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Aronia melanocarpa: A Review of Potential Antioxidants on Neuroprotection and Cognitive Performance

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ABSTRACT

For appropriate neural activity and protection against the detrimental effects of oxidative stress and inflammation, a balanced diet should provide needed nutrients, especially bioactive components. Berry fruits have been shown to help reduce age-related neurodegeneration and enhance motor and cognitive skills. The berry fruits can also affect inflammatory response, cell growth, neurogenesis, and plasticity via regulating signal transduction pathways. Phytochemical compounds such as anthocyanins, procyanidins, flavonoids, and phenolic acids are linked to the neuroprotective effects of berry fruits on neurological illnesses. The present review discussed the preventive properties of Aronia melanocarpa against a variety of neurological disorders.

Keywords: *Aronia melanocarpa*, anthocyanin, neuroprotection, depression, cognitive effect.

1. INTRODUCTION

For appropriate neural activity and protection against the detrimental effects of oxidative stress and inflammation, a balanced diet should provide needed nutrients, chiefly bioactive components. Berry fruits have been shown to help reduce age-related neurodegeneration and enhance motor and cognitive skills. The berry fruits can also affect inflammatory response, cell growth, neurogenesis, and plasticity via regulating signal transduction pathways. Phytochemical compounds such as anthocyanins, procyanidins, flavonoids, and phenolic acids are linked to the neuroprotective effects of berry fruits on neurological illnesses. The present review discussed the preventive properties of *Aronia melanocarpa* against a variety of neurological disorders.

Oxidative stress is thought to be harmful to brain health. The brain is prone to oxidative stress induced by free radicals or other reactive molecules disrupting cellular energy metabolism because it requires chemically varied reactive species for signal transmission.[2] Excess pro-oxidant pathways can cause lipids, proteins, nucleic acids, and other biomolecules to react, changing their structure and function. The membrane lipids in the brain have a high concentration of polyunsaturated fatty acids. In Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), cerebrovascular disorders, psychiatric disorders, and other neurodegenerative diseases, reactive oxygen species (ROS) increases susceptibility to neuronal damage and functional decline via brain oxidation. These diseases are the leading causes of clinical complications in developed countries and a financial burden on the health-care system.[3,4]

Antioxidant defense systems against ROS exist in abundance. Antioxidants help organisms repair

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damaged biomolecules by directly scavenging oxidizing radicals. Given that oxidative stress is one of the most major risk factors for the initiation, maintenance, and advancement of neurodegenerative illnesses, a healthy and balanced diet, together with the consumption of natural antioxidants that results, may play a critical role in their prevention.[5] The World Health Organization (WHO) recommended that people increase their physical activity, intake of fruits, vegetables, and fiber as a way to lower their risk of neurological illnesses. There is an appropriate product division that can contribute to health, among which the phenols are the key one, in addition to nutrients included in fresh fruits and green vegetables such as vital nutrients.[6]

Because the majority of the neurological load has few identified controllable hazards, new research is needed to develop effective prevention and treatment measures. The term "phenolics" refers to a diverse set of phytochemicals that all contain at least one phenyl and one hydroxyl group. Polyphenols in the diet have been shown to reduce oxidative stress and the risk of neurological disorders such as Alzheimer's disease, stroke, multiple sclerosis, Parkinson's disease, and Huntington's disease.[7,8] As a result of the prior research, polyphenol appears to have positive impacts on human brain activity. *Aronia melanocarpa*, a multiyear shrub native to North America but brought into the country only a few years ago, was chosen as one of the least studied plants in our country with a strong antioxidant impact.

Aronia melanocarpa (black chokeberry: *A. melanocarpa*), a Rosaceae family member, is a fruit rich in polyphenols such as anthocyanins (cyanidin glycosides), flavonoids (quercetin glycosides), flavanols, fibers, triterpenes, chlorogenic acids, and caffeic acid derivatives.[9] *A. melanocarpa* has anti-inflammatory, hepato-protective, and gastroprotective properties.[10] A key component in *A. melanocarpa*, cyanidin-3-O-galactoside, exhibits significant antioxidant action.[11] *A. melanocarpa* has recently gained in popularity due to its health benefits rather than its nutritional worth. It is commonly used to treat diabetes and atherosclerosis; however, its neuroprotective properties have yet to be discovered. This review discusses the most recent neurological studies to explain neurological implications.[12]

2. CHEMICAL COMPOSITION

A. melanocarpa vary in their content of carbohydrates, fats, organic acids, minerals, amino acids, vitamins, aroma compounds, and polyphenols, substances that have a beneficial effect on health, depending on factors such as cultivar, fertilization, maturation, or climate conditions, as well as the date of harvest.[13] Antioxidative, anti-inflammatory, hypotensive, antiviral, anticancer, antiplatelet, antidiabetic, and anti-atherosclerotic properties are all influenced by the total quantity of the most important components, polyphenolic compounds.

