

## Research Article

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# Berry fruits advances in understanding the pathogenetic mechanisms of neurodevelopmental disorders and neurodegenerative diseases

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### Abstract

A berry is a little, pulpy fruit that is frequently edible. Berries often lack a stone or pit, are juicy, spherical, vibrantly colored, sweet, sour, or tart, and may contain a large number of pip or seed. Strawberries, Bill berries, Mulberries, blueberries, blackberries, red berries, and blackcurrants berries etc. Berries are a common ingredient in cakes, pies, jams, and preserves around the world. Some berries are significant commercially. The berry business and varieties of cultivated or wild berries vary from nation to nation. Berry fruits help prevent age-related neurodegenerative diseases (NDD) and enhance motor and cognitive abilities, according to recent clinical studies. The berry fruits can also alter signaling pathways that are important in neurotransmission, cell survival, inflammation, and neuroplasticity. Phytochemicals like caffeic acid, anthocyanin, quercetin, catechin, kaempferol, and tannin are linked to the neuroprotective agents of fruits berry Strawberries, Bill berries, Mulberries, blueberries, blackberries, red berries, and blackcurrants berries on neurodegenerative diseases Alzheimer disease, Parkinson disease (PD), Hungtiton disease (HD), ischemic diseases. According to scientists, berries fruits are one of the best sources of vitamins, minerals, and disease-fighting nutrients and can help lower the risk of many age-related Neurodegenerative diseases in the society. We attempted to concisely highlight the positive effects of several berries advances in understanding the Pathogenetic mechanisms of neurodevelopmental disorders and neurodegenerative diseases.

**Keywords:** Alzheimer's disease; Berry fruits; Ischemic diseases; Nerve regeneration; Neurodegenerative disease; Neuroprotection; Neural regeneration

## Introduction

Numerous epidemiological studies have revealed a link between frequent consumption of flavonoid-rich fruits and delayed onset Alzheimer's, Parkinson's, ischemic diseases, and ageing effects [1–5]. As of their, antioxidative, antiproliferative, anti-inflammatory and antiviral properties, data from in vitro and animal studies recommend that among the sources of antioxidants, phyto-chemicals in fruits and berries (such as anthocyanin and caffeic acid) have a useful role in ageing brain and (NDD) [6, 7]. Numerous academics have demonstrated the neuroprotective properties of bilberries, strawberries, blackberries, black currants, mulberries, and blueberries [8, 9]. Because of the increased generation of (ROS), neuro-inflammatory processes in the brain are thought to be particularly important in the emergence of neurodegenerative disorders [10, 11]. The brain is more vulnerable to oxidative stress than other organs because antioxidant defense mechanisms are underactive [12, 13]. In addition, several neurotransmitters undergo autoxidation, which produces ROS [14]. The neurodegenerative diseases like ischemic diseases, (AD) (PD) and ageing are all thought to be significantly influenced by increased oxidative stress [15]. Numerous poly-phenols' unique neuroprotective properties depend on their capacity to penetrate the (BBB), directly scavenge pathological levels of (RO) and (NO), and metal ions chelate transition [16]. Dissimilar poly-phenolic substances were displayed to possess scavenging action and the capacity to activate important enzymes anti-oxidant in the brain, thereby halting the destructive cycle of oxidative stress and tissue damage [14, 15]. Growing evidence suggests that the polyphenols included in berries may enhance learning, memory, and other cognitive functions [17, 18]. These beneficial side effects are mostly sought after in the prevent

of damage brain, such as ischemic diseases neurodegenerative, lowering apoptosis neuronal, boosting learning and cognitive functioning, and enhancing memory [19, 20]. Several types of berry fruits beneficial effects in neuroprotective agent.

### Strawberry

The tree strawberry is to the Mediterranean region that is also grown in areas outside of Europe Eastern. The strawberry fruit's wide variety of antioxidants [21] makes it is a food that promotes "health." In addition to tannins, quercetin, anthocyanins, catechin, kaempferol, gallic acid, derivatives, vitamins C and E and carotenoids, caffeic acid, ellagic acid, and flavonoids are the most prevalent antioxidants [22–25]. Performance on the Morris water maze demonstrates how strawberries can enhance cognitive function. According to a recent study, strawberries can enhance rod-walking performance in terms of motor behaviour [26, 27]. These conclusions recommend that phyto-chemicals existing in strawberry benefit related age deficits in addition to the known useful effects on cardiovascular diseases, carcinoma. [28].

### Bilberry

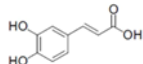
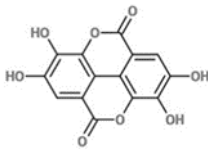
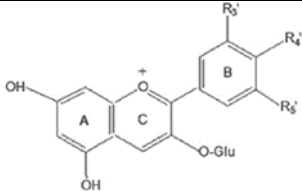
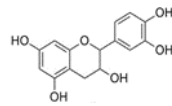
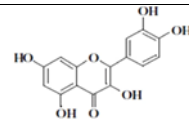
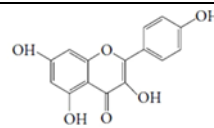
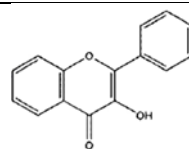
Due to their high anthocyanin, flavonol, vitamin C, E, and manganese content as well as their carotenoid, lutein, and zeaxanthin content, bilberries have significant health benefits [29, 30]. The biological effects, which include advantages for the health of the eyes, mouth, and gums, as well as potent anti-inflammatory [31–35], antioxidant, and anti-hyperglycemic effects, can shield blood vessels and enhance blood circulation [36–39]. Few relevant animal models exist to inspect the role of supplementary antioxidants in age-related learning and memory impairments. Potential genetic murine models include OXYS rats, who have hereditary traits of accelerated ageing and high oxidative stress sensitivity. The longevity of these rats is severely reduced (28% less time than Wistar rats). As a result,

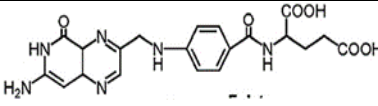
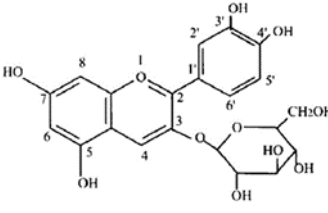

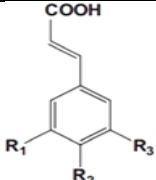
OXYs rats have been used as an animal model murine to clarify the fundamental underlying related age alterations in brain functions, including deficits in learning and cognition in age-related disorders [40-43]. It is known that the production of (ROS) can stimulate the expression of several genes in cells that produce proteins with antioxidant properties. The aforementioned information lends credence to the hypothesis that one of the primary causes of ageing and neurological diseases is a decrease in antioxidant protein expression and activity within cells. The ability of the bilberry

extract to decrease lipid peroxides and raise dismutase superoxide activity in the brain was also demonstrated. Additionally, long-term bilberry extract protects OXYs rats from memory and learning deficiencies. The bilberry fruit flavonoid might be fighting disease [13, 44].

Similar to fruits, berries (such as strawberry, bilberry, blackcurrant, blackberry, blueberry, and mulberry) mitigate Neurodevelopmental and neurodegenerative diseases. Berry Fruits Strawberry, blackberry, blueberry, blackcurrant, Mulberry can have neuroprotective properties (Table 1).

**Table 1: Structures of important active compounds of the berry fruits**

Compounds	Fruits	Chemicals Structures
Caffeic Acid	Strawberry & Blueberry	
Ellagic Acid	Strawberry	
Anthocyanins	Strawberry, Bilberry, Blackcurrant, Blueberry, Mulberry	
Catechin	Strawberry	
Quercetin	Strawberry	
Kaempferol	Strawberry	
Flavonols	Bilberry, Blackcurrant, Blueberry	

Folate	Blackberry	
Cyaniding -3-O-glucoside	Blackberry & Mulberry	
Salicylate	Blackberry	
Hydroxycinnamates	Blueberry	

### Blackcurrant

Blackcurrant is a fruit that has a good chance of offering neuroprotection in AD. Blackcurrant has a large number of polyphenols called anthocyanins, which make up about 80% of all measured components [45]. Flavonols from blackcurrant are also effective at preventing the generation of ROS when -Amyloid (A) is present [46]. Fruits Blackcurrant contain polyphenolic compounds that have been shown to have antimicrobial, antioxidant, antiviral, and antibacterial effects [47-52]. Additionally, they discovered that cells exposed to anthocyanin-rich blackcurrant extracts produced considerably less ROS. Bilberries and blackcurrants are rich in polyphenols, which have been found to impede A fibril production and extension as well as to destabilizing the produced A fibril in vitro [52]. Supplemented diets with bilberries and blackcurrants also lessened the behavioural impairments in APdE9 mice. A black currant diet boosted swimming speed in a demanding swimming environment, eliminating the idea that this is the result of a

motor deficit. The Morris swim test was similarly found to have a moderately positive effect of the berry extracts: bilberry and blackcurrant fed mice spent less time near the pool wall and performed fewer search rotations while swimming [53].

### Blackberry

The antioxidants, rich polyphenols, folate, manganese, fibre, vitamin C, salicylate, cyaniding-3-O-glucoside and high tannin found in blackberry fruits are well known. Blackberries have biological qualities that include anti-hyperglycemic [54], antioxidant, antiseptic, antibacterial/antiviral, and anticancer effects. They can also reduce pain, slow down the ageing process, normalize cholesterol, and improve blood circulation [55, 56]. discovered that wild blackberries from Braganca (in Portugal's northeast), including brigantinus and vagabundus, showed achievable neuroprotective benefits by lowering intracellular Reactive oxygen species (ROS) levels, modifying glutathione levels, and preventing the appearance of caspases during treatments. One of the most significant aspects of neurodegeneration,

oxidative damage, was prevented by these effects on neuronal cells. Blackberries are said to have strong anti-inflammatory and antiproliferative capabilities according to *in vitro* investigations [57, 58]. Additionally, the antioxidants in these fruits enhanced the behavioural performance of older rats participating in motor neuron tests. The (MWM) testing also revealed enhanced measures of spatial working memory and learning, as well as balance and fine motor coordination [59].

### **Blueberry**

Anthocyanins, caffeic acid, flavanols, and hydroxycinnamates are just a few of the flavonoids that are abundant in blueberries [60–67]. Eating blueberries can reduce oxidative stress, reduce inflammation, protect against kidney damage, and enhance vascular health. Their comparatively high flavonoid content, particularly anthocyanins, has been credited with these advantageous effects. According to a recent study, taking supplements of blueberries can help treat behavioural changes brought on by high-fat diets and ageing [68]. Oxidative damage, ageing, and neurodegeneration are all accelerated by an imbalance in homeostasis calcium and the buildup of protein AB. Inhibition of PKA and CREB, a downstream signaling target of PKA in embryonic neurons, by A alone or in combination with glutamate. At the synaptic locations damaged by AD, CREB is closely related to memory and learning. Related Age variations in memory, processing signal, and Reactive Oxygen Species vulnerability complicate the situation even more [69–72]. reported that therapy with blueberry extract protects against A42 in old (neurons isolated about 24 months) and aged middle (isolated neurons in 10–12 months) neurons in a specified culture medium. Treatment with blueberry extract reduced A-42 toxicity in hippocampus neurons of middle-aged and old age. The age-dependent enhancement of pERK signaling,

which results in the highest rise in MAPK activity, is accompanied by an increase in glutathione levels in aged neurons following A therapy [73]. Blueberry extract can enhance cognitive performance in ageing rats by controlling transitory stress signaling and ROS formation. Pretreatment with blueberry extract avoids calcium dysregulation and inhibits CREB and ERK activity through ROS stress response. In an animal model of ageing, blueberry supplementation improved motor and cognitive function, according to a preclinical investigation [74, 75]. Inhibition of the CREB/brain-derived neurotrophic factor pathway successfully prevents the animals receiving blueberry supplements from experiencing changes in their spatial memory [76]. Additionally, enhanced neuronal signaling in the hippocampus may be linked to the dispersion of anthocyanins there [77]. These findings are consistent with the idea that flavonoids, especially anthocyanins, may improve cell signaling and reduce damage oxidative. These findings also imply that flavonoids might influence cognition directly, which could help stop age- and disease-related brain degenerative processes [78, 79]. There is proof that blueberry supplementation effectively restored the cognitive losses in object identification in addition to Morris water maze performance [80]. Caspase-3 activity in the ischemic hemisphere was considerably reduced in animals given blueberry. Chronic use of blueberries lessens cerebral infarction and apoptosis brought on by ischemia/reperfusion [81].

[82] Additionally, mice fed a diet supplemented with blueberries had more striatal TH-positive nerve fibres. When given blueberry supplements, adult mice (3-month-old mice) performed better on memory tests and showed less DNA damage in the cerebral cortex and hippocampus [83]. Blueberries to a diet has positive effects by raising antioxidant levels, boosting anti-

inflammatory activities, and controlling distinct signaling pathways at different times [84, 85] and corrected cognitive performance abnormalities [86]. In older Fischer-344 rats, a short-term blueberry-enriched diet both prevents and restores impairments in object recognition memory [87-89]. showed that giving senior persons with modest memory deterioration a 12-week dosage of wild blueberry juice enhanced their memory. The control of cognitive processes depends on the central cholinergic system [90-92]. Increased endogenous acetylcholine levels have been successfully achieved by treating cognitive impairments using antagonists of cholinergic receptors and inhibitors of acetylcholinesterase. Acetylcholine is converted into choline and acetyl-coenzyme by the enzyme acetylcholinesterase. (2009) A. Papandreou et al [93] revealed that giving healthy adult mice a polyphenol-rich wild blueberry extract reduced acetylcholinesterase activity, elevated ascorbate and glutathione levels, and alleviated brain oxidative stress (MDA levels). Therefore, supplementing adult mice with blueberry extract with concentrated polyphenols improves their cognitive performance by raising antioxidant levels in the brain and decreasing acetylcholinesterase activity. The important influence of wild blueberry bioactive components on brain function is emphasized by these findings. [94]. shown that blueberry polyphenols mitigated learning deficits brought on by kainic acid in rats, deficits that were comparable to those seen in ageing animals. Blueberry polyphenols protect the brain by reducing the negative consequences of an inflammatory stimulus by changing the expression of genes related to inflammation. Experimental autoimmune encephalomyelitis exhibits histological and clinical characteristics, including as

inflammation and neurodegeneration, that are comparable to those of multiple sclerosis. According to a study by [95].

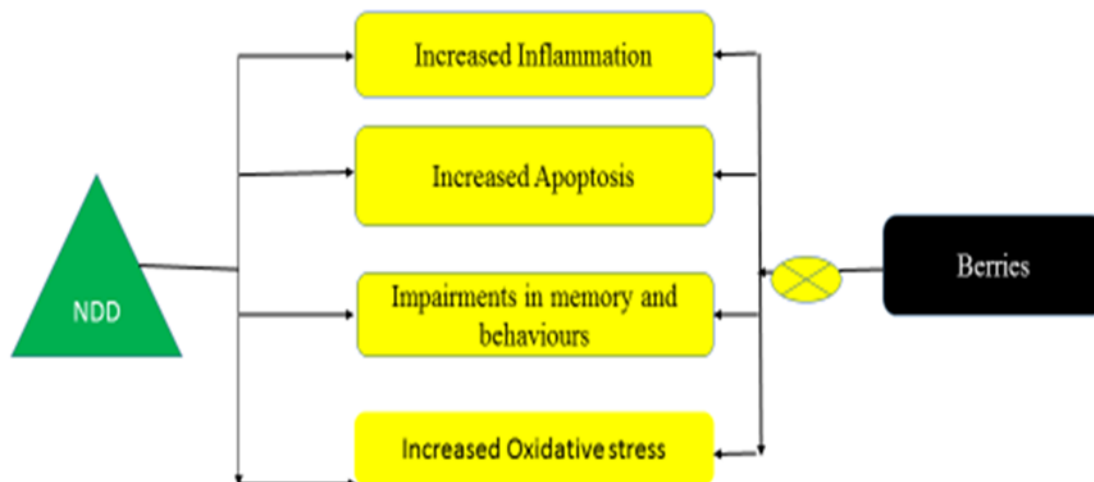
### **Mulberry**

In oriental traditional medicine, mulberries (*Morus alba* L., Moraceae) are used for diuretic, anti-inflammatory antitussive, antipyretic, and anti-hyperglycemic purposes [96]. C3G boosted cell viability in PC12 cells that were oxygen- and glucose-depleted. Additional research has shown that mulberry fruit extract protects against ischemia oxidative stress in both in vivo and in vitro models, indicating that C3G is a key component of the fruit mulberry extract that protects against oxidative stress [97].

Similar to fruits, berries (such as strawberry, bilberry, blackcurrant, blackberry, blueberry, and mulberry) in particular can have neuroprotective properties (Table 2).

The berry fruit may also have direct effects by altering cell signaling in ways that enhance or promote neural communication, calcium buffering, neuroprotective stress shock proteins, plasticity, antioxidant/anti-inflammatory action, stress signaling pathways, and acetylcholinesterase inhibition. Berries may improve cognitive and motor behavioural performance through these alterations and others that are under investigation. In order to reduce or delay the onset of age-related neurodegenerative illnesses, dietary treatments high in phytochemicals (for example, anthocyanins and caffeic acid), such as berry fruits, may be a beneficial asset in preventing against ageing (Fig. 1). To further confirm the effects of berry fruits and develop new therapeutic medicines for disorders associated to the brain, extensive clinical trials must be conducted.





**Figure 1. Graphical showing the possible mechanism of fruits berry against (NDD)**

### Literature review

Goji berries are used as food or in folk medicine and have a number of bioactivities. The anti-inflammatory and antioxidant effects of the methanolic extracts from red and black goji berries were compared in this study. Numerous chronic disorders, including neurological diseases, have been linked to inflammation and the associated oxidative stress. Our findings indicate that these goji berries, especially the dark ones, may have the potential to be a source of chemical compounds that are pharmacologically effective in treating conditions that have an inflammatory and oxidative background [98].

Consumed as a healthy fruit, blueberries have a number of advantages for the neurological system. Researchers have discovered that blueberries can be consumed as a daily dietary supplement to help youngsters learn and retain information better as well as prevent and lessen the complexity of age-related disorders. Finally, we go over the most recent technological advancements that have been made to increase the bioavailability of blueberry anthocyanins and create efficient delivery systems that enhance brain health. [99].

The recent study has suggested that vitamin C may have an anticancer mechanism in addition to being an anti-inflammatory agent and potent antioxidant in the treatment of cardiac disease, neurological disorder, liver disorders, kidney. It will also inspect the protective agent of vitamin C combat Pb-induced toxicity in both animals and humans [100].

Before being employed, a variety of medications, whether synthetic or natural, used to treat brain problems must cross the BBB. This essay discusses numerous studies on phytochemicals that are used to treat neurodegenerative diseases. [101].

Several berry species, including blueberries, lingonberries and (Vaccinium angustifolium) (Vaccinium vitis-idaea L.), have received a lot of interest from scientists recently, particularly because of their purported anti-inflammatory and antioxidant capabilities. Like other plant species, berries have evolved metabolic defenses to withstand a variety of environmental challenges. In cellular models of toxicity and inflammation, extracts from these species have also shown neuroprotective properties that are now being investigated in animal models. [102].

Using the information found in the literature, this study focuses on the numerous known

actions of natural products in vitro and vivo preclinical models, as well as their prospective neuro-therapeutic applications. [103].

Ellagitannins, which are more pertinent for food applications than lipoprotein settings, so considerably contribute to the antioxidant capacity of cloudbberries and red raspberries. [104].

## Results and Discussion

The neuroprotective effects of berry fruits on neurodegenerative diseases Alzheimer disease, Parkinsonian disease are related to phyto-chemicals such as caffeic acid, anthocyanin, quercetin, tannin kaempferol, catechin. Berries are a beneficial drug as promising neuroprotective agents.

hypothesize that consuming blueberry fruits, leaves, or supplements as part of a healthy diet may protect against neurodegenerative diseases with a neuroinflammatory component [105].

They came to the conclusion that berry fruit supplements for human nutrition might be a great source of antioxidants and an alternative for preventing and reducing the symptoms of diseases like anxiety, depression, Parkinson's and Alzheimer's [106].

In our final section, we talked about how new technologies have been used to increase the bioavailability of blueberry anthocyanins and create efficient delivery systems that enhance brain health [107].

Based on the modification of oxidative stress in the paw edoema model, these results suggested that quercetin, rutin, or another phenolic component present in the extracts of these berry fruits could cause an anti-inflammatory response [108].

In particular, the black goji berries have the potential to be a source of pharmacologically active chemicals in conditions oxidative background with an inflammatory, according to the researcher's assessment [109].

Researchers proposed that the blueberries exert their advantageous effects either indirectly by changing the signaling involved in neural transmission or directly by lowering oxidative stress and inflammation. Age-related cognitive and motor function deficits may be prevented by these therapies [110].

Here, we discovered that açai berry could lessen hippocampus mortality and behavioural changes brought on by VaD in the CA1 and CA3 areas. Future care of vascular dementia may benefit from supplements that utilize the preventive properties of açai berries [111].

This article provides a succinct summary of the benefits of several fruits, notably berries, grapes, and citrus fruits, in preventing neurological disorders. The ability of these fruits to protect against neurodegeneration and psychological disorders is the main focus. The selection of fruits was made in light of the numerous published pharmacological research on their neuroprotective efficacies [112].

This protective effect of berry extracts may be brought on by a reduction in the detrimental effects of oxidative stress, nitrosative stress, or other processes brought on by glutamate exposure [113].

Humans are just one of the many flora-bearing fruits and vegetables found in nature. A significant source of natural antioxidants is found in berries. As a diversified source of a wide range of nutritive, nonnutritive, and bioactive chemicals, berries have a crucial role in the prevention and management of different neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease (AD), and other neuronal dysfunctions. The diversely occurring bioactive components of the berries have been utilized and tabulated in this review to discuss their neuroprotective capabilities in Alzheimer's [114].



**Table 2. Neuroprotective effects of berry fruits [115]**

Natural compounds	Class/mechanism/therapeutic mode	Therapeutic effect
Strawberry	<ul style="list-style-type: none"> <li>• Stimulated guanine triphosphate-ase activity inhibition</li> <li>• Reducing oxidative stress</li> <li>• Cyclooxygenase • Anti-inflammatory activity</li> </ul>	<ul style="list-style-type: none"> <li>• Improving Morris water maze performance</li> <li>• Preventing neurochemical and behavioral changes</li> <li>• Anti-inflammatory activity</li> </ul>
Bilberry and blackcurrant	<ul style="list-style-type: none"> <li>• Decreasing the ratio of insoluble amyloid beta-42/40</li> </ul>	<ul style="list-style-type: none"> <li>• Alleviating behavioral abnormalities</li> </ul>
Bilberry	<ul style="list-style-type: none"> <li>• Free radical scavenging activity</li> <li>• Alleviating memory deficits</li> </ul>	<ul style="list-style-type: none"> <li>• Alleviating memory deficits</li> </ul>
Blackberry	<ul style="list-style-type: none"> <li>• Reducing intracellular reactive oxygen species levels, modulating glutathione levels and inhibiting caspases activity</li> </ul>	<ul style="list-style-type: none"> <li>• Improving behavioral performance in motor tests and Morris water maze (cognitive test)</li> </ul>
Blueberry	<ul style="list-style-type: none"> <li>• Changes in brain-derived neurotrophic factor</li> <li>• Decreasing A<math>\beta</math> levels</li> <li>• Decreasing the levels of interleukin-1<math>\beta</math>, tumor necrosis factor-<math>\alpha</math> and transcription factor nuclear factor-kappaB</li> </ul>	<ul style="list-style-type: none"> <li>• Enhancing motor and memory performances</li> <li>• Significant cognitive enhancement</li> </ul>
Mulberry	<ul style="list-style-type: none"> <li>• Decreasing the infarct volume of the brain</li> </ul>	<ul style="list-style-type: none"> <li>• Neuroprotection</li> </ul>

## Conclusion

The main causes of ageing and the emergence of age-related neurodegenerative disorders are oxidative stress and inflammation. Numerous naturally occurring anti-inflammatory and antioxidant chemicals, particularly those found in berries including strawberries, bilberries, blackberries, blueberries, and mulberries, are present in plant food matrices and can have neuroprotective effects. The berry fruit may also have direct effects by altering cell signaling in ways that enhance. Berries may improve cognitive and motor behavioral performance through these alterations and others that are under investigation. By lowering or delaying the onset of age-related (NDD), dietary treatments containing phytochemicals (such as caffeic acid and anthocyanins) such as berry may be a beneficial drug in combating ageing. To further confirm the effects of berry fruits,

develop new therapeutic medicines for disorders associated to the brain, extensive clinical trials must be conducted.

## Authors' contributions

Conceived and designed the experiments: WA Khan & A Khan, Performed the experiments: WA Khan & A Khan, Analyzed the data: I Khan & I Mateen, contributed materials/ analysis/ tools: A Khan, Wrote the paper: WA Khan.

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