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İKÇÜSBFD

DERLEME / REVIEW

Potential Effects of Anthocyanin on Depression: A Review

Antosiyaninin Depresyon Üzerindeki Potansiyel Etkileri: Bir Derleme

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Abstract

Nutrition is helpful in preventing depression and reducing its symptoms in depressed patients. This is because when the pathophysiology of depression is examined, deficiencies in certain nutrients are observed. Oxidative stress is also known to cause inflammation, which can contribute to the pathophysiology of the disease. We examined the effectiveness of anthocyanin, which is known to be an antioxidant, on depression. Related articles were searched in the Web of Science database. The combinations of the following terms were used for the search: "Anthocyanidin" OR "Anthocyanidins" OR "Anthocyanin" OR "Leucoanthocyanidins" AND "depression". 71 abstracts were reviewed, 55 full-text articles were examined, and 7 papers met all of the inclusion criteria. According to these studies, anthocyanin may offer protection against depression and can alleviate its symptoms. Oxidative stress and deterioration in neurogenesis are the mechanisms behind inflammation. Various human, animal, and in vitro studies demonstrate that anthocyanins possess strong anti-inflammatory and antioxidant properties.

Keywords: Anthocyanins, depression, antioxidant.

Öz

Beslenme, depresyon hastalarında depresyonun önlenmesinde ve semptomlarının azaltılmasında yardımcıdır. Çünkü depresyonun patofizyolojisi incelendiğinde bazı besinlerde eksiklikler görülür. Oksidatif stresin ayrıca hastalığın patofizyolojisine katkıda bulunabilecek inflamasyona neden olduğu bilinmektedir. Antioksidan olduğu bilinen antosiyaninin depresyon üzerindeki etkisi incelenmiştir. Web of Science veritabanında "Antosiyanidin" VEYA "Antosiyanidinler" VEYA "Antosiyanin" VEYA "Leucoantosiyanidinler" VE "depresyon" terimleri taranmış ve bu tarama sonucunda çıkan makaleler incelenmiştir. Tarama sonucunda 71 makale bulunmuş ve özeti incelenmiştir. Uygun görülen 55 makalenin tam metini incelenmiş ve 7 makale dahil edilme kriterlerinin tümünü karşılamıştır. Bu çalışmalara göre, antosiyanin depresyona karşı koruma sağlayabilir ve depresyonun semptomlarını hafifletebilir. Oksidatif stres ve nörogenezdeki bozulma inflamasyonun arkasında yatan mekanizmalardır. Çeşitli insan, hayvan ve in vitro çalışmalar, antosiyaninlerin güçlü anti-enflamatuar ve antioksidan özelliklere sahip olduğunu göstermektedir.

Anahtar Kelimeler: Antosiyaninler, depresyon, antioksidan.

1. Giriş

The term "depression" is defined as a condition of pessimism and low mood. "Depression" is derived from the Latin word "depressus" and means "to suppress or to be low." The symptoms of depression include constant and intense negative emotions, difficulty with daily activities, and a lack of mental and physical energy (1). Over 300 million people worldwide suffer from depression (4.4% of the adult population) (2). It has also been reported that there has been a significant increase in these rates with the COVID-19 pandemic (3,4). There are several risk factors for depressive disorders, including gender, income, social status, alcohol and drug use, genetic and epigenetic mechanisms, stress, inflammation, and dietary habits (5).

During the last few years, scientific research has demonstrated a connection between mental health and nutrition, and scientists have concluded that mental and physical health are intertwined (6,7). Depressive disorders can be reduced through improvements in diet, which is a manageable risk factor for depression (5). Foods can have an effect on the chemical composition of our brains by altering our mental state. Microbiota, neurotransmitters, and certain compounds in foods play a significant role in mood regulation (8). It has been determined in human studies that dietary components have antioxidant/ anti-inflammatory activities and improve cognitive and depression outcomes (9). It is well-known that dietary polyphenols are among the most important antioxidants

in foods. Numerous dietary polyphenols have been linked to the reduction of depression symptoms. Flavonoids, an influential class of polyphenols, have antidepressant content and are protective against depressive symptoms (10). Anthocyanins are natural flavonoids, meaning "blue flower" in Greek (11). It is abundant in seeds, flowers, leaves, and fruits in plants. There are numerous examples of fruits and vegetables that turn from green to purple or red when ripe and accumulate anthocyanins (12). The biological activities of anthocyanins have been extensively studied; researchers have found that components in the anthocyanins possesses antimutagenic, antioxidant, anti-inflammatory, and antimicrobial properties (13). This review examines the effectiveness of anthocyanin on depression-related symptoms in light of the relevant literature, taking into consideration the pathophysiological pathways that contribute to depression.

