Current Alzheimer's management with berries fruits therapy.

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Abstract

Nature has lots of flora-bearing fruits, vegetables with human beings. Berries contain a powerful source of natural antioxidants. Berries plays an essential role in prevention and therapy of various neurodegenerative diseases, like Alzheimer's disease (AD), Parkinson's disease and other neuronal dysfunctions as they are a diverse source of a large variety of nutritive, non-nutritive and bioactive compounds. Polyphenolic antioxidants present in different varieties of berries present in phyto-compounds which are present in nature may be used as a cure to delay neuro-degeneration, improvement of memory and cognitive function of frontal lobes. Berries such as Strawberry, Blueberry, Blackberry etc., have also confirmed neuroprotective effect against the AD. The molecular mechanism behind this therapeutic effect is the association of discrete signalling pathways by the work of phytonutrients which results in protein folding and neuro-inflammation. In Alzheimer's, the neuroprotective properties of the diversely occurring bioactive components of the berries have been used and tabulated in this review.

Keywords: Alzheimer's disease, Antioxidant, Neurodegeneration, Wnt signalling, Flavonoids

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Introduction

Increased adequate amount consumption of fruits and vegetables is recommended in dietary guidelines worldwide and intake of fruits like berries are rich in vital nutrients and phyto-nutraceuticals can prevent various diseases and disorders and more Neurodegenerative disorders. Fruits and vegetables may have noticeable long-term physiological effects due to their metabolic bioactivity and also enhance remarkable effect in the laboratory and epidemiological studies have been associated with a variety of nutrient and non-nutrient constituents, being many of them characterized by their antioxidant properties [1-5]. Compounds like ascorbic acid, tocopherols, β-carotene and phenolic compounds, flavonoids have high antioxidant capacity and promising potential against current therapeutic neuroproteins [6]. The colorful berries fruits such as blackberry (*Rubus species*), black raspberry (*Rubus occidentalis*), blueberry (*Vaccinium corymbosum*), cranberry (*Vaccinium macrocarpon*), red raspberry (*Rubus idaeus*), and strawberry (*Fragaria ananassa*) are remarkably good source countered to therapeutic neuro targets of neurological disorders. Researchers analyzed berry fruits extracts for most common abnormalities and obtained significant results and have suggested that consumption of colored fruits and vegetables are associated with reduced risk of human breast cancer [7,8], human melanoma cancer [9,10], human ovarian cancer, and also help in the prevention of Alzheimer's disease [11-13]. The majority of the compounds examined to date with a direct relevance to the AD are primarily from plants, from animal, marine and microbial sources. The review focuses on the berries compounds that might underlie the purported beneficial improvements in memory and cognition, neurovascular function, and in neuro-protection.

Occurrence and Season

Berries are used worldwide since ancient times and still popular in Europe and North America today. The industries dealing with berry varies from country to country because of different cultivation and growth condition. Some berries such as raspberries and strawberries have been bred for hundreds of years and are distinct from their wild counterparts, while other berries, such as lingonberries and cloudberries, grow almost exclusively in the wild. Besides of their different growing season, they also differ in temperature and time duration. For example, many soft fruit berries require a period of temperatures between 0°C and 10°C for breaking dormancy. Generally, strawberries require 200-300 hours, blueberries 650-850 hours, blackberries 700 hours, raspberries 800-1700 hours, currants and gooseberries 800-1500 hours, and cranberries 2000 hours [14]. Moreover, temperature regimes also severely affect growth and productivity of berries. The tolerable temperatures range from -29°C to -31°C, depending on variety [14].

Major Classes of Berries

The word "berry" meets the true botanical nomenclature as a fruit. For example Wild rose, Grapes, Elderberry, Currant, Barberry, Rosehips, Gooseberry etc. are true berry. "Stone fruits" is a drupe berry fruit with a fleshy fruit having a small stone. Acai, Hackberry, Sugarberry, Persimmon, Barbados cherry, Acerola, Indian plum, West Indian cherry, Goji berries do not meet the botanical classification but come under the category of berries. The botanical classification is not met by a few Epignyous types. Lingonberry, Cranberry, Bearberry, Crowberry, Blueberry, Bilberry, Juniper berries, Cowberry, Foxberry, Mountain cranberry, Red chokeberry, Black chokeberry, Purple chokeberry, etc. are the example of epignyous fruits. Rasberry, Strawberry, Blackberry, Dewberry, Salmonberry, Bayberry, Boysenberry, Mulberry, Cloudberry, Chehalm Berry, Loganberry, Thimbleberry, Wineberry, Youngberry, Juneberries etc contain multiple fruit seeds which are present in compound fruits.

Classification of berries found in nature is of two types mildy poisonous (causing gastric upset) and extremely poisonous (dangerous). Example-Holly berries, Yew berries, Rivet berries, Pokeberry, Daphne berries, Elderberry, Baneberry, *Actea pachypoda*, Jerusalem cherry, Green nightshade, Red nightshade, etc.

Besides being delicious in nature, berries contain an excessive amount of various nutrients, minerals vitamins, and other bioactive compound [15]. This review will be an effort to explore the medicinal property of different berries in neurodegenerative diseases mainly Alzheimer's disease.

Blackcurrant

Blackcurrant is a strong candidate fruit to provide neuro-protection in the AD where anthocyanin, a major group of polyphenols account for about 80% of the total amount of quantified compounds and have been shown to inhibit the formation and extension of Aβ fibrils and to destabilize the preformed Aβ fibrils *in vitro* [16,17]. Flavonoids by blackcurrant inhibit formation of induced β-Amyloid (Aβ). investigated the effects of anthocyanin-rich blackcurrant extracts on neuro-protection and amyloid precursor protein (APP) expression in human SH-SY5Y neuroblastoma cells overexpressing APP751 isoform under AD-related stress conditions [17,18]. Moreover, the cells also experienced significantly reduced ROS production. Promising antioxidant activity is shown by blackcurrant extracts rich in anthocyanin which is beneficial as depicted in the observations made.

Blackberry

Anticancer, antibacterial/antiviral, antiseptic, antioxidative, anti-hyperglycemic are some of the biological properties shown by Blackberry fruits [19,20]. They are also rich sources of antioxidants, polyphenols maganese, folate, fibers, cyaniding-3-0 glucoside, vitamin C, salicylate and high tannin possessing compounds. Boosting blood circulation reducing pains, preventing anti-aging, reducing blood cholesterol levels are some more functions [21,22].

Attainable neuroprotective effects like reducing intracellular ROS levels, modulating gluthathione levels and inhibition of the caspases occurance during treatments is displayed by Wild blackberries, bringalies and vagabundus that are collected from Braganca that lies in Northeast of Portugal [23]. These effects protected neuronal cells against oxidative injury, one of the most important features of neurodegeneration. *In vitro* studies have also reported that blackberries have potent anti-inflammatory and antiproliferative properties [24,25]. In addition, the antioxidants present in these fruits improved behavioural performance in motor neuron tests in aged rats. Demonstration of the measurers of spatial working memory and learning is due to the balance and fine motor coordination in the cognitive test that also showed improvement in the Moris water maze [26].

Blueberry

Flavonoids, notably Anthocyanin, caffeic acid, flavanols, and hydroxycinnamates are a rich source for Bluberries [27-31]. A recent study has demonstrated that blueberry supplementation can alleviate age-related behavioural deficits and high-fat diet-related behavioural declines, besides helping in prevention and inhibition of oxidative stress, inflammation, kidney injury, as well as improving vascular health [32-35].

A preclinical study has demonstrated that blueberry supplementation enhances motor and memory performance in aged animals [36,37]. Changes that occur in brain-derived neurotrophic factor-mediated protein synthesis, such as Arc/Arg3.1, are directly related to blueberry consumption. Inhibition of CREB/brain-derived neurotrophic factor pathway effectively blocks the changes in spatial memory in the blueberry-supplemented animals [38].

Anthocyanin distribution in the hippocampus might be related to increase neuronal signaling in this region [39]. A study involving psychopharmacological screening to evaluate potential effects of a lyophilized extract of different cultivars from *Vaccinium ashei*, Reade (Ericaceae) berries, which are commonly known as rabbiteye blueberries and are shown to have memory-enhancing, anxiolytic and locomotion increasing properties in mice, as well as the protective effects against free radical-induced DNA damage in the brain Barros et al. (2006) [40]. These results are reliable with the hypothesis that flavonoids (including Anthocyanin) can show beneficial effects on cell signaling and decrease oxidative damage. These results also suggest that flavonoids might directly act on cognitive function, which may help prevent age-related and pathological degenerative processes in the brain.

Strawberry

Strawberry tree (*Arbutus unedo*) is a shrub, belonging to Ericaceae family and prevalent in most of Europe. The polyphenols such as Anthocyanin, gallic acid, tannins, vitamin C, vitamin E, and carotenoids makes it an important part of the normal diet. Oxidative stress due to Ab protein is one of the major reasons for the pathogenesis of AD [41]. The anti-oxidative effect of strawberry has been evaluated using PC12 cells. Pre-treatment with strawberry extract showed improved cell viability in H2O2 induced neurotoxicity induced PC12 cells which may be due to the presence of Ellagitannins [42-44]. Notably, the strawberry extract has proven its potential to attenuate undesirable behavioural changes caused by 56Fe irradiation.

Grape Seed

Grape seed extract (GSE) is abundant in phenolic antioxidants and proanthocyanidins. The accumulation of Ab is the major causative factor for the pathogenesis of AD [45]. Several studies have shown that the polyphenol-enriched grape seed extract can reduce amyloid beta accumulation and protect against neurotoxicity and oxidative stress *in vitro* [46]. Another important causative factor of the AD is inflammation by microglia activation that was significantly reduced by 70% due to the polyphenol content in the GSE diet [47,48]. Resveratrol (trans-3, 40, 5-trihydroxystilbene) is the non-flavonoid polyphenol abundant in grapes and red wine and has the potential to reduce accumulation of amyloid protein in cell culture by enhancing proteolytic cleavage [49]. The mechanism behind the neuroprotective effects of resveratrol is due to its allosteric activity on the sirtuin proteins.

Alzheimer's disease associated with berries fruits

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder in the world, exerting an escalating socioeconomic burden on modern society [50,51]. Most often, the AD is diagnosed in people over 65 years of age [52], who develop a progressive pattern of cognitive and functional impairments [53,54] that gradually increase as the disease advances. Memory impairment, in particular, the loss of the ability to form and retain new episodic memories, is a hallmark of the early AD and may help in differentiating AD from common age-related cognitive decline. This impairment is often attributed to synaptic dysfunction and neuronal loss in the perforant path connecting the medial temporal lobe, entorhinal cortex, and hippocampus [50,55]. Accordingly, cognitive changes in AD start with specific difficulties in the encoding and storage of new information, also indicative of a deficiency in semantic memory [56-58] and executive function impairment [59]. The etiology of the AD is not well understood, except in 1 to 5% of cases in which genetic differences can be identified [60]. It is increasingly recognized that AD is a proteinopathy characterized by specific neuropathological markers: amyloid deposits, tau-laden tangles and the loss of neurons and synapses in the cerebral cortex and subcortical regions, associated with gross atrophy of the affected regions [61-68]. The accumulation of amyloid beta (Aβ) fragments is thought to be due to the uncontrolled cleavage and defective clearance of amyloid precursor protein [62]. Current treatments only partly alleviate symptoms but cannot stop or reverse the progression of the disease. Due to their favorable safety profile and availability, dietary approaches, in particular using polyphenol-enriched diets [69-71], are drawing attention as tools to prevent AD development [72-77]. The use of cheap and widely available compounds, like polyphenols, a nutraceutical or pharmaceutical tools in brain disorders such as AD may provide new strategies for the prevention or delay of cognitive decline.

Types of Alzheimer 's Disease

A minority (less than 1%) of those affected with the AD is dominant familial forms [78], caused by mutations in one of three genes and having an early age of onset before 65 years [78,79]. The more common sporadic version has no commonly acknowledged causes and the risks pertaining to the disease are not well understood.

Genetic differences of less than 1% cases have been identified and the major cause of Alzheimer's is still unknown. Many things have been attributed to trigger the AD, but as with many complex diseases, it may require a certain threshold to be surpassed before actual disease manifestation occurs. Multiple factors including genetic, environmental, dietary, or a combination of these could determine disease initiation, as well as disease progression.

The root cause of the disease can be explained by various competing hypotheses that exist:

- Amyloid hypothesis
- Cholinergic hypothesis
- Tau hypothesis
- GSK3β hypothesis
- Other hypothesis

Amyloid Hypothesis

People suffering from Down syndrome having entire gene copy in their chromosome have the universal chance of getting AD by the age of 40 [80-82] as the gene being located on chromosome 21 for amyloid precursor protein. The extracellular amyloid beta (AB) deposits are the root cause of this disease [83,84] as postulated in 1991.

Cholinergic Hypothesis

The oldest, on which most currently available drug therapies are based, is the cholinergic hypothesis [85]. According to this hypothesis, Alzheimer's disease is caused by reduced synthesis of the neurotransmitter acetylcholine that is accountable for the transmittance of a neuronal message from one neuron to another that are associated by synapses [86,87].

Tau hypothesis

Cell death and malfunctioning of biochemical communication of neurons result as abnormalities occurring in the tau protein, initiating the disease cascade [82]. The pairing which occurs between hyper-phosphorylated tau with other threads of tau results in collapsing the neuron's transport system due to the emmitment of cytoskeleton from the disintegration of microtubules [88-91].

