracellular Mitogen-Activated Protein Kinase (MAPK) and protein kinase (PKA) pathways (Fig. **4**). Anthocyanins protect MAPK, its components, including c-JNK, ERK1/2, and members of the NF-κB pathway, which are provoked due to neuron damage. The potent anti-inflammatory activity of anthocyanins is attributed to the presence of ortho-dihydroxyphenyl in their structure [60]. The activation of MAPK could be initiated by stimulating Toll-like receptors (TLRs), IL-1β, and TNFα. MAPKs convey these signals to the nucleus resulting in cell proliferation, differentiation, regulation of gene transcription, and transcription of inflammatory factors leading to cell death. Also, oxidative stress induces the phosphorylation of MAPKs, ERK, and JNK pathways. Hence, MAPKs activation promulgates the phosphorylation of several target proteins, protein kinases, adaptors, and transcriptional proteins localized in the cytosol and nucleus. In addition, NF-κB, signal transducer, and activator of transcription (STAT)-1/2/3, c-Jun, and CREB are activated in the process, contributing to the inflammatory response (Fig. **2**) [82]. MAP kinases enhance the formation of pro-inflammatory cytokines by working in consonance with IκB kinases (inhibitor of NF-κB protein). Also, the phosphorylation of MAPK induces AP-1, a transcription factor that binds to discrete promoter sequences, influencing the transcription of pro-inflammatory genes. Furthermore, MAPK induction mobilizes STAT-1, a downstream transcription factor of the extracellular signal-regulated kinase (ERK1/2) and p38 pathways (p38αβγδ), which is perceived to play an essential role in the pro-inflammatory response in neuronal cells. Furthermore, induction of MAPKs leads to the enhanced production of cytokines such as TNF-α (Fig. **3**). Also, phosphorylation of Src kinase, p38MAPK, JNK, and ERK1/2 kinases facilitates the expression of eNOS, elevating the expression of NO (Fig. **3**) [83]. On the other hand, iNOS inhibits cytochrome C oxidase (complex IV), resulting in the disruption of neuronal ATP synthesis and an increased generation of ROS [83-85].

Kim *et al.* have reported that black soybean anthocyanins counter the death of J77 (Mus musculus ascites reticulum cells) by preventing the phosphorylation and expression of apoptosis signal-regulating kinase (ASK1), JNK, and p38 pathways. The seed coat of black soybean (*G. max* L. Merr.) contains 68.3 % of Cy3G, 25.2 % of delphinidin-3-O-glucoside, and smaller amounts of petunidin-3-O-glucoside (6.5 %). In addition, ASK1 induces and activates other crucial members of MAPK, p38, and JNK pathways provoking cell death [86].

Blackberry extract ameliorated inflammation and damage caused by LPS [87]. Exposure of J774 cells to blackberry extract (11-90 μg/ml concentration) for 24 h curbed the

expression of iNOS. In addition, ERK-1/2-mediated breakdown of IκBα and the activation of ERK-1/2 were blocked. If ERKs are not activated, they will disable the phosphorylation of several regulatory proteins, reduce the expression of iNOS and eventually reduce the output of NO.

Blueberry extract rich in cyanidin-3-O-galactoside (Cy-3-Gal) also interrupted MAPK activation in LPS-exposed BV2 cells, particularly on ERK1/2 [86], preventing the phosphorylation of target proteins and the activation of transcription factors such as NF-κB, STAT-1/2/3, c-jun, and CREB.

Microglia express mixed-lineage kinases (MLKs), particularly MLK3a, belonging to the family of serine/threonine protein kinases that lie upstream to JNK and p38 MAPKs. *Lycium ruthenicum* Murr. (Black wolfberry) minimizes neuroinflammation and improves cardiovascular health. *Lycium ruthenicum* anthocyanins administered to male CD-1 mice in a dose of 50 & 100 mg/kg suppressed the activation of MLK3, consequently preventing the activation of p38 and JNK. Thus, *Lycium ruthenicum* Murr anthocyanins abrogate microglial activation and neuroinflammation [88].

8. ANTHOCYANINS AVERT INTERFERON-MEDIATED NEUROINFLAMMATION

Elderberries *(Sambucus nigra* subsp. *canadensis)* are richly endowed with anthocyanins such as cyanidin 3-sambubioside and C3G with intense free radical scavenging activity. *E*lderberry extract prevented interferon γ (IFNγ) mediated transcription of several factors of the inflammatory cascade. IFNγ stimulates the Janus-associated kinase/signal transducers and activators of transcription (JAK-STAT) pathway leading to the phosphorylation of STAT1 dimers and stimulation of interferon regulatory factor-1 (IRF1). The binding of IRF-1 and STAT1 dimer to the promoter region of the iNOS genes augments its expression. Moreover, IFNγ-activated JAK-STAT promotes NOX activity and can increase ROS production [89]. Also, IFNγ directly induces microglial iNOS resulting in the abundant release of NO. Pretreatment of BV2 cells with elderberry extract (400 μg/ml) for one h reversed the detrimental effects of IFNγ and LPS exposure. The extract prevented ERK1/2 phosphorylation, inhibited NOX activation, and preserved cell morphology. Thus, the unusual discharge of ROS, release of pro-inflammatory cytokines and chemokines were suppressed [74].

Elderberries grown in different regions and of varying genotypes produce substantially diverse anthocyanin content. Jiang *et al.* [76] have assessed the impact of elderberry juice of the Wyldewood genotype against IFNγ-mediated neuroinflammation in BV-2 cells. The cells were exposed to elderberry juice at a 12.5 μg/ml concentration to 100 μg/ml for one h, and then exposed to LPS and IFNγ. Elderberry juice prevented the activation of the p-ERK1/2 pathway and inhibited NOX activation, thereby suppressing ROS generation. Besides, the presence of other substances in the Wyldewood elderberry extract induced iNOS and NO formation plausibly mediated through several transcription factors [76].

9. AMYLOID BETA (AB) INDUCED NEURONAL DAMAGE

Amyloid β precursor protein (APP), a transmembrane protein expressed on neuronal tissues, undergoes cleavage to form beta-amyloid (Aβ) protein containing 40-42 amino acids. Shorter variants such as Aβ 25-35 are formed when proteases truncate Aβ42 (Aβ1-42). Generally, Aβ1-40 is abundantly produced while Aβ1-42 accounts for less than 10 %; however, in some forms of Alzheimer's disease, the formation of Aβ1-42 is enhanced. The neurotoxic monomeric form of Aβ25-35 has also been used in several studies [90]. The neurotoxicity of Aβ is manifested when it hyperactivates glycogen synthase kinase-3β (GSK-3β), consequently hyper-phosphorylating tau. As a consequence to this process, neurofibrillary tangles are formed, ultimately causing degeneration of neurons. As neuroinflammation contributes to the development of neurofibrillary tangles, suppression of neuroinflammation might benefit in intercepting neuron damage [91].

C3G administered orally in a dose of 10 mg/kg to rats for 30 days significantly reversed the toxicity of Aβ 1-42 peptide. Regression in the neuropathological symptoms was due to attenuation of GSK-3β hyperactivation and the hyperphosphorylation of tau [91, 92].

Colored rice (black, purple, and red) develops its hue due to anthocyanins. Purple rice (*Oryza sativa* L. indica) contains anthocyanins such as C3G and peonidin-3-glucoside. Their use protected SK-N-SH (Human Neuroblastoma cell line) cells against Aβ25-35 induced apoptosis via mitochondrial-dependent pathway [93]. Pre-treatment of SK-N-SH cells with purple rice bran extract or cyanidin for two hours, in a concentration of 0.001 mg/ml, 0.01 mg/ml, and 0.1 mg/ml averted the neurotoxic effects of Aβ25-35. Rice bran obtained by the milling of rice are a rich source of pelargonidin-3-glucoside, delphinidin-3-glucoside, peonidin-3-glucoside, malvidin-3-glucoside, and cyanidin-3-glucoside. In addition, exposure to Ab25-35 for variable periods decreased the expression of anti-apoptotic proteins such as Bcl-xL, cytochrome c, cleaved caspase-9, and caspase-3 protein. Reactive nitrogen species (RNS) and ROS accentuate the release of cytochrome c and initiate apoptosis by disrupting the mitochondrial membrane potential. Thus, purple rice bran extract or cyanidin prevented apoptotic cell death and exerted a cytoprotective response [93].

Gold nanoparticles are widely used as nanocarriers in medicine to deliver drug moieties to the target sites. Anthocyanin-loaded PEG-gold nanoparticles (AuNPs) have been formulated to enhance bioavailability and facilitate site-specific delivery. A study examined the effects of anthocyanin-loaded nanoparticles in reducing neuroinflammation and neurodegeneration induced by the injection of Aβ1-42 in BV2 microglial cells as well as in mice [94]. Overexpression of Receptor for Advanced Glycation End Products (RAGE) instigates NF-kB signaling. It sequentially prompts the activation of IL-1β, TNF-α, and COX-2, finally leading to the activation of microglia and promoting neuroinflammation. Anthocyanin-loaded PEG-AuNPs restrained the expression of inflammatory mediators such as RAGE, Aβ, and beta-site amyloid precursor protein cleaving enzyme-1(BACE-1) in the hippocampus of mice as well as in BV2 microglial cells [94]. RAGE expressed on neurons and macrophages functions as a receptor for ligands such as high-mobility group box-1 (HMGB1), advanced glycation end products (AGEs), S100/calgranulin, and Aβ peptide. Over-expression of RAGE is detrimental to neuronal survival, as it increases the expression of NF-κB, MAPKs,

Erk1/2, p38, and several pro-inflammatory cytokines such as IL-6 and TNF-α. Aβ1-42-mediated oxidative stress activates JNK favoring neuronal apoptosis. AuNPs intercepted neuronal apoptosis by reducing the levels of phospho-JNK, hindering the expression of Bax, caspases, and cytochrome C but enhancing the formation of Bcl2 proteins. Also, AuNPs increased the levels of phosphorylated GSK3β, reduced the levels of p-CDK5 and p-tau, thereby averting damage to the hippocampus and cortex [94].

Cyanidin-3-O-glucopyranoside, an anthocyanin present in brightly colored vegetables and fruits, was assessed for alleviating cognitive impairment through *in vitro* and *in vivo* models. Song *et al.* [95] have reported that cyanidin-3-O-glucopyranoside reversed the effects of $A\beta_{25–35}$ by preventing morphological changes in the cell membranes of SH-SY5Y cells, counteracting oxidative stress, and improving cell viability. Treatment of SH-SY5Y cells with cyanidin-3-O-glucopyranoside (25 μM) for 24 h up-regulated expression of PPARγ (Peroxisome proliferator-activated receptor-γ) protein. PPARγ, a nuclear receptor, regulates the expression of several genes involved in the metabolism of Aβ and modulates the inflammatory response. Cyanidin-3-O-glucopyranoside also reduces intracellular ROS formation in SH-SY5Y cells. Aβ25–35-induced injury of SH-SY5Y cells is characterized by the loss of membrane integrity and hypertrophy of the Golgi complex [95]. The hydroxyl groups of cyanidin-3-O-glucopyranoside form hydrogen bonds with the amino acid residues of Aβ 25–35, thereby alleviating its detrimental effects. It is also perceived that cyanidin-3-O-glucopyranoside exerts neuroprotection by linking with the polar heads present at the lipid–water interface of the cell membrane, thus preventing their interaction with Aβ 25–35. In the same study, treatment with cyanidin-3-O-glucopyranoside (5 mg/kg/day/oral) for eight weeks reversed the effects of Aβ 25–35 by improving glucose metabolism rates in the hippocampus and frontal lobe. As glucose is an important energy source for the brain, glucose metabolism can reflect neuron function and neuroinflammation.

Bilberry (*Vaccinium myrtillus* L.) anthocyanins significantly reduced neuroinflammation and improved memory in the APP/PSEN1 (presenilin 1) transgenic mouse model of Alzheimer's disease. Li *et al.* [96] suggested that consuming 20 mg/kg/day of bilberry anthocyanins (~ 120 mg/day for an adult weighing 60 kg) alleviated neuroinflammation. Bilberries are rich in cyanidin 3-O-galactoside, C3G, delphinidin 3-O-glucoside, delphinidin 3-O-galactoside, and smaller fractions of malvidin, peonidin, and petunidin. Bilberry anthocyanins exert a dual response by decreasing the expression of chemokine receptors such as CX3CR1 and inflammatory mediators such as TNF-α, IL-1β, NF-κB, COX-2, iNOS. Also, bilberry anthocyanins upregulate TLR2 mRNA and TLR4 mRNA expression. Enhanced TLR2 and TLR4 facilitate microglia's phagocytic activity, thereby reducing the accumulation of beta-amyloid peptides. Chemokine receptors such as CX3CR1(C-X3-C motif chemokine receptor 1) and TYROBP (tyro protein tyrosine kinase binding protein) are expressed in partially and completely activated microglia. Bilberry anthocyanins enhance TYROBP mRNA expression and curb CX3CR1mRNA expression. Activation of TYROBP increases their binding with TREM2 (triggering receptor expressed on myeloid cells), an immunoreceptor vital for clearing beta-amyloid plaques. Also, these anthocyanins turn off CD33, a switch on microglia, which subdues the phagocytic activity of microglia [96].

10. ANTHOCYANINS INHIBIT HYDROGEN PEROXIDE-INDUCED NEURONAL DAMAGE

Hydrogen peroxide (H_2O_2) activates ASK1–JNK/p38 pathways, leading to free radicals and apoptosis. Kim *et al.* [86] reported the impact of H_2O_2 on human neuroblastoma SK-N-SH cells and the protective role exerted by pretreatment with black soybean (*Glycine max* L.) cv. Cheongja anthocyanins (1, 2, 5, 10, and 25 μg/ml concentrations). Black soybean anthocyanins dose-dependently reduced ROS generation, regulated antioxidant homeostasis and thwarted apoptotic death of neurons by up-regulating the expression of heme oxygenase-1 (HO-1) mRNA, elevating HO-1 protein levels, inhibiting the activation of NF-κB, and averting the phosphorylation of MAPK kinase [86]. HO-1, an inducible enzyme of the heme oxygenase cascade, exerts a protective role by removing pro-oxidant heme, thereby reducing the availability of free iron, its utilization in the Fenton reaction, and the formation of hydroxyl free radicals. However, elevation in the levels of HO-1 has also been reported in traumatic brain injury, cerebral ischemia, Alzheimer's disease, Parkinson's disease, and multiple sclerosis [97], possibly as a defense against heme-induced neuron damage.

Pretreatment of SK-N-SH cells with black soybean extract (1-10 μM) for six h mitigated the effects of H_2O_2. Free sialic acid is liberated when Neu1 sialidase acts on sialoglycoprotein, combating oxidative stress. Black soybean anthocyanins in optimal concentration produced an increase in the expression of Neu1 mRNA, thereby increasing total sialidase activity [86].

11. ETHANOL-INDUCED NEUROTOXICITY: ROLE OF ANTHOCYANINS

Excessive exposure to ethanol induces the signaling of NF-κB and MAPK signaling. It also upregulates the expression of COX-2 and iNOS, leading to oxidative stress, activation of microglia, and neuroinflammation [98]. In addition, ethanol provokes neuronal apoptosis by activating GABAB1 receptors, interfering with GABA synaptic neurotransmission, activating p-CREB, a downstream signaling protein, increasing the release of cytochrome c caspase 9, and caspase 3 in the rat brain [98]. Furthermore, in prime areas such as the cortex and hippocampus, ethanol reduces the phosphorylation of CREB, a transcription factor essential for neuronal plasticity. Also, ethanol accentuates the phosphorylation of GSK3β at tyrosine 216, thereby enhancing its activity.

Korean black bean anthocyanins averted ethanol-induced changes in rat pups and mouse hippocampal cell lines (HT22). The expression of inflammatory markers such as p-NF-κB, p-JNK, and COX-2 was identified in the hippocampus of young rats. Black bean anthocyanins (100 mg/kg) administered as a single dose diminished the expression of these markers in the CA1, CA3, and dentate gyrus of the hippocampus. Also, these anthocyanins scaled down the apoptotic death of neurons by decreasing Akt dephosphorylation through the phosphatidylinositol-3-kinase (PI3K)-Akt pathway, as well as neuro-apoptosis mediated by GSK3β.

Exposure of HT22 cells to black bean anthocyanins (0.1 mg/ml) for 20 min effectively suppressed oxidative stress and apoptotic damage, thereby increasing the viability of HT22 cells [99].

The positive impact of black soybean anthocyanins has been demonstrated *in vivo* also. For example, black soybean anthocyanins (24 mg/kg) administered along with vitamin C (100 mg/kg) for four weeks reversed the effects of ethanol. In addition, they prevented neuron damage by amplifying the phosphorylation of CREB and PKA [100].

Ke *et al.* [55] have reported the protective effects of C3G (30 mg/kg) against ethanol-induced neuroinflammation and toxicity. Cyanidin-3-glucoside administered in two doses minimizes ethanol-induced microglial activation, prevents GSK3β activation, and impedes neuroapoptosis in the cerebral cortex. At 12 and 24 h post-administration, the extent of microglial activation was assessed in the sectioned cerebral cortex. The impact on GSK3β, lipid peroxidation, and p47phox (Neutrophil cytosol factor 1) levels was estimated eight h after treatment. Ethanol accentuated the phosphorylation of GSK3β at tyrosine 216, which was reversed with C3G. Besides, C3G increased phosphorylation at serine 9, thereby inactivating GSK3β. C3G also prevented the activation of NOX by blocking the up regulation of p47phox and reducing the formation of ROS, thus impeding neuronal apoptosis [55].

12. IMPACT OF ANTHOCYANINS ON KETAMINE-INDUCED MANIC EPISODES

Mania, a neuropsychiatric manifestation, is characterized by mood fluctuations and a substantial risk of suicide. Ketamine, an N-methyl-D aspartate (NMDA) receptor antagonist, is used experimentally to induce mania. Ketamine activates glutamatergic neurotransmission and substantially increases ROS formation in the striatum, cerebral cortex, and hippocampus. Generally, bipolar disorders require long-term treatment with mood stabilizers, but the treatment causes significant toxicity. Thus, the need for safe alternatives or adjunct therapies is rising. The therapeutic potential of blueberry extract (200 mg/kg) given alone and along with lithium has been explored in circumventing ketamine-induced manic symptoms. However, the concomitant use of blueberries with lithium did not yield significant benefit as against the therapies used alone, and a definite reason has not been elucidated. Interestingly, Spohr *et al.* have reported that blueberries might have similar molecular sites of action as lithium, contributing to their therapeutic effect. Also, blueberry extract can scavenge free radicals and reduce inflammation, thereby minimizing the symptoms of ketamine-induced mania [101].

13. ANTHOCYANINS AVERT HIGH-FAT DIET-INDUCED NEUROINFLAMMATION

High-Fat-Diet (HFD) consumption increases brain oxidative stress and impairs mitochondrial brain function. As mitochondria are the key producer of ROS, cellular oxidative damage can ensue due to mitochondrial dysfunction [102].

Recent studies demonstrated that consuming food containing anthocyanins is positively associated with a reduced risk of obesity and associated chronic diseases. Blackberry anthocyanins minimize dementia induced by a high-fat diet in rats [103]. The expression of inflammatory markers such as RAGE, chemo-attractants such as Cytokine-Induced Neutrophil Chemoattractant, Ciliary Neurotrophic Factor (CNTF), tissue inhibitor of metalloproteinase (TIMP-1), and IL-10 was elevated four-fold in the cortex of rats fed on a high-fat diet. Blackberry anthocyanins partially negated this effect, thereby suppressing neuroinflammation [103].

Feeding rats with a high-fat diet induces oxidative stress and causes variation in the levels of neurotransmitters. High fat diet dysregulates the levels of GABA in the frontal cortex and hippocampus. Strawberry extract (0.2%) in the UV-irradiated or non-irradiated form was added to a high-fat diet and administered for eight weeks. UV-irradiation of strawberries promotes the formation of anthocyanins and phenolic compounds. Fortified food effectively countered oxidative stress in the frontal cortex of rats by reducing the levels of lipid peroxides, and the non-irradiated form significantly curtailed the formation of protein carbonyls. Further, UV-irradiated strawberry fortified diet modulated the level of neurotransmitters [104].

14. ANTHOCYANINS AND 3-NITROPROPIONIC ACID (3-NP) INDUCED HUNTINGTON'S DISEASE (HD)

3-NP elevates oxidative markers and causes striatal microgliosis; hence, it is used in the experimental induction of HD. HD is a neurodegenerative disorder characterized by motor difficulties, poor cognition, and psychiatric disturbances. Eventually, neuronal loss in the striatum is evident. Neuroinflammation caused by morphologically transformed microglia facilitates neuronal death. Natural products with powerful antioxidant and anti-inflammatory activity, such as elderberries, are rich in anthocyanins and have been examined for their benefits in HD. For eight weeks, rats receiving a diet fortified with 2 % elderberries exhibited symptomatic improvement. Feeding rats with a fortified elderberry diet resulted in decreased expression of pro-inflammatory cytokines such as TNF-α. Moreover, microglia activation was inhibited, thereby preventing microgliosis in the striatum and improving the symptoms of HD [105].

15. IMPACT OF ANTHOCYANINS ON GLUTAMATE AND KAINIC ACID-INDUCED DAMAGE

Glutamate excitotoxicity stimulates calcium influx, neuroinflammation, and oxidative stress, leading to neurodegenerative disorders. Moreover, glutaminergic dysfunction is also implicated in the occurrence of psychiatric illnesses. Glutamate excitotoxicity escalates in the presence of inflammatory mediators and oxidative stress. Anthocyanins are envisaged to deter the effects of glutamate, indicating that they could plausibly be used in neurological and neuropsychiatric disorders. Black bean anthocyanins (100 mg/kg) averted neuroinflammation induced by glutamate in young rat pups four h after administration by significantly diminishing the expression of NF-κB and COX-2 proteins. Glutamate also lowers the expression of a transcription factor such as NRF2 (NF-E2-related factor 2), which regulates antioxidant encoded genes, particularly HO-1. Black bean anthocyanins were found to increase cellular defense by promoting

Nrf2/HO-1 signaling, as increased HO-1 can rescue neurons against inflammation [106].

Strawberry and blackberry-rich anthocyanin fractions contain callistephin (3-O-glucoside of pelargonidin; 91%) and kuromanin (cyanidin-3-O-glucoside; 87 %), respectively. Winter *et al.* [60] have assessed the effects of anthocyanin-rich fractions of strawberry (0.15%), anthocyanin-enriched blackberry extract (0.25%), pure callistephin (100 μM), and pure kuromanin (100 μM) against glutamate-induced toxicity in primary rat cerebellar granule neurons. Standardized strawberry and blackberry-rich anthocyanin exposure for 24 h improved neuron viability against excitotoxic glutamate. Although the two anthocyanins are structurally homologous, strawberry extract and blackberry anthocyanin fraction showed a differential response in scavenging RNS. Callistephin containing extract exerted a weaker response against nitrosative stress. Structurally, the presence or absence of the catechol moiety on the B ring of anthocyanins is responsible for this differential response. Also, pure kuromanin effectively averted nitrosative stress substantiating the effects of blackberry-rich kuromanin containing anthocyanin fraction. Hence, the propensity to circumvent oxidative stress progressively declines as the number of hydroxyl groups increases in anthocyanins [60]. Nevertheless, identifying and utilizing more lipophilic anthocyanins could benefit neurodegenerative disorders.

Kainic acid (KA), an analog of excitotoxic glutamate, produces abundant ROS that damage the hippocampal CA1 and CA3 areas. KA-mediated release of oxidative markers and enhanced phosphorylation of AMPK induce neuroinflammation and provoke neuroapoptosis [107]. A diet enriched with 2 % blueberry extract fed to KA-treated young Fischer-344 rats for eight weeks resulted in a decline in the levels of inflammatory markers such as MHC class II marker (OX-6), IL-1β, TNF-α, NF-κB and an elevation in the levels of neurotrophic factors such as insulin-like growth factor-1 [108]. Similarly, in another study, supplementing rats with a diet enriched with blueberry extract increased ERK activity and improved hippocampal neurogenesis [109]. Cyanidin-3-O-β-D-glucoside (kuromanin), an anthocyanin aglycon abated cerebral ischemia induced by ischemia-reperfusion injury. Kuromanin (10 mg/Kg, i.p.) was used an hour before cerebral ischemia or used during reperfusion. Kuromanin facilitates the expression of HO-1, which has a beneficial role during ischemia-reperfusion injury. C3G decreases the expression of neuronal iNOS and increases the expression of eNOS, thereby maintaining cerebral blood flow [110].

16. ANTHOCYANINS AGAINST ETHIDIUM BROMIDE INDUCED NEUROINFLAMMATION

Ethidium bromide (EBr), a frameshift mutagen, intercalates with nucleic acids, inhibits DNA polymerase, and induces extensive demyelination in the brain areas such as the striatum, hippocampus, spinal cord, and optic nerves. EBr activates microglia, amplifies the release of pro-inflammatory mediators, and reduces the level of IL-10, thus deranging neurotransmission. Grape skin contains glycosides of malvidin, delphinidin, peonidin, cyanidin, pelargonidin, and petunidin. Grape skin anthocyanins at a dose of 100 mg/kg effectively attenuated the infiltration of inflammatory cells, the release of inflammatory markers such as IL-1β, IL-6, IL-12, IL-18, TNF-α, and INF-γ, and the activation of microglia [111].

17. ANTHOCYANINS AGAINST ROTENONE-INDUCED NEUROINFLAMMATION

Rotenone, a herbicide, is used to experimentally induce Parkinsonism as it enhances oxidative stress and induces neuroinflammation in the nigrostriatal dopaminergic tract. Thus, rotenone subjugates dopaminergic cell survival by activating microglia and disrupting the activity of complex-1 of the respiratory chain in rat brain and *in vitro* in cell cultures [112]. The neuroprotective effects of anthocyanin-rich blueberry, blackcurrant, and purple basil extract against rotenone-induced toxicity were assessed in primary midbrain cultures. Exposure to blueberry extract anthocyanins in a concentration of 0.01 μg/mL for 72 h reduced rotenone-mediated dopaminergic neuron damage. In addition, incubation of primary midbrain cultures with malvidin-3-O-glucoside, cyanidin-3-O-sophoroside, and delphinidin-3-O-glucoside present in blackberry, black plums, and prunes improved the viability of dopaminergic cell cultures. The protective response is ascribed to the activation of pro-survival pathways and their ability to curb microglial activation; however, the extent of neuroprotection differed among anthocyanins [113].

The intra-striatal injection of 6-hydroxydopamine triggers oxidative stress and microglial activation damaging the dopaminergic neurons. 6-hydroxydopamine elevates the levels of pro-inflammatory cytokines, mainly in the microglia, causing neuroinflammation. The effects of fortifying the diet with blueberry and spirulina were assessed in 6-hydroxydopamine treated rats. Blueberry (2 %) or spirulina (0.1%) showed promising results by blunting the presence of OX-6- (MHC class I) positive microglia at one month in intrastriatal injured animals. However, microglial expression of OX-6 in the striatum and globus pallidus was transiently enhanced during early injury. Blueberry and spirulina diet activated microglia initially, aiding phagocytosis and regeneration of neurons. Also, *Spirulina platensis* contains c-phycocyanin, an inhibitor of COX-2, which assists in the restoration of tyrosine hydroxylase-positive nerve fibers [114].

18. WINGLESS-TYPE MMTV INTEGRATION SITE SIGNALING: A POSSIBLE SITE OF ACTION

Microglia and astrocytes serve as ligands for Wingless-type MMTV integration site (Wnt) and reciprocate to Wnt signals; hence, overactivation or suppression of the canonical and non-canonical Wnt pathways can be instrumental in damaging neurons. β-catenin, a crucial component of the canonical Wnt/β-catenin signaling pathway, has a defensive role [115, 116]. In an environment of oxidative stress, neuroinflammation, and neurodegeneration, up-regulated expression of GSK3β, a kinase propagating tau expression, results in the repression of β-catenin, along with the expression of Dickkopf-1, a negative modulator of the Wnt cascade. Anthocyanins have impacted Wnt signaling at peripheral sites, but their effects on the Wnt cascade in the CNS

have not been elucidated so far. This, however, could be an important molecular target for anthocyanins, which would need further elucidation to establish its link to GSK3β.

19. ANTHOCYANINS VERSUS NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Anthocyanins tend to act on any three crucial steps in the inflammatory cascade (Fig. **5**). They are, firstly, preventing signal transduction by attenuating the activation of TLR4, inhibiting the nuclear translocation of NF-κB, and inhibiting post-translational modification, particularly the phosphorylation of ASK1. The other events that occur could be a sequel to these crucial steps. Anthocyanins act on NF-κB signaling by interfering with IKK kinase phosphorylation, preventing activation of p65, and blocking the nuclear translocation of the NF-κB p65 subunit (Fig. **5**). Anthocyanins avoid the activation of ASK1, a member of the MAP3K family, thereby preventing the activation of downstream MAPKs. They also block JNK and p38 pathways; hence, we presume that the activation of MAPK4/7 and MAPK 3/6 is avoided, both directly and indirectly, through ASK1. When JNK and p38 are not activated, ROS formation and inflammatory signaling is not induced. Besides, the intense antioxidant action of anthocyanins might prevent the oxidation of the redox protein, thioredoxin, which binds to ASK1, thereby preventing its release and its post-translational modification. Thus, ASK1 and its post-translational change is an essential target for anthocyanins.

On the other hand, non-steroidal anti-inflammatory agents (NSAIA) have been proposed to exert a beneficial response in neurodegenerative disorders. Unlike anthocyanins, NSAIA acts mainly on the isoenzymes of COX and irreversibly inhibits them, reducing the formation of prostaglandins and minimizing oxidative stress [117]. Also, they exert their response by preventing the translocation of NF-κB and the activation of pro-inflammatory genes. In addition, anthocyanins and NSAIA prevent microglia activation [118]; however, anthocyanins exert their impact on several signaling pathways, exhibiting a versatile response, and are safer compared with AIA.

20. EXTRAPOLATION OF ANIMAL DOSE TO MAN

In human subjects, preclinical and *in vitro* studies form a basis for decision-making on doses. The direct translation of an animal dose to humans results in an unreasonable dose. Unfortunately, clinical studies have not clearly described the mode of deriving the human dose for anthocyanins. Moreover, even in advanced countries, the dietary reference intake has not been precisely clarified. However, in one study, the dose of blackcurrant extract in human subjects was chosen above the minimal effective dose or by using a quantity based on the dietary serving [119].

Allometric scaling is typically an approach to arrive at a dose that involves the dose-by-factor method and pharmacokinetics-guided dose. The safety of an extract is determined using the dose-by-factor method by establishing the no observed adverse effect levels (NOAEL). The body surface area (BSA) is considered while converting NOAEL to the human equivalent dose (HED). Therefore, establishing BSA-based HED is feasible and can be extrapolated between species. The body weight and the species-specific km factor are required for the BSA-related method [120].

On the other hand, the NOAEL and its area under the curve are ascertained in several species in the pharmacokinetically directed approach. The species with the lowest NOAEL is used for scaling. However, this approach is suitable only if the parent compound is active and must be modified if the assumptions are not met.

21. ANTHOCYANINS AND CLINICAL TRIALS

Anthocyanins can potentially counter neuroinflammation and neuron damage when examined on preclinical models in response to a wide range of external stimuli. However, translational studies are essential to discern their impact clinically.

Older adults with mild cognitive impairment exhibited reduced serum concentrations of TNF-α after consuming queen garnet plum anthocyanin juice for eight weeks [121]. However, this beneficial effect was observed only in subjects receiving a higher dose (201 mg/day) of anthocyanins. The decline in the levels of TNF-α can be of clinical significance as TNF-α is considered a trigger for several chronic diseases.

In a placebo-controlled, parallel-arm designed clinical trial, men and women aged 40 to 74 years were treated with Medox, a combination of purified anthocyanins isolated from blackcurrant (*Ribes nigrum*) and bilberry (*Vaccinium myrtillus*). Medox constitutes up to 40 % of 3-O-β-glucosides of cyanidin and delphinidin. Besides, 3-O-β-galactosides and 3-O-β-arabinosides of cyanidin, peonidin, delphinidin, petunidin and malvidin are present. Also, it contains 3-O-β-rutinosides of cyanidin and delphinidin. Subjects consumed 275-mg Medox capsules (n=59) for three weeks, two times/d (~100 g fresh bilberries correspond to 300 mg of anthocyanins), or placebo (n=59). Promising results were seen with the levels of IL-8, Regulated Upon Activation Normal T Cell Expressed and Secreted (RANTES), and IFNα as it reduced by 5, 15, and 40 %, respectively. Besides, NF-κB induction mediated by IL-4 and IL-13 was also suppressed [122].

In another randomized controlled trial, older patients (n=21) aged between 68 to 92 years were supplemented with freeze-dried blueberry fruit (*Vaccinium*) powder for 16 weeks. The anthocyanin content was 14.53 mg cyanidin 3-glucoside equivalents/g dry-weight powder, and subjects consumed one powder packet twice a day. An improvement in neural response was found when functional neuroimaging was performed during the working memory task in older patients [123].

Twenty-six subjects older than 65 years were supplemented once a day with blueberry extract (30 ml) for a period of 12-weeks. Approximately 30 ml of blueberry extract provides 387 mg anthocyanidins. Specifically, the extract contains cyanidin (108 mg), delphinidin (86 mg), peonidin (63 mg), petunidin (55 mg), pelargonidin (41 mg) and malvidin (34 mg). Cognitive tasks were tested, including memory, attention, language, verbal fluency, and visuospatial skills. The numerical Stroop test also evaluated cerebral perfusion, protein carbonylation, glutathione concentration,

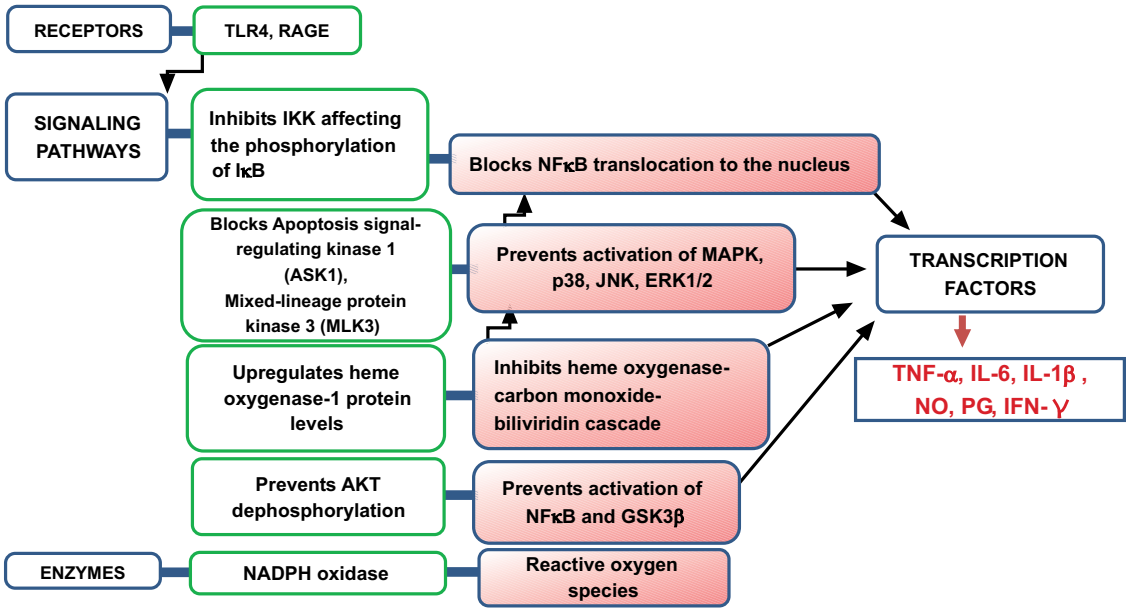

Fig. (5). Molecular sites of action of anthocyanins. Anthocyanins have a multifaceted role by exerting an action on receptors, signaling pathways and enzymes. The activation of transcription factors and the expression of pro-inflammatory cytokines is blocked. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

serum C-reactive protein (hsCRP), and brain-derived neurotrophic factor (BDNF). The thalamus, Brodmann areas, and anterior cingulate had enhanced brain activity along with increased perfusion of the parietal and occipital lobes. However, minor changes in C-reactive protein levels, BDNF protein, and oxidation product formation was seen. Bowtell *et al.* [124] assumed that the beneficial effects of the blueberry extract could be attributed to the increased nitric oxide availability. This potent vasodilator improved cerebrovascular function and working memory.

Older subjects diagnosed with mild to moderate dementia were administered 200 ml/day of cherry juice (n=24;138 mg anthocyanins/day), while the control group received apple juice (n=25). The anthocyanin content of cherry juice was determined analytically and contained 69 mg anthocyanins/100 g juice. A battery of seven cognitive tasks was performed at baseline, 6-weeks, and 12-weeks. Significant improvements in verbal memory and cognitive tasks were observed following 12-weeks of supplementation. It is perceived that cherry juice mediates its action through signaling cascades; however, the levels of IL-6 were not significantly altered [125].

A randomized trial deciphered the response of delphinol from maqui berry extract (*Aristotelia chilensis*) on oxidative stress markers. Overweight (body mass index, 25 or 30 kg/m^2) smokers (n=16) were treated for four weeks with anthocyanins, while 26 subjects received a placebo. The standardized maqui extract contains approximately 35% anthocyanins and 28% delphinidins. The subjects consumed three capsules containing 150 g of standardized maqui berry extract (each containing ~54 mg AN), accounting for 162 mg of anthocyanins/day. Primary and secondary outcomes were measured at baseline, at four weeks, and 40 days after treatment. After weeks of treatment, the delphinol-treated group suppressed the formation of Ox-LDL and 8-iso-PGF2a, a urinary biomarker that is critical for oxidative stress and inflammation [126].

A few clinical trials are initiated to ascertain the protective effects of anthocyanins. A randomized, parallel-group placebo-controlled phase 2 trial (N= 212 participants) has been registered. The phase 2 study will be conducted in three centers and the treatment duration will be 24 weeks involving patients at risk of dementia. Two capsules of Medox corresponding to 80 mg will be administered daily and compared with the placebo-treated group. Cognitive performance, levels of IL-1, IL-2, IL-6, TNF-α as markers for inflammation and antioxidant status will be evaluated, among other tests [127, 128].

A randomized, parallel-group, double-blind, placebo-controlled study enrolled young adults (N=66) afflicted with mild to moderate depression. The study aims to assess the impact of wild blueberry powder (22 g) in alleviating the symptoms of depression and anxiety. In addition, cognitive profile, inflammatory markers, and the metabolism of neurotransmitters will be assessed acutely and after eight weeks [129].

22. TOXICITIES WITH ANTHOCYANINS

In general, anthocyanin toxicities have not been reported. One study found anthocyanins safe at a dose of 20 and 25 mg/kg/day [130]. Countries like China have established the recommended dose of anthocyanins' intake; yet, the tolerable upper intake limit is not indicated [131].

A study estimated the acceptable daily intake of anthocyanins in humans to be 2.5 mg/kg body weight per day and is safe at this dose. The value was based on the no-observed effect level in rats estimated to be 225 mg/kg body weight. However, this is merely an estimated value and cannot be the actual margin of safety, as computation of the safe dose might be difficult with anthocyanin extracts [67]. Grape an-

thocyanins such as malvidin-3-O-β glucoside decreased the transcription of inflammatory genes but did not exert any toxicity in human peripheral blood mononuclear cells [132].

23. LIMITATIONS WITH THEIR USE

Several *in vitro*, *in vivo* animal models, and clinical studies have reported the benefits of anthocyanins. However, the exact dose of anthocyanins to be used, anthocyanin-drug interactions, their impact on metabolizing enzymes, and the effects on a larger patient population are limited. Hence, more studies would be needed to provide indisputable evidence about the benefits of anthocyanins.

CONCLUSION

Microglial activation augments the expression of several pro-inflammatory mediators, cytokines, and chemokines, eliciting an inflammatory immune response. Anthocyanins act on multiple molecular targets showing promising outcomes in animal and human studies. They prevent the activation of signaling cascades, suppress the release of pro-inflammatory cytokines, and reduce oxidative marker turnover, thereby preventing neuroinflammation, a critical contributor to neuron damage. Moreover, as most of these signaling pathways are redox-sensitive, they respond to anthocyanins with intense antioxidant action. However, more robust clinical studies on a wide array of anthocyanins can provide more substantial evidence to support the preclinical and invitro findings. Hence, anthocyanins could be harnessed as a stand-alone therapy or along with other treatments to provide a synergistic response.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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