Polyphenolic substances, such as anthocyanins, procyanidins, flavonoids, and phenolic acids, are responsible for all of the above actions in various rates and amounts.[14,15] Different bio-transformative processes occur in the human body, enhancing their bioactivity both inside and outside cells. Aronia berries are low in calories but high in fibre, vitamin C, manganese, protein, and fat, so they're a nutritious powerhouse. Folate, iron, and vitamins A and E are also found in berries.[16]

More than 48 volatile chemicals have been found in *A. melanocarpa*, with amygdalin being the most abundant in terms of amount, followed by phenylacetaldehyde, hydrocyanic acid, benzaldehyde cyanohydrin, benzyl alcohol, benzaldehyde, 2-phenylathanol, and a number of others. Procyanidins, anthocyanidins, and phenolic acids are abundant in chokeberries, while flavonols are scarce. Polymeric procyanidins were discovered to be the most common type of polyphenolic component, accounting for 66% of the polyphenols in the fruit.

Chokeberries are one of the most abundant anthocyanin-rich plants. Anthocyanins account for

roughly 25% of total polyphenols in Aronia.[17] 3-O-glucoside, 3-O-galactoside, 3-O-xyloside and 3-O-arabinoside, are the four cyanidin glycosides that make up the majority of them. Chokeberry polyphenols include 7.5% phenolic acids, with chlorogenic acid being the most abundant compound in the fruit. Chokeberries contain only 1.3% of total polyphenols, according to many studies.[16-18]

3. NEUROLOGICAL ACTIVITIES

3.1 Aging

One of humanity's major issues is ageing and its repercussions. It is the leading cause of most neurodegenerative disorders, and it is linked to a decline in cognitive function and a reduction in life quality in the aged. Polyphenols, flavonoids, and anthocyanins are phytochemicals with significant geroprotective potential.[19]

Platonova et al., 2021 investigated the lifespan, locomotor activity, and stress tolerance of Drosophila melanogasters using ethanol Aronia fruits extract. The ethanol extract of chokeberry was discovered to enhance median life expectancy by 5% in both males and females, implying that intervention can be effective even in old age. Furthermore, locomotor activity was found to have no negative consequences on fly health. Stress tolerance to heat and oxidative stress was improved with Aronia extract, but the resilience of flies to hunger was not affected by the extract. Heat shock proteins (Hsp27, Hsp68, Hsp83), oxidative stress resistance genes (Keap1, NRF, Sod1), several circadian clock genes (Clk, per), and the longevity gene Sirt1 were all upregulated by Aronia extract intake.[20]

Chokeberry anthocyanins, according to Xu and his colleagues, may have anti-aging properties. They injected D-galactose into mice and gave them 15 or 30 mg/kg anthocyanins via gavage. Anthocyanins inhibited age-related cognitive loss and reaction capacity in senescence-accelerated mice, according to the research findings. In all age tests, mice exhibited superior redox system balance (SOD, GSH-PX, and MDA). The levels of inflammatory cytokines (COX2, TGFβ-1, and IL-1) transcription and DNA damage were considerably reduced in the brains of anthocyanin-treated mice as compared to aged models. Anthocyanins were also shown to control the DNA damage signaling system.[21]

3.2 Alzheimer's Disease

Protein misfolding disorders have an impact on many people's life. Because many diseases are now incurable, prevention is critical. Hyper-stimulation of microglia is one of the mechanisms thought to have a role in the progression of Alzheimer's disease (AD). Fruit, such as black chokeberries, provide potent fibril production inhibitors and should be consumed.[22]

Meng et al. (2018) studied the cytoprotective properties of anthocyanins in *A. melanocarpa* against apoptosis caused by $A\beta_{1-42}$, a critical mediator of Alzheimer's disease pathogenesis. Anthocyanin pretreatment was found to prevent apoptosis, reduce intracellular calcium and reactive oxygen species (ROS), and boost ATP and mitochondrial membrane potential. Anthocyanins protected SH-SY5Y cells from $A\beta_{1-42}$ induced apoptosis via regulating Ca^{2+} homeostasis and apoptosis-related genes and inhibiting mitochondrial dysfunction, according to RT-PCR and Western blotting studies.[23]

Because black chokeberry juice's total polyphenol content was substantially higher than that of most other fruits, Kotormán and Szarvas, 2020 discovered that it was particularly effective in preventing α-chymotrypsin amyloid-like fibril formation in aqueous ethanol in a concentration-dependent manner.[24]

3.3 Anti-Neuroinflammatory Effect

Ohgami et al., 2005, found that Aronia crude extract (ACE) with high polyphenol components had antioxidative effects *in vitro* and *in vivo*. To clarify the anti-inflammatory impact of ACE, the researchers looked at endotoxin-induced uveitis (EIU) in rats, as well as the proteins nitric oxide synthase (iNOS) and cyclooxygenase (COX2) in a mouse macrophage cell line (RAW 264.7) treated with Aronia extract *in vitro*. In the mice treated with Aronia extract, the number of inflammatory

cells, protein concentrations, and nitrogen oxide (NO), prostaglandin E2, and tumor necrosis factor-α (TNF-α) levels in the aqueous humor were all dramatically reduced in a dose-dependent manner. Furthermore, 100 mg of extract had the same anti-inflammatory impact as 10 mg of prednisolone. ACE had a higher anti-inflammatory effect than either quercetin or anthocyanin when given alone. ACE suppressed the synthesis of inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX2) proteins in RAW 264.7 cells in a dose-dependent manner.[25]

The neuroprotective effects of Aronia extract and quinic acid on amyloid β-induced cell death in rat hippocampus primary neurons were validated by Lee et al., 2018. The anti-inflammatory impact of the ethanolic extract of Aronia extract in BV2 cells was investigated, as well as its neuroprotective effect in the lipopolysaccharide (LPS) induced animal model of Alzheimer's disease. Following LPS stimulation of BV2 cells, exposure to Aronia extract lowered nitric oxide production as well as mRNA levels of inflammatory markers like iNOS, COX-2, IL-1β, and TNF-α and decreased tissue damage in the hippocampus, according to the findings. Using liquid chromatography-mass spectrometry (LCMS), the researchers determined the quinic acids in BCE to be responsible for the neuroprotective action.[26]

3.4 Anxiety and Depression

Nutraceuticals are becoming increasingly popular for treating mood and anxiety problems. *A. melanocarpa* berries and extracts have become well-known for having the highest *in vitro* antioxidant activity of any fruit.[27] Tomi et al., 2016 investigated the behavioral effects of a month-long unlimited consumption of Aronia berry juice and/or juice reconstruct without polyphenols in young male rats. Spectrophophotometric tests and HPLC-DAD were used to assess the amount of phenolic compounds in Aronia berry juice. *In vitro* tests revealed that the phenolic compounds of berry juice inhibit monoamine oxidase (MAO) A & B, which could be the *in vivo* mechanism for such behavioral effects. From the second or third week on, daily Aronia berry juice solution consumption increased dramatically, which was particularly noticeable in the treated animal group. In forced swimming tests, the Aronia berry juice treated rats showed less depression-like behavior. These data demonstrated that one month of unrestricted drinking of phenolic-rich Aronia berry juice in rats has stimulating, anxiolytic, and antidepressant-like effects.[28]

3.5 Anticholinesterase Effect

Gironés-Vilaplana et al., 2012 investigated the anticholinesterase effect of black chokeberry 5% w/v concentrate with lemon juice. The new blend's phytochemical content, antioxidant capacity, and inhibitory activity against cholinesterase were determined and compared to lemon juice and chokeberry in citric acid. Chokeberry concentrate, which is high in cyanidin-glycosides, quercetin derivatives, and 3-O-caffeoylquinic acid, and lemon juice, which is high in flavones, flavanones, quercetin derivatives, and hydroxycinnamic acids, were studied. For all of the studied methods, the novel drink outperformed the chokeberry or lemon controls, with the exception of hypochlorous acid, where lemon juice exhibited greater quantity. The novel combinations improved the inhibitory impact of the lemon juice and chokeberry controls on acetylcholinesterase and butyrylcholinesterase measured based on Ellman's method. According to the results of the several radical scavenging assays, the lemon-black chokeberry combo was more antioxidative than the individual controls. Furthermore, their cholinesterase inhibition is of interest in neurodegenerative diseases like Alzheimer's, Parkinson's, and senile dementia.[29]