GSK3β Hypothesis

Aβ peptides and hyperphosphorylated tau play a considerable role in the pathogenesis of Alzheimer's disease. According to this hypothesis, Neurofibrillary tangles and Aβ sensible plaques are produced by two different mechanisms causing Alzheimer's disease. A key enzyme GSK3β regulates cellular metabolism along with including phosphorylation of tau protein [92]. Wnt signaling leads to the inactivation of GSK3β. usually, GSK3β has been found in a hyperactive state that is accountable for hyperphosphorylation of TAU [93]. But in several cases GSK3β also regulates the metabolism of amyloid precursor beta protein, and assist in amyloidogenic cleavage leads to overproduction 12 of Aβ, condensed neurogenesis and increased apoptosis [94]. Activation of GSK3β leads to neuronal changes and loss of neuronal cells that are observed in the AD. But the inhibition of GSK3β activity protects in opposition to neuronal degeneration and death induced by Aβ and Tau hyperphosphorylation [95].

Berries derived phyto-nutraceuticals with special relevance to Alzheimer's disease

Berries contain abundant vitamins such as A, C, E, and B complex, also considered as antioxidants that help to boost the immune system, reduce inflammation, and help to fight the effects of oxidative stress leading to chronic diseases such as heart disease, diabetes, and certain cancers. Berries contain ascorbic acid, a water-soluble compound that performs numerous functions in living systems among all the berry fruit species reported [96].

The components present in berries are reported to protect against damage induced by ROS, known to be implicated in the development of neurological conditions such as Alzheimer's disease. The increased production of reactive oxygen species (ROS) is one of the major cause in the development of neurodegenerative diseases [97,98] crucial role, Because of low activity of antioxidant defense systems, the brain is susceptible to oxidative stress more than other organs [99,100]. Moreover, many neurotransmitters are autoxidized to generate ROS [101]. The neuroprotective effects [102] and chelation of metal ions is performed by the polyphenols which have the ability to cross the blood brain barrier and to directly mimic high concentration of ROS and nitrogen species. A special ability to activate key oxidant enzymes in the brain and scavage activity, resisting the oxidative stress (viscous cycle) and tissue damage was shown by a large number of Polyphenolic compounds [101,103]. A number of berries show beneficial effects and act as a promising agent of neuro-protection in this article.

More than one hydroxyl group along with a large heterogeneous group of chemical components containing few aromatic rings in a conjugated aromatic construct being present in the Phenolic Compounds. Phenolic compounds occur in free and conjugated forms with sugars, acids, and other biomolecules as water-soluble (phenolic acids, flavonoids, and quinones) or water-insoluble compounds (condensed tannins). They possess the ability to donate an electron or a hydrogen atom to a free radical and convert it into an inoffensive molecule. Consequently, phenolics have significant *in vitro* and *in vivo* antioxidant activities [104]. That Furthermore, phenolic compounds include flavonoids, such as Anthocyanin (i.e., cyanidin glucosides and pelargonidin glucosides), flavonols (quercetin, kaempferol, myricetin), flavanols (catechins and epicatechin) and phenolic acids (hydroxybenzoic acids and hydroxycinnamic acids) and hydrolyzable tannins, such as ellagitannins, act as important BAC.

Flavonoids (FL) represent the most diverse group of phenolics, with two aromatic (A and B), rings associated via C-C bonds by a 3 C oxygenated heterocycle. On the basis of the oxidation state of the central ring, FLs are further divided into Anthocyanin, flavonols, flavanols, flavones, flavanones, and isoflavonoids. Berries are particularly rich in Anthocyanin, which are responsible for their typically vibrant colours [105]. Anthocyanin are colored pigments that act as powerful antioxidants; they are especially abundant in berries with red, blue, or purple pigments.

Tannins are classified into hydrolyzable and condensed (or nonhydrolyzable) forms. Hydrolysable tannins are multiple esters of gallic or ellagic acid with glucose and products of their oxidative reactions and are known as galloyl tannins and ellagitannins, respectively [106,107] and are found in strawberry, raspberry, and blackberry but are less common in other berry fruits[108,109]. Together with Anthocyanin, ellagitannins are the major antioxidant phytochemicals in raspberries [110].

Stilbenes are another subgroup of phenolic compounds with a particular carbon skeleton, viz. C6-C2-C6 [111]. Resveratrol is the best-known stilbene. Small quantities of resveratrol, pterostilbene, and piceatannol have been found in blueberry, bilberry, cranberry, and strawberry [112-115].

Conclusion

Berries have been implicated in health benefits relevant to a number of disease conditions. Much of the evidence has focused on the polyphenol components but other components (such as carotenoids, fibers, and terpenes) may also have roles to play. A number of natural antioxidant and anti-inflammatory compounds are found in plant food matrix.

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