1.1. Relationship Between Depression and Anthocyanin

An important aspect of depression's pathophysiology is the fact that it is a complex disorder, with multiple mechanisms involved (10). These mechanisms include disorders in the hypothalamic-pituitary-adrenal axis (HPA), biogenic amine hypothesis, neuroinflammation, genetic, immune and environmental factors. Decreases in an individual's neurogenesis, abnormalities in the second messenger system, and elevated corticotropin-releasing factor (CRF) levels may also contribute to depression (14). As of right now, depression has been associated with oxidative stress, which occurs when the ratio of reactive species overflows and the antioxidant defenses fail to detoxify these reactive components, resulting in potential damage to lipids, proteins, and DNA (15). In spite of this, the precise mechanism responsible for the development of depression and progression of the disease after it develops remains unclear (10). Several in vivo studies have investigated the anti-depressant properties of natural flavonoids and carotenoids, with largely positive outcomes (16). The flavonoids rutin, quercetin, apigenin, epigallocatechin gallate, myricetin, hesperidin, kaempferol, naringenin, formononetin, beta-carotene, beta-cryptoxanthin, lutein, and genistein have been demonstrated to have antidepressant properties in animal model (10). In recent studies, there has been a negative association between phenolic acid, flavanones, and anthocyanin intake and depression symptoms (10,17,18). A high antioxidant activity is attributed to anthocyanins, which have the potential to damage DNA, activate estrogen, inhibit enzymes, inhibit inflammation, and inhibit the peroxidation of lipids (19–21).

There is increasing demonstration to suggest that increased monoamine oxidase (MAO) level is associated with different neurological disorders, including depression (22). Changes in mood can result from diminished levels of monoamine neurotransmitters in the brain. As a result of the increase in monoamine neurotransmitters and their receptors, depression can be treated; this is the basis for using antidepressants as a first-line treatment in the treatment of major depression. (19). It has been reported that anthocyanidins isolated from hibiscus flowers inhibited the MAO-A and MAO-B activities of mice in a study based on forced swimming and tail suspension tests. In their study, hibiscus flower extract significantly alleviated depressive-like behavior, primarily via modulation of the serotonergic, noradrenergic, and dopaminergic systems (23). Similarly, another study showed that purified anthocyanins from purple cauliflower (PAPC) significantly improved depression-like behaviors, increased level of monoamine neurotransmitters, and inhibited monoamine oxidase in the mice's brain. PAPC increased the monoamine neurotransmitter level by inhibiting MAO and improved depression. It promoted neurogenesis and dendrite

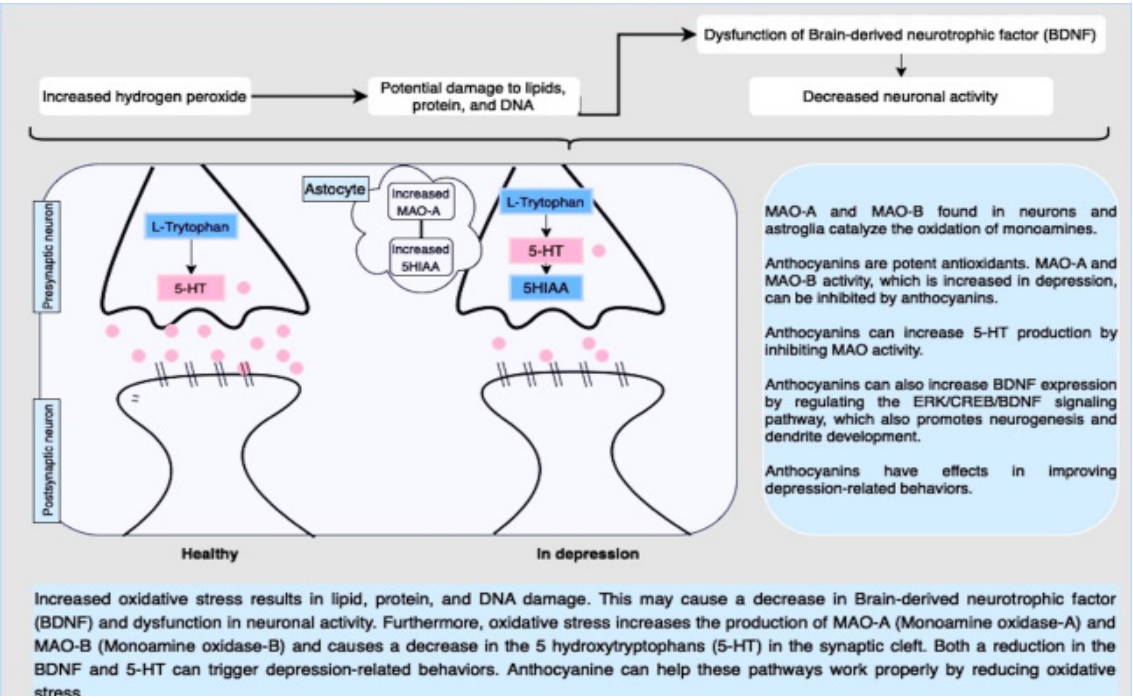

Figure 1. MAO and depression (Created by the authors based on information highlighted in the study of Dreiseitel et al. (2009) and Fang et al. (2020))

development as a result of increasing BDNF (Brain-derived neurotrophic factor) expression by regulating the ERK/CREB/BDNF signaling pathway (Figure 1) (18, 22).

2. Methods

Related articles were searched in the Web of Science database. Studies were systematically and comprehensive reviewed using inclusion and exclusion criteria (Fig 2). A combination of the following terms was used to conduct the search: "Anthocyanidin" OR "Anthocyanidins" OR "Anthocyanin" OR "Leucoanthocyanidins" AND "depression". Inclusion criteria were studies evaluating the relationship between nutrients and Chronic Fatigue Syndrome (CFS) in the English language and open access articles were scanned using associated keywords without year limitation. As an additional step, the references of the last remaining articles related to the subject were manually scanned. Articles that did not directly mention the relationship of anthocyanins to depression and that evaluated all flavonoids in plants together were excluded (Figure 2).

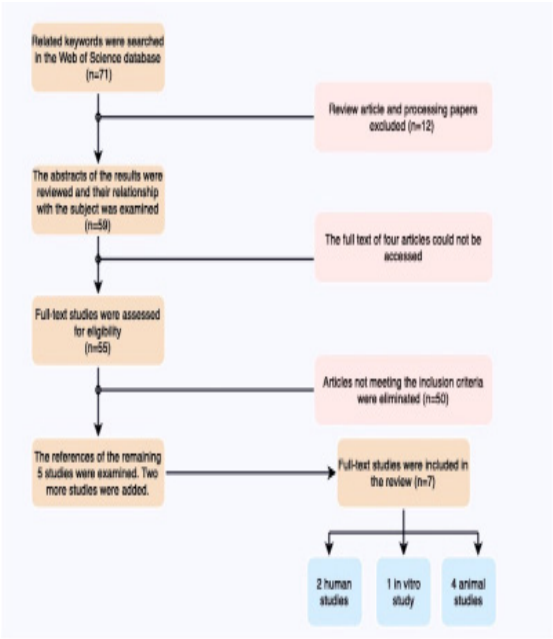

Figure 2. Flow chart of the study

3. Results

In this review, the full texts of seven studies were reviewed. Two of these are human studies, one of these is an in vitro study, and four are animal studies (Table 1).

Chang et. al. (24) evaluated the flavonoid consumption of 10752 individuals with incident depression between the ages of 36-80. The consumption of total flavonoid and subclasses (anthocyanins, flavones, flavanones, flavan-3-ols, flavonols, proanthocyanidins, and polymeric flavonoids) was evaluated every 2-4 years by validated food-frequency questionnaires. Participants were categorized into five quintiles based on their flavonoid consumption. Participants' depression-related symptoms were evaluated using the 10-item version of the Center for Epidemiologic Studies Depression (CESD-10), 5-item Mental Health Index, and the 15-item version of the Geriatric Depression Scale (GDS-15). It was found that flavonol, flavone, and flavanone intakes inversely correlated with depression risk. In a comparison of the consumption of flavonoid-rich foods among quintiles, the risk of depression in the quintile 5 group was reduced by 7-10% compared to the quintile 1 group. According to adjustment for age and response to the survey, the group with the highest anthocyanin and proanthocyanidin intake (quintile 5) had a significantly lower risk for depression than the group with the lowest intake (quintile 1). The highest anthocyanin and proanthocyanidin intake group showed significant reductions in depression symptoms when compared with the quintile 1 among participants with late-life depression (>65 years), as assessed by physician diagnosis, regular use of antidepressant medications, or severe depressive symptoms.

Another study (10) