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Chapter

Berry Supplementation and Their Beneficial Effects on Some Central Nervous System Disorders

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Abstract

This chapter is based in the compilation and analysis of different in vitro, preclinical, and clinical studies, which explored the potential beneficial bioactivity of supplementation with berries on some alterations in the central nervous system (CNS). The last section of the chapter describes the possible mechanisms of action of polyphenols, anthocyanins, and other compounds present in berries as well as their relationship with anxiety, depression, and Alzheimer's (AD) and Parkinson's diseases (PD) and their implication in the prevention of cognitive decline and senescence motor functions. Electronic databases as Springer, PubMed, Scopus, and Elsevier were used. Papers were selected by topic specially those related with berries, year of publication, and authors. The present chapter evidenced the potential health effect as neuroprotector of different berries and their bioactive compounds mainly flavonoids, polyphenols, and anthocyanins, on diseases such as anxiety, depression, and Alzheimer's and Parkinson's diseases. In conclusion, for human nutrition berry fruit supplementation might be an excellent source of antioxidant and alternative for prevention and reduction of symptoms in diseases such as anxiety, depression, Alzheimer's, and Parkinson's.

Keywords: berry, anthocyanins, polyphenols, neuroprotection, prevention

1. Introduction

Berries with a high antioxidant activity have drawn the attention of scientists due to their potential antioxidant, anticancer, anti-inflammatory, and neuroprotective-related effects, identified in in vivo studies [1]. It is well established that many species of berries, for example, strawberries (*Fragaria ananassa*), blueberries (*Vaccinium corymbosum*), raspberries (*Rubus idaeus*), and blackberries (*Rubus fruticosus*), are rich in bioactive compounds such as flavonoids, polyphenols, and anthocyanins. These compounds could be a supplementation alternative because

they are able to cross the blood-brain barrier and accumulate in various structures [2, 3] related to learning, memory, cognition process, and modification of behavior. In addition, their anti-neurodegenerative properties have been observed in diseases such as anxiety associated with stressful events [4] and reduction of depression, AD, and PD symptoms. Additionally, an association has been observed between the consumption of berries and increase in dendritic spine density in some brain structures and hippocampal neurogenesis [5]. In this way, the berry consumption and their bioactive compounds (i.e., polyphenols and anthocyanins) might be an excellent alternative for human nutrition when consumed fresh. They can be consumed as yogurt, juice, jam, or like dietary supplements that can be used as functional and nutraceutical foods.

Food is considered as a functional food if, in addition to its basic nutritional, it generates a beneficial effect in the physiological processes in the organism [6]. In the same way, a nutraceutical is a food or part of a food that produces health benefits besides its nutritional content [7, 8]. In the present chapter, we discuss the potential beneficial effects of berries and their derivatives on some central nervous system diseases.

2. Berries

Enhanced consumption of fruits and vegetables is highly recommended in dietary guidelines. Specially, the consumption of berries is recommended due to their antioxidant properties [1]. Berries, in botanical terms, are defined as fleshy fruits that emerge from the plant ovary that encloses the seeds; due to this, berries include grapes, blueberries, black currants, and coffee beans [9].

In this chapter we will focus on strawberries, blueberries, raspberries, chokeberries, black currants, and blackberries, among other endemic fruits. We selected these fruits because, in addition to being rich in polyphenols and anthocyanins, they are the most consumed in human diet; therefore, more studies related to their supplementation and chemical composition have been published.

Berries (i.e., blackberry, black raspberry, blueberry, cranberry, red raspberry, and strawberry) are popularly consumed either fresh, frozen, or processed as yogurts, beverages, jam and jellies, as well as dried or canned. Furthermore, berry extracts have been used as a functional food or dietary supplement [1].

Berries (blueberry, strawberry, blackberry, and Brazilian berries {*Eugenia uniflora L.*}) are considered an important group within functional foods, since multiple investigations have shown that their consumption produces beneficial health effects ranging from the mitigation of adverse physiological processes related to cardiovascular diseases and metabolic disorders to the amelioration of cognitive brain functions [10]. This highlights their ability to modulate neuroinflammation [11], glucoregulation [12], brain vascular function [13], and hippocampal neurogenesis [5]. These effects have been linked to their chemical compounds, specifically, to the presence of phenolic compounds in these fruits [14]. **Table 1** shows specifically most consumed berries, their effect produced, and metabolite involved.

Even though the composition and the content of these compounds are dependent on the plant species, production status, agricultural processing, and storage, berries are an excellent source of polyphenols, flavonoids, and anthocyanins [20, 21], which have been related to their potential beneficial effects on health.

Berry	Effect	Metabolite involved	Ref
Blueberry *(Vaccinium Virgatum A.)*	Antioxidant	Anthocyanins (1202 mg)	[9]
Strawberry *(Fragaria ananassa Duch.)*	Antioxidant	Polyphenols (13550 mg)	[9]
Blackberry *(Rubus sp.)*	Antioxidant	Anthocyanins (870 mg)	[9]
Blueberry *(*NS)*	Modulate neuroinflammation	Flavonoids: various concentrations of blueberry (50-500 μg)	[10]
Blueberry Highbush *(Vaccinium corymbosum)*	Glucoregulation	Anthocyanins-flavonols (220 mg)	[11]
Blueberry *(Vaccinium corybosum)*	Synaptic plasticity	Anthocyanins (10.2 mg)/ Total phenolics (33 mg)	[12]
Blueberry *(*NS)*	Hippocampal neurogenesis	Blueberry extract diet (20 g) (*NS anthocyanins or polyphenols)	[5]
Rasperry *(Rubus idaeus)*	Anti-cancer	Anthocyanins (314 mg)	[14]
Strawberry Beverage *(*NS)*	Anti-inflamatory/ hypoglycemic	Total phenols (94.7 mg)/ Anthocyanins (39 mg)	[15]
Grape (*NS)	Genoprotective	Anthocyanins (1576.5 mg)/ Total phenolics (2750.4 mg)	[16]
Blueberry Highbush *(Vaccinium corymbosum)*	Neuroprotection/ Proneurogenesis	Anthocyanins (4968·3 ng)	[17]
Cranberry *(Vaccinium oxycoccus)*	Vascular	Polyphenols (835 mg)/ Anthocyanins (94 mg)	[18]
Rabbiteye Blueberry *(Vacciniumn ashei)*	Motor and cognitive function Anxiolytic Genoprotective	Anthocyanins (2.6-3.2 mg)	[19]

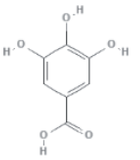
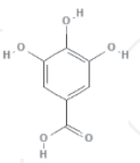
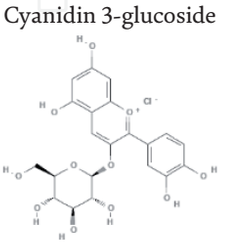
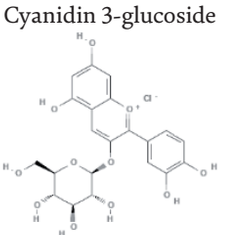
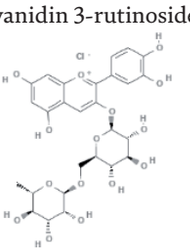
NS: not specified; Ref: reference

Table 1.
Berries: effects and metabolites involved.

3. Active metabolites from berries with pharmacological activity

Berries are rich in phytochemicals such as minerals, vitamins, fatty acids, and dietary fibers and specifically contain provitamin A, minerals, vitamin C, and B complex vitamins. Additionally, fruits contain soluble solids, fructose, and chemopreventive agents as A, C, and E vitamins, folic acid, calcium, and selenium. Carotene and lutein are present in berries as well as phytosterols such as sitosterol and stigmasterol and also contain triterpene esters, and there is an excellent source of phenolic molecules such as flavonols, flavanols, proanthocyanidins, ellagitannins, phenolic acids, and anthocyanins specially cyanidin-3-glucoside, gallic acid, pelargonidin, delphinidin, peonidin, and malvidin, among others [22].

The metabolism, bioavailability, and biological effects attributed to berries depend specifically on the type of chemical structure contained in its phenolic compounds that individually or synergistically exert protection against several health disorders [23]. **Table 2** shows the main phytochemical compounds present in berries and their representative chemical structures.

Berry	TP mg/100 g	TA mg/100 g	Characteristic structure	Ref
Blueberry (FW)	711.3 ±	360 ± 0.76	Gallic acid 	[22]
Blackberry (FW)	2611	104	Gallic acid 	[23]
Cranberry (DW)	59	117	Cyanidin 3-glucoside 	[24]
Raspberry Black Red (FW)	267 234.25	197.2 ± 3.5 68.17 ± 3.02	Cyanidin 3-glucoside 	[25]
Blackcurrant (DW)	2382.4 ± 60.8	403.3 ± 11	Cyanidin 3-rutinoside 	[26]

Chemical structure was determined according to berry bioactive compound. TP: total polyphenols; TF: total flavonoids; TA: total anthocyanins; FW: fresh weight; DW: dry weight.

Table 2.
Total polyphenols, anthocyanins and characteristic structure content of berries.

3.1 Polyphenols

Polyphenols or phenolic compounds are phytochemicals that result from the secondary metabolism of plants coming from the metabolic pathway of shikimic acid and acetate-malonate. They are composed of various chemical structures characterized by an aromatic nucleus of benzene substituted by a hydroxyl group called phenol [21]. Differences between subclasses are given by the number of phenolic rings and the elements attached to them, thus creating several families of compounds, such as flavonoids, anthocyanins, flavones, tannins, and coumarins, among others [21, 27–29].

Polyphenols are present in fruits, vegetables, leaves, nuts, seeds, flowers, and barks [30] and act as inhibitors or activators for a wide variety of mammalian enzyme systems and as metal chelators and oxygen free radical scavengers [31, 32]. Moreover, it has been reported that some flavonoids rise ion chlorine flow at the $GABA_A$ receptor in male rats [33, 34]. They can act as positive or negative

modulators by direct actions on the effect of GABA [35, 36]. Considerable scientific evidence has shown that flavonoids are able to cross into the brain and influence brain function [37, 38]. They have a variety of effects like relief of anxiety, antidepressant actions, and neuroprotective [29] and sedative actions [39].

The ability of polyphenols to modulate the activity of different enzymes and consequently interfere in signaling mechanisms and different cellular processes may be due, in part, to the physicochemical characteristics of these compounds, which allow them to participate in different oxide-reduction cellular metabolic reactions [40].

A diet rich in polyphenols has been shown to augment health [41]. It is best known for its biological effects in humans as anti-inflammatory [42] and anticarcinogenic [43]; in vitro as antiviral [44]; and in animals as gastroprotector [45] and antibacterial [46]; among others. More than 8000 phenolic compounds are known in nature [47], which according to their chemical composition are divided into 2 groups: phenolic acids (benzoic and cinnamic) and flavonoids (flavonoids, anthocyanins, and tannins) [48]. For the purposes of this chapter, we will focus on describing flavonoids in a general sense and anthocyanins in a particular manner.

3.2 Flavonoids

Their name derives from the Latin *flavus*, which means "yellow," and constitutes the most abundant subclass of polyphenols within the vegetable kingdom [49]. They are low molecular weight compounds sharing a common diphenylpyrane skeleton (C6-C3-C6′), composed by two phenyl rings (A and B) bound through a heterocyclic pyran C ring. All flavonoids are hydroxylated structures in their aromatic rings and are therefore polyphenolic structures [41].

The main subgroups of flavonoid include flavonols, flavones, flavanones (dihydroflavones), isoflavones, and anthocyanins [50]. The flavonoid quercetin (4 mg/day) produces antineoplastic effects [51] and cholesterol-lowering effects in Japanese women aged 29–79 years old (9.3 ± 7.4 mg/day) [52], and at preclinical research in rats, quercetin (25 and 50 mg/kg) produces antithrombotic effects [53], while a hepatic regenerative effect was detected with supplementations of silymarin (100 mg/kg/day) [54].

Among the most reported effects of flavonoids on the central nervous system are their participation in learning and memory mechanisms in Sprague Dawley rats supplemented with nobiletin (725 mg; extracted from *Citrus depressa* peels) [55]; in vitro aid in the treatment of AD by inhibiting the formation of plaques related to memory loss (myricetin, 1 mM) [56] and their neuroprotective role in PD (quercetin, 0.1 μM, or sesamin, 1 pM) [57]; and in male Swiss mice, antidepressant effect supplemented with *Schinus molle* L. (0.3–3 mg/kg) [58] and anxiolytic activities in Wistar rats (1 mg/kg of chrysin i.p.) and zebra fish (1 98 μL/0.1 g b.w.) [59].

3.3 Anthocyanins

Anthocyanins are an important group of water-soluble flavonoid compounds responsible for the red, purple, and blue colors in flowers, fruits, and other parts of plants that are not toxic for human consumption [48]. Their name derives from the Greek *ανθός* (*anthos*) meaning "flower" and *κυανός* (*kyáneos*) meaning "blue" [60].

They are polyhydroxy- or polymethoxy-glycosides derived from the basic structure, 2-phenyl benzopyryllium [61]. They consist of structures known as anthocyanidins or aglycones, which consist of an aromatic ring attached to a heterocyclic ring containing oxygen which, in turn, is linked to a third aromatic ring. When anthocyanidins are found in glucosylated form, they are then known as anthocyanins and are mainly accompanied by glucose, rhamnose, galactose, arabinose, xylose, and other disaccharides and trisaccharides [62]. These carbohydrates are

always bound to anthocyanidin position 3, and glucose is often found additionally in position 5 and, less commonly, in positions 7, 3′, and 4′ [63].

Anthocyanins are less water-soluble than when they are found in glucosinolates and rarely exist in free form in food. Today, about 19 natural anthocyanidins are known, although the most commonly found in foods are six: pelargonidin, delphinidin, cyanidin, petunidin, peonidin, and malvidin [64], names derived from the plant source from which they were first isolated. In the same sense, a measure of the antioxidant capacity of anthocyanin pigments revealed that cyanidin-3-glucoside and delphinidin-3-glucoside have the highest antioxidant activity [65] and have been identified in fruits coming from the berry family [66], specifically in blackberries [67, 68].

It is important to mention that anthocyanins resist passage through the digestive tract of mammals and are absorbed in the stomach and in the middle portion of the small intestine, reaching the bloodstream almost intact [69]; they reach organs such as the liver, eyes, and brain, thus accumulating in them [14, 70].

4. Biological effects

The biological functions of anthocyanins can be classified into two types: those related to their antioxidant capacity and those involved in the modulation of cell signaling pathways [71]. In general, they are attributed with effects such as the prevention and/or reduction of atherosclerosis [72]; reduction in the incidence of cardiovascular disease [73]; anticancer [74] and anti-inflammatory activity [75]; hypoglycemic effects [76]; and augmented visual acuity [77] and cognition [78].

Specifically, anthocyanins cross the blood-brain barrier and accumulate in brain regions related to learning and memory, such as the hippocampus and cerebral cortex, modifying behavior [2]. It has been observed in in vitro studies that consumption of these compounds inhibits the enzyme monoamine oxidase (MAO), in which increased activity is related to AD and other neurological disorders [79]. In addition, they display antioxidant capabilities, such as decreasing free radicals and stress signals controlling calcium homeostasis in the brain [80, 81], as well as the presence of hydrogen peroxide (H_2O_2) and radicals peroxide (ROO) and superoxide (O2) [82, 83]. They also exert protective effects against oxidative stress in cellular models of PD [84] and promote optimal neurotransmission, primarily in advanced age [21].

It has also been observed that anthocyanins ameliorate anti-ocular-inflammatory in male Lewis rats supplemented with crude aronia extract (*Aronia melanocarpa*) in doses of 100 mg/kg, an effect similar to that found in ophthalmic prednisolone in a dose of 10 mg; this effect is evidenced by the direct blockage of the expression of the iNOS and COX-2 enzymes leading to suppression of NO, PGE2, and TNF-α production [85]. Another study in female Wistar rats ovariectomized and supplemented with anthocyanin (200 mg/kg, 7 days of treatment) showed an augment in learning and memory in rats with estrogen deficiency caused by ovariectomy, showing lower errors and latency times in shuttle box test [86].

5. Berries and bioactive compounds on brain diseases

The recent increase in life expectancy worldwide has augmented the incidence of age-related diseases, particularly neurodegenerative diseases and psychiatric disorders.

Below, we will describe the effects of berry consumption and the relationship between diseases such as anxiety, depression, Alzheimer's and Pasrkinson's diseases, as well as human cognition, because those are the most common mental illness and neurodegenerative diseases [5].

In addition, you will find in **Table 3** the most recent research carried out related with supplementation in humans and in animal models and, additionally, study design and summarized findings.

5.1 Anxiety

Anxiety is a common and chronic psychiatric disorder that is a source of suffering and impairment [96]. In 2017, the World Health Organization reported that more than 260 million people suffer from an anxiety disorder [97]. Its pharmacological treatment is based on the use of benzodiazepine drugs, as well as some antidepressants with anxiolytic activity [98]. Unfortunately, these drugs are accompanied by severe side effects such as sedation, pharmacological tolerance, and drug dependence [99, 100]; in this sense, some patients complement their therapies with natural compounds coming from plants.

The study of the potential effect of berries on anxiety, due to their high content of polyphenols and anthocyanins associated with anxiolytic activity at the preclinical level, has attracted important interest [101, 102]. It has been observed that these compounds, present in blueberries, have shown anxiolytic effects in animal models and their possible mechanisms of action are related to the antioxidant properties of anthocyanins [103] which inhibit the enzyme monoamine oxidases (MAOs), decreasing its activity and providing neuroprotection [77, 104].

Supplementation with blueberries in mice for 30 days has shown to increase the time spent in the open arms (anxiolytic effect) in the elevated plus maze test (EPM); in addition, it is shown to reduce oxidative damage to neural DNA, and this antioxidant neural protection has been proposed as a mechanism for the anxiolytic property of berries [19].

One of the most studied berries for anxiety at the preclinical level is the black chokeberry (*Aronia melanocarpa)* belonging to the Rosacea family [105], for example, in male Wistar rats, the acute administration of the juice at doses of 5 and 10 ml/kg exerts dose-dependent anxiolytic activity in the social interaction test in a manner comparable to diazepam [102]. While, subchronic administration of *Aronia melanocarpa* fruit juice (10 ml/kg, orally) in male Wistar rats induces a time-dependent anxiolytic effect [106]. Furthermore, the month-long unlimited consumption of black chokeberry juice (>20 ml/kg b.w daily) exerts reduction of anxiety-like behavior associated with MAO-A/MAO-B inhibitions [104], which is probably due to the high antioxidant activity that black chokeberry has shown to have [107].

On the other hand, this berry fruit has been evaluated in different concentrations and behavioral tests such as the EPM and the social interaction test [102]. Likewise, a methanolic extract of blackberry (*Rubus fruticosus*) was used and reported an anxiolytic effect (100, 200, and 300 mg/kg, orally) in the hole-board test in a dose-dependent response [108]; also, the effect of *Rubus brasiliensis* fruits in Wistar rats has been studied, reporting an anxiolytic effect in EPM, in a dose of 2.5 mg/kg administered per gavage [109]. In turn, an anxiety-related effect has been reported in treated male Swiss mice through supplemented water (2.6–3.2 mg/kg) per day of anthocyanins present in blueberry (*Vaccinium ashei*) [19].

Our working group [4] recently reported the anxiolytic effect from blackberry juice (doses intermediate: 5.83 mg/kg anthocyanins, 27.10 mg/kg polyphenols) on EPM in male Wistar rats, and the design was accompanied by the forced swim test (6 min). A decrease in the anxiety index was observed, without alterations in locomotor activity. This was similar to the group administered with the anxiolytic drug diazepam. Results revealed a better response to behavioral stress in the rats treated with blackberry juice, reinforcing the effects previously reported in EPM (**Table 3**).

The anxiolytic effect of some flavonoids and anthocyanins has been identified by affinity to $GABA_A$ receptors [89, 110]. However, its antioxidant capacity is still

Topic	Author/ location	Study design	Intervention	Summarized findings
Anxiety	Fernández-Demeneghi *et al*., 2019 [4]/ Mexico	n=45, 21 days treatment, Wistar male rats (200- 250 g)	Five groups were used: Veh (control group administered with 8.7 ml/kg), BL (low dose group of blackberry juice, 2.6 mg/kg of anthocyanins, 14.57 mg/ kg of polyphenols) BM (medium dose group of blackberry juice, 5.83 mg/ kg anthocyanins, 27.10 mg/kg polyphenols) BH (high-dose blackberry juice group 10.57 mg/kg anthocyanins, 38.4 mg/kg polyphenols) DZP (diazepam group administered 2 mg/kg).	The intermediate dose of blackberry juice (5.83 mg/kg of anthocyanins, 27.10 mg / kg of polyphenols) had an anxiolytic effect similar to DZP, improving coping strategies at the behavioral level. These results were supplemented by the forced swim test, where medium and high doses improved the response to acute stress.
Depression	Chang *et al*., 2016 [85]/ USA-UK	n=82643 women. Prospectively, the study examined the associations between the estimated usual intake of flavonoids in the diet and the risk of depression. Semiquantitative food frequency questionnaire was applied (FFQ).	Two samples were used: Nurses' Health Study (NHSI) (from 1976 nurses aged 30-55) and NHSII (from 1989 nurses aged 25-42).	Higher flavonoid intakes may be associated with lower depression risk, particularly among older women.
	Khalid *et al*., 2017 [86]/United Kingdom	n=21 university students (18-21 years)/ The Positive and Negative Affect Schedule-NOW (PANAS-NOW) was used to assess current mood.	Two groups were used: The flavonoid-rich wild blueberry (WBB), which administered 253 mg of anthocyanins, a combination of 30 g of lyophilized WBB, 30 ml of Rocks Orange Squash and 220 ml of water), placebo (4 mg of WBB, 30 ml of Rocks Orange Squash and 220 ml of water were combined).	In both studies, an increase in positive affection was observed after 2 hours of consumption of the WBB drink. Flavonoid supplementation can play a key role in promoting positive mood and are a possible way to prevent dysphoria and depression.
		n=50 children (7-10)/child version of the Positive and Negative Affect Scale (PANAS-C).	Two groups were used: The flavonoid-rich wild blueberry (WBB) 253 mg anthocyanins, combination of 30 g lyophilized WBB, 30 ml Rocks Orange Squash and 170 ml water); placebo (4 mg WBB, 30 ml Rocks Orange Squash and 170 ml water were combined).	
	Nabavi *et al*., 2018 [87]/Iran	n=40, 7 days treatment, balb/c strain mice (5 weeks old, 20-25 g).	Four groups were used: control (healthy group), BCCAO (group with bilateral occlusion of the common carotid artery) 10 mg/kg (group with lesion + 10 mg/kg of aqueous extract of red berries of *H. Androsaemum* (WE) 30 mg/kg (group with lesion + 30 mg/kg of WE).	The protective effects of WE in post-stroke depression in a mouse model were demonstrated *in vivo*, both groups administered with WE reduced immobility time in forced swim and tail suspension tests. These findings are correlated with the antioxidant capacity of its bioactive constituents.
	Di Lorenzo *et al*, 2019 [88]/Italy	n=50, 7 days treatment i.p., balb/c strain mice (2 weeks old, 20-25 g).	Five groups were used: 1) control: healthy group, 2) BCCAO (group with stroke common carotid artery bilateral occlusion), 3) 25 mg/kg (lesion + 25 mg/kg Maqui berry extract (MBE)), 4) 50 mg/kg (lesion + 50 mg/kg MBE), 5) 100 mg/kg (lesion + 100 mg/kg MBE).	The results showed that the antidepressant-like activity provided by the extract, which was found to restore normal mouse behavior in both despair swimming and tail suspension tests, could be linked to its antioxidant activity, leading to the conclusion that maqui berries might be useful for supporting pharmacological therapy of Post-stroke depression by modulating oxidative stress.

Topic	Author/ location	Study design	Intervention	Summarized findings
Alzheimer's disease	Gutierres *et al*., 2014 [89]/Brazil	Male Wistar rats (3-months-1-year-old, 350-400g), 7 days of treatment with 200 mg/kg anthocyanin (ANT) the rats were injected with intracerebroventricular streptozotocin (3 mg/kg) (STZ), and four days later the behavior parameters were performed.	Four different groups: control (CTRL), anthocyanin (ANT), streptozotocin (STZ) and streptozotocin + anthocyanin (STZ + ANT).	A memory deficit was found in the STZ group, but ANT treatment showed that it prevents this impairment of memory. This work demonstrated that anthocyanin is able to regulate ion pump activity and cholinergic neurotransmission, as well as being able to enhance memory and act as an anxiolytic compound in animals with sporadic dementia of Alzheimer's type.
	McNamara *et al*, 2018 [90] / USA	n=76, 24 weeks treatment, study conducted in men and women aged 62-80 with cognitive impairment. They used the Dysexecutive Questionnaire.	Four groups were used: FO (fish oil + placebo powder), BB (blueberry [*Vaccinium sp*] powder + placebo oil), FO+BB (fish oil + cranberry powder), PL (oil + placebo powder). Fish oil (400 mg EPA (1.6 g) and 200 mg DHA (0.8 g)) and cranberry powder (phenolic concentration (20.4±0.31), anthocyanins (14.5±0.04)).	It was demonstrated that supplementation with FO and BB showed a reduction of self-reported inefficiencies in daily operation, by the BB group showed less interference in memory.
Parkinson's Disease	Fan *et al*., 2018 [91] / New Zealand	n= 11 male patients with Parkinson's disease and older than 40 years old. 2 sessions where samples of plasma and cerebrospinal fluid (CSF) were taken (in both sessions a 12-hour low anthocyanin diet was requested before taking the samples).	Study of pre and post treatment samples, where patients were supplemented with 300 mg blackcurrant capsules (35% anthocyanins, Super Currantex® 20) twice daily for four weeks.	The neuropeptide cyclic glycine protein (cGP), a natural BCA nutrient, was shown to be effectively absorbed in the brain after supplementation. The increase of cyclic glycine proline (cGP) in plasma and cephalorachidian fluid in Parkison patients is mainly due to central uptake of the neuropeptide in plasma. Thus, the role of insulin-like growth factor 1 (IGF-1) improves in patients with Parkinson's disease.
	Qian *et al*., 2019 [92] / China	n=45, 3 weeks treatment, 6-week old male C57BL/6 mice (18-22 g). This study was designed to investigate the effects of the ANC rich blueberry extracts (BBE) on behavior and oxidative stress in the mouse model of PD induced by 1- methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP).	Five groups were used: 1) control (received i.p. saline), 2) MPTP (received i.p. MPTP 30 mg/kg for 5 days and saline, 3)BBE 50 mg/kg (received i.p. MPTP 30 mg/kg for 5 days and 50 mg/kg blueberry extract (BBE), 4) BBE 100 mg/kg (received i.p. MPTP 30 mg/kg for 5 days and 100 mg/kg of BBE) and 5) i.p MPTP and fed daily with levodopa and benserazide (10 mg/kg/day).	BBE improved motor function in MPTP- induced Parkinson's mice through a possible mechanism of their antioxidant capacity to eliminate free radicals and reduce oxidative damage to neurons.

Topic	Author/ location	Study design	Intervention	Summarized findings
Other effects	Devore *et al*., 2012 [93]/USA	n=16,010 women, aged ≥70; follow-up assessments were conducted twice, at two-year intervals.	Follow-up questionnaire on eating habits (2-year period) and assessment of congenital impairment. Six cognitive tests were administered: Telephone Interview of Cognitive Status, a telephone adaptation of the Mini-Mental State Examination; East Boston Memory Test – immediate and delayed recalls; category fluency; delayed recall of the Telephone Interview of Cognitive Status 10- word list; and backwards digit span.	Increased consumption of berries and anthocyanidins, as well as total flavonoids, was shown to be associated with slower progression of cognitive impairment in older women.
	Watson *et al*., 2015 [94]/New Zealand	n=36 healthy, young participants (18-35 years). The battery used was formed: digit vigilance, stroop, rapid visual information processing (RVIP) and logical reasoning.	Three intervention drinks were used: 1. control (containing 0 mg polyphenols), 2. Blackadder (7.78 mg/kg anthocyanins from an extract of Ribes nigrum). 3. DelCyan (trademark) (8.05 mg/kg anthocyanins from a blackcurrant extract).	It was demonstrated that the consumption of drinks supplemented with blackcurrants produce a cognitive benefit in healthy young people, evidenced by greater accuracy in the RIVP test; likewise, Blackadder improved reaction times in the task of monitoring digits. Clinically significant inhibition of monoamine oxidase-B and monoamine oxidase-A was identified using a commonly consumed fruit.
	Whyte & Williams (2015) [95]/United Kingdom	n=16 children (8-10 years), 7 days of treatment. Two hours after consumption, the children completed a battery of five cognitive tests comprising the Go-NoGo, Stroop, Rey's Auditory Verbal Learning Task, Object Location Task, and a Visual N-back.	Two intervention drinks were used: 1. blueberry (prepared by mixing 200 g of Star variety blueberries with 100 ml, which contained 143 mg of anthocyanins). Control (combined with blueberry drink for sugars and vitamin C by adding 0.02 g of vitamin C powder, 8.22 g of sucrose, 9.76 g of glucose and 9.94 g of fructose to 100 ml of semi-skimmed milk).	It was identified that anthocyanins (143 mg) present in blueberry juice have memory benefits in children aged 8 to 10 years, however, little evidence in attention, visuospatial, working memory were observed.

Table 3.
Recent research in humans and animal models related to supplementation with berries.

considered the main mechanism of action [106], since oxidative stress has been proposed as an important contributor to anxiety generation [79].

5.2 Depression

Depression is the most prevalent psychiatric disorder; according to the World Health Organization, it affects 300 million people worldwide [97]. Depressive disorders are characterized by the presence of a sad and irritable mood accompanied by somatic and cognitive changes that negatively impact everyday life function [97] and result in high financial costs [111]. A great variety of drugs exist for its treatment [112], in which therapeutic effects are driven by actions on diverse neurotransmission systems (serotonergic, dopaminergic, and noradrenergic), exerting long-term changes which can restore neuronal function, for example, restoration of basal levels of neurotransmitters mainly serotonin, increase in neurotrophic factors (brain-derived neurotrophic factor and nerve growth factor) that can indirectly modify neuronal microarchitecture, reduction of oxidative stress, as well as neuroinflammation processes in structures related to the pathophysiology of depression which can impact at the affective level exerting favorable effects on the quality of life of the subjects. These drugs include tricyclic antidepressants (i.e., imipramine), selective serotonin recapture inhibitors (i.e., fluoxetine), monoamine oxidase inhibitors (phenelzine), and dual antidrepressant drugs (venlafaxine), among others [113]. Most of these drugs have a late onset and are often accompanied by side effects when taken for prolonged periods. This has encouraged a search for new substances with potential antidepressant effects and, most importantly, the use of possible natural alternatives.

An association between the role the hippocampus and the etiology of depression has been suggested, given that a reduction in hippocampal neurogenesis has been observed in depressed patients with respect to the non-depressed control group, which is accompanied by a decrease in the hippocampal volume [114]. In this sense, antidepressants such as fluoxetine have been shown to ameliorate neurogenesis in the hippocampus [115].

At the preclinical level, the administration of *Aronia melanocarpa* juice showed a decrease in total immobility time in the forced swimming test [107], similar to animals treated with imipramine. In addition, the study was supplemented with in vitro testing, where inhibition of the enzyme monoamine oxidase was observed, both in its A form and to a lesser extent in its B form [104]. MAO-A and MAO-B inhibitors are used clinically for the treatment of psychiatric and neurological disorders, respectively [116]. This activity has been proposed as another mechanism for the action of berries in mental disorders, as it is related to increased levels of serotonin, dopamine, and noradrenaline.

In addition, human studies related to blueberry and red berry supplementation have shown that a higher intake of these foods is associated with a lower risk of depression [85, 86]. Similarly, studies in mice have shown similar effects with the consumption of red berries, observing a reduction in depressive-like behaviors [87, 88] (**Table 3**).

5.3 Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive memory loss, as well as cognitive decline [117] in which prevalence augments with age [118]. The neuropathologic changes underlying AD include senile plaques formed by the peptide β-amyloid and neurofibrillary tangles composed of hyperphosphorylated Tau protein that promotes synaptic dysfunction and neuronal death early and consistently [119].

Oxidative stress has been associated with the onset and progression of AD [120]. This is supported by the high vulnerability of neurons to reactive oxygen species (ROS) [121]. Oxidative stress can induce damage to membrane lipids, changes in glial and neuronal function, structural damage to DNA, synaptic dysfunction, and apoptosis [122].

Several studies have demonstrated the potential protective effect of blackberry fruits (*Rubus L.* subgenus *Rubus Watson*), in the prevention of age-related neurodegenerative disorders [123], specifically with PD. Berry fruits such as blackberry, black raspberry, blueberry, and strawberry are good sources of phytochemicals that provide protection against neurological disorders [93].

Extracts of black currant have been shown to inhibit the formation and spread of β-amyloid [124] and ROS fibrils. Supplementation of blackberry in in vitro studies has been reported to exhibit potent anti-inflammatory and antiproliferative properties [125, 126]; also, the consumption of blueberries is related to neuronal augment in the hippocampus [5].

Recently a neuroprotective effect of anthocyanins has been observed in a model of AD induced by streptozotocin that resulted in a cognitive deficit (in short-term memory and spatial memory), as well as dysfunction in the activity of the enzyme acetylcholinesterase, while inducing lipid peroxidation and a decrease in antioxidant enzymes in the cerebral cortex [127]. These alterations were attenuated in the group administered with anthocyanins. Similarly, it has been observed that blueberry powder (*Vaccinium* sp.) supplementation in patients with Alzheimer's disease and cognitive decline reduces the self-reported inefficiencies in daily functioning [90] (**Table 3**).

5.4 Parkinson's disease

Parkinson's disease (PD) is characterized by tremors, stiffness, and akinesia. It is caused by the progressive degeneration of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies. Many Parkinson's risks and preventive factors have been investigated. The onset of this disorder has been associated with exposure to certain pesticides and heavy metals [128], tobacco consumption [129], and coffee consumption [130], among other environmental factors. While current treatments have shown effectiveness in early management of the motor symptoms of the disease [131] and both surgery and deep brain stimulation are useful, PD is currently not yet curable [132]. A diet enriched in phenolic compounds has been shown to have some efficacy in relieving Parkinson's symptoms [133]. Most of the studies related to fruit consumption and disease focus on supplementation with blueberries, strawberries, black currant, and grapes, due to their powerful antioxidant effects related to their high content of polyphenols and anthocyanins [134].

Cell models have reinforced studies of neurodegenerative disorders, recently demonstrating that anthocyanins from grape seed, blueberry, and mulberry enhance mitochondrial function [135] and suppressed dopaminergic cell death caused by rotenone (insecticide and pesticide) in mitochondrial respiration. This has suggested that anthocyanins may alleviate neurodegeneration in PD by improving mitochondrial function. In addition, polyphenols are able to ameliorate inflammatory responses associated with glial activation [136]. Phenolic compounds are known for their ability to eliminate reactive oxygen species (ROS) due to their antioxidant action; however, since their concentrations in the brain are lower than those of endogenous antioxidants, it has begun to be seen that they also exert their neuroprotective effects through additional mechanisms [137, 138], highlighting the inhibition of MAO, in its two forms, A and B [77, 104]. At the preclinical level, one of the most widely used models in PD research is the administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that causes a severe Parkinson's-like syndrome in humans, monkeys, and mice [139–142]. It has been observed that daily administration of

resveratrol (red wine polyphenol) in male mice C57BL/6 prevented a decrease in striatal dopamine and maintained striatal tyrosine hydroxylase levels. In addition, mice that received resveratrol as pretreatment showed a greater number of immunopositive tyrosine hydroxylase neurons, indicating the protective role of resveratrol over nigral neurons [143]. In the same disease model, it was observed that blueberry extract attenuated behavioral impairment (motor coordination) as well as decreased levels of malondialdehyde in the brains of mice [92]. These data reveal the ability of resveratrol and polyphenols present in blueberry extract to counteract the toxic effects of MPTP administration and in the near future may be used as a complementary neuroprotective therapy (**Table 3**). Current PD therapies act by controlling the disease's symptoms, but do not slow the underlying neurodegeneration in the brains of PD in patients [135]; this is an opportunity to use functional foods as adjuvant therapy in the presence of disease.

5.5 Human cognition

Polyphenols present in berries have also been associated with cognitive amelioration and neuronal function, as is the case with grape juice, which in both young [144] and older adults [145] ameliorate neurocognitive functions of memory, attention, and calmness, compared to the placebo group. In this same regard, in mothers (40–50 years) of preadolescent children, an association of grape juice consumption has been observed (≥30 h/week 355 ml, during 12 weeks) with subtle augment in immediate spatial memory and safer driving behavior in a virtual simulator [146]. At the same time, it was found that, in a double-blind crossover design of children (7 and 10 years old), supplementation of 15 or 30 g freeze-dried wild blueberry powder significantly ameliorates word acquisition and recognition, as well as the ability to overcome the effects of response interference [147].

In a pilot study in healthy young adults in both genders (18–35 years old), it has been observed that the acute administration of black currant juice (500 mg/day of polyphenols, supplemented only 1 day per week, during 31 days) exerts an anxiolytic-like effect, as well as ameliorates alertness, less fatigue, and reaction speed [94].

In a randomized, double-blind placebo-controlled trial, dietary blueberry of 24 g/day for 3 months raised the cognition in tests of executive function in adults between 60 and 75 years old of both sexes by increasing accuracy during task switching and reduced repetition errors during word-list recall [148]. The positive effects on cognition have been related to activation of the prefrontal cortex using functional magnetic resonance imaging [149]; therefore, the administration of blueberry to have the same effects on these tasks could be exercising greater activation of this structure to raise cognition. Another study found that daily consumption of 6 and 9 ml/kg for 12 weeks of blueberry (*Vaccinium angustifolium* Aiton) juice exerted neurocognitive benefits measured by California Verbal Learning Test-II (CVLT) augmented associate learning and word-list recall in older adults of both sexes who had experienced age-related memory decline [145]. Similarly, randomized controlled trial has shown that dietary berry juice (200 ml/day) for 12 weeks ameliorate memory and cognition in adults (70–80 years old) with cognitive impairment measured using a battery Rey Auditory Verbal Learning Test (RAVLT) [150].

Furthermore, a randomized, double-blind, placebo-controlled study showed that the daily administration of two capsules (10o mg) of a purified extract of blueberry (wild blueberry extract) for 3 months raised episodic and working memory in older adults of both sexes [151]. Additionally, a randomized, single-blind, parallel group design showed that the acute consumption of 200 ml of wild blueberry drink (253 mg anthocyanins) in healthy children aged 7–10 years significantly enhanced the memory and attentional aspects of executive function with respect to the placebo group 2 h after consumption; therefore, the consumption of

the wild blueberry drink during the critical period of development (as is the case of childhood) could provide acute cognitive benefits [152]. Therefore, a double-blind, counterbalanced, crossover intervention study showed that acute supplementation with haskap berry extract "*Lonicera caerulea* L." (200 and 400 mg anthocyanins) raised the episodic memory and exerts benefits in cognitive performance following a single acute dose in older adults compared to placebo [153].

These findings support that the consumption of berries produces beneficial effects on cognition in humans, which are probably related to the effects of the berries on the nervous system. For example, blueberry diets are associated with enhanced working memory which is accompanied by an increase in the neurogenesis of the hippocampus [17]. A randomized, controlled, double-blind, crossover studio showed that the administration of 766 mg total blueberry polyphenols in healthy young men reduced neutrophil NADPH oxidase activity at 1, 2, 4, and 6 h after consumption [154]. In this sense, NADPH oxidase has been shown to play an important role in oxidative stress induction in the brain [155], because it uses oxygen and NADPH to generate superoxide [156]. Therefore, the administration of blueberry could be generating a reduction of superoxide and indirectly preventing oxidative stress events a long term. The mechanisms by which flavonoids and polyphenols exert these actions on cognitive performance are still being studied, including evidence suggesting that they can increase brain blood flow, as well as modulate the activation state of neuronal receptors, signaling proteins, and gene expression [157].

6. Berry side or toxicity effect

According to our knowledge, there are some reports relating berry consumption in humans with side effects or toxicity. Data of toxicity in vivo was reported in 1997, in a study of the relation between flavonoid intake and subsequent cancer risk in 9959 Finnish men and women, aged 15–99 years and who are initially cancer free. Food consumption and dietary history method calculated the consumption of lingonberries, blueberries, black currants, raspberries, and gooseberries. People with higher consumption of berries were found to have a high risk of lung cancer. Apparently, the phenolic compounds produce toxicity proliferating cancer cells, but are not toxic in healthy cells [49].

Another study of 5-weeks-old Swiss Webster male mice, supplemented with lyophilized nightshade berries (*Solanum dulcamara*, 8 g/kg) with two different stages of maturity, showed that immature fruit supplementation produced gastrointestinal lesions; however, this condition was not observed in mice administered with mature lyophilized fruit. The authors concluded that these effects were attributed to the presence of saponin in the immature fruit [158]. In 2015, the first toxicity report by *Solanum dulcamara* was reported in a dog puppy (Labrador Retriever); the toxicity was attributed to steroidal glycoalkaloid solanine. After causing vomiting to the dog, dried stems and immature berries were observed, and gastric contents were evaluated by a local botanist identifying *Solanum dulcamara* intake, concluding that dog poisoning was due to the consumption of this fruit [159].

Another report was in 2009, when dozens of dead cedar waxwings in Thomas County, Georgia, USA, were found. In this case report, after evaluating five birds, the investigation group observed pulmonary, mediastinal, and tracheal hemorrhages and also found berries (*Nandina domestica* Thunb.) intact and partly digested into the gastrointestinal tracts. Due to their voracious feeding behavior, these birds ingested toxic doses of *N. domestica* and at the same time high concentrations of cyanide present in fruit berry [160]. It is important to note that *S. dulcamara* and *N. domestica* species are found wildly and are not consumed by humans.

Regarding berries supplementation and synergy, it is recently reported that gallic acid, quercetin, ellagic acid, and cyanidin have a market antioxidant activity [161, 162], due to the synergistic effects between the numbers of aromatic ring mixtures. In addition, polyphenols present in berries can interact between them, improve their antioxidant properties, and, therefore, increase human's health benefits [162]. According to our knowledge, no studies were found related with pharmacological interactions and berry supplementation. It is necessary to carry out studies involving pharmacological molecules, berries' activities, and their phenolic compounds in order to generate new therapies and identify the existence of side or toxic effects.

7. Final comments

According to the research reported in this chapter, the supplementation of berries and their bioactive compounds as flavonoids, polyphenols, and anthocyanin suggests a potential health benefit for human nutrition.

The objective of this research is to contribute with knowledge to the development of new strategies for the treatment of diseases such as anxiety, depression, AD, and PD, which includes natural products, particularly berry fruits that work as preventive or coadjuvant therapy in the treatment of these diseases.

A further evaluation of fruits berry supplementation in neural processes is required, as well as the identification of the effect of each particular bioactive compound on psychiatric and neurological disorders. More studies will be necessary to identify the mechanisms of action of this substance. It is also important to understand the scope in other neural processes and their application, effectiveness, synergy, pharmacological interaction, and side or toxic effects at clinical and preclinical levels of studies.

8. Conclusions

The present chapter evidenced a number of investigations in vivo related with the use of different berry fruit supplement doses, not only in humans but also in animal models. These results suggest the potential health effect of berries due to bioactive compounds mainly flavonoids, polyphenols, and anthocyanins, used commonly for its antioxidant capacity. According to our knowledge, the cases reported in the literature by animal toxicity are related with the consumption of wild berries. In humans the relationship between phenol compound consumption and lung cancer has been reported; however, there is no evidence of side or toxic effects related with berry supplementation or their bioactive compounds, and pharmacological interaction related to their consumption due to no dietary intervention studies has been reported.

In addition, berry consumption has shown to be effective in a number of cardiovascular and metabolic diseases, and also recent investigations are proposed for the management of berry fruit supplementation as neuroprotector and the reduction of symptoms in diseases such as anxiety, depression, AD, and PD, among others. The use of this biological berry compounds might promote an alternative for prevention and give excellent opportunities for human nutrition as a functional food and nutraceutical. Future research in this field is necessary, in order to clarify and support the evidence of the effects of flavonoids, polyphenols, and anthocyanins at the brain level, as well as their potential direct and indirect mechanisms of action.

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Conflict of interest

The authors declare no conflict of interest.

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