3.6 Glutamate-Induced Oxidative Stress

High quantities of glutamate lead to the development of neurodegenerative disorders. *A. melanocarpa* berries are strong in antioxidants and include anthocyanins. Lee et al., 2017 investigated if the berries of *A. melanocarpa* might protect neuronal cells from glutamate-induced oxidative stress. MTT assay revealed that *A.*

melanocarpa berries protected HT22 mouse hippocampus cells from cytotoxicity. To elucidate the mechanism of its neuroprotective impact, researchers measured oxidative stress markers in HT22 cells, including ROS levels, intracellular Ca^{2+} levels, glutathione levels, and antioxidant enzyme activity. The berries of *A. melanocarpa* lowered ROS and intracellular Ca^{2+} levels and reduced mortality of HT22 cells. These findings revealed that *A. melanocarpa* berries provided antioxidant protection to HT22 cells.[30]

3.7 Cognitive, Mood, and Vascular Function

Overweight, high blood pressure, and a poor nutrient composition have all been linked to cognitive impairment. Dietary anthocyanins have been shown to improve cognition in both children and adults in research.

Ultrasonicated ethanolic extract of Aronia (UE) and ethanolic extract (EE) were assessed for cognitive performance by water maze and passive avoidance tests. In the water maze test, mice treated with EE and UE had escape latencies of 62.6s and 54.3s and in passive avoidance, they had retention times of 45.9s and 38.9s, respectively. In comparison to EE, UE decreased the expression of acetylcholinesterase genes by 1.46 times. In the hippocampus, however, there were no significant histological differences between the mice fed EE and those fed UE. Furthermore, the UE was found to have a higher antioxidant impact than the EE. The intermittent ultrasonication procedure may boost Aronia's cognitive functions by eluting higher levels of cyanidin-3-galactoside, as seen by a comparison of the extracts' high-performance liquid chromatography chromatograms. This was the first study to show that the crude extract from the intermittent ultrasonication process improved cognition more than a single major bioactive substance, C3G, possibly due to the synergistic effects of other anthocyanins in the extract, such as delphine galactoside, cyanidin arabinoside, and cyanidin glucoside.[31]

The impact of long-term treatment with Aronia extract (AME) on mental function, depression, and endothelial function in young, mid, overweight adults was researched by Ahles et al., 2020. 101 individuals ingested 90 mg AME, 150 mg AME, or placebo for 24 weeks in a randomized double-blind placebo-controlled parallel research. The grooved pegboard exam, number cross-out test, and Stroop test were used to measure psychomotor speed, attentiveness, and mental abilities. A visual analogue scale was used to assess mood, serum brain-derived neurotrophic factor (BDNF) was measured, and vascular function was tested using carotid ultrasounds and blood pressure readings. In comparison to placebo, AME enhanced psychomotor speed. Furthermore, when compared to 90 mg AME, but not to placebo, 150 mg AME reduced brachial diastolic blood pressure. BDNF, attention, and other vascular markers were not altered. The research finally improved the cognitive performance and blood pressure by AME supplementation in people at risk of cognitive deterioration.[32]

Using the Morris water maze and passive avoidance test, the researchers confirmed the effect of *A. melanocarp*a berries extract on scopolamine-induced memory impairment in mice. In addition, Lee et al., 2016 discovered that acetylcholinesterase (AChE) activity, BDNF, and phosphorylated cyclic-AMP responsive element binding protein (p-CREB) expression in the hippocampus of mice was involved in the cognitive-enhancing action. In the Morris water maze and passive avoidance tests, *A. melanocarpa* berries extract reduced the learning and memory impairment generated by scopolamine. In the hippocampus of scopolamine-injected mice, *A. melanocarpa* berries extract decreased AChE levels while increasing BDNF and p-CREB expression. Memory loss was likewise reversed by the main component, cyanidin-3-O-galactoside. By suppressing AChE and boosting BDNF and p-CREB expression, *A. melanocarpa* berries extract successfully alleviated memory impairment.[33]

In the year 2020, Wen and his colleagues used simulated moving bed (SMB) chromatography to isolate and purify *anthocyanins* from black

chokeberry, and to test the neuroprotective efficacy of SMB purified anthocyanin against amyloid β oligomer induced memory loss in rats. An intracerebral ventricle injection in the rat brain established the amyloid β induced animal model. The DPPH and ABTS free radical scavenging activities of SMB purified anthocyanins were higher than those of crude anthocyanin extract. In addition, rats given 50 mg/kg of SMB pure anthocyanins showed better spatial memory in a Morris water maze test, as well as protection of hippocampal cells from amyloid β toxicity. These findings suggested that anthocyanins from *A. melanocarpa* could be used to treat Alzheimer's disease as antioxidants and neuroprotectants.

A. melanocarpa cyanidin 3-O-galactoside (C3G) has been shown to improve cognitive function. Metformin is gaining popularity as a potential treatment for neurological illness. The neuroprotective and metabolic health-promoting benefits of both are, however, unknown. The senescence accelerated mouse prone 8 (SAMP8) was chosen by Wen et al., 2021 as a model of spontaneous learning and memory impairment. Behavioral and histological experiments, as well as metabolite analyses, were used to explore the synergistic neuroprotective impact of metformin and C3G in SAMP8 mice. The SAMP8 mice treated with metformin and C3G had better spatial learning and memory than the SAMP8 model group, according to the behavioral trials. The metformin and C3G mice had much more neurons than the SAMP8 mice, and the metformin and C3G mice had significantly less amyloid β aggregation in the brain, which was higher in SAMP8 mice. By modulating fatty acid production and breakdown, the metformin and C3G group demonstrated lower indole, methyl esters, and ketones in feces and urine, while increasing short-chain fatty acids and alcohols. The neuroprotective effects of metformin and cyanidin 3-O-galactoside coadministration in SAMP8 mice were verified in this study, which also revealed a favorable effect on delaying Alzheimer's disease progression.[35]

3.8 Glioblastoma Cell Line

Although malignant brain tumors are uncommon, they are among the most difficult malignancies to cure. Despite the availability of traditional multimodality procedures for their treatment, the prognosis for most individuals remained bleak due to the tumor cells' capacity to penetrate the normal brain. Novel treatment strategies, such as the utilization of micronutrients, are increasingly receiving more attention. Natural pigment-rich *Aronia melanocarpa* has been shown to have anticancer effects in a variety of malignancies.

Abdullah Thani et al. (2012) investigated the therapeutic potential of *A. melanocarpa* by assessing its capacity to trigger apoptosis in a glioblastoma cell line (U373). The Annexin-V assay was used to determine if the cells had been treated for 48 hours with chokeberry extract. By using quantitative real-time polymerase chain reaction (RT-PCR), the effects of mediators of invasion on gene profiles of metalloproteinases i.e., 8 MMPs (2, 9, 14, 15, 16, 17, 24, and 25) and 4 TIMPs (1, 2, 3 and 4) were investigated. Chokeberry extract along with curcumin had IC_{50} values of 15 and 200 µg/ml. Curcumin appeared to trigger apoptosis in this cell line, but chokeberry extract caused necrosis. Furthermore, MMP-2, -14, -16, and -17 gene expression was downregulated in both micronutrients, according to RT-PCR data. The findings showed that curcumin and chokeberry extract have anticancer properties via triggering apoptosis and preventing invasion by lowering MMP gene expression.[36]

4. FUTURE CONCERN

Data from the literature on *Aronia melanocarpa*'s putative neuroprotective properties must be thoroughly considered. Future research should look on the connection among active compounds' biological activity and their elemental composition. Furthermore, the bioactivity of plant active elements has primarily been demonstrated *in vitro* or in animal models, despite the fact that the bioactive characteristics of *Aronia melanocarpa* were yet to be examined in many neurological disorders. The molecular pathways

that have been identified in cells or animal models are mostly unknown. Clinical research of the effectiveness of plants and their active compounds should be paid greater emphasis in order to substantiate health claims.

5. CONCLUSION

Our findings suggested that anthocyanins could be used to improve cognitive and mental abilities possibly via controlling the redox system and lowering inflammation buildup, with DNA damage inhibition being the most essential role. Chokeberry's impacts on human health have not been studied in large-scale research. In addition, limited animal studies, have been conducted to investigate the effects of the berries and berry extract. Chokeberry supplements are not yet recommended for any health issue due to a lack of scientific evidence. There is a need to investigate the mechanisms of action of black chokeberry on humans in the future. Furthermore, the widespread demand of chokeberry is expected to grow in the future, expanding its treatment option for neurological disorders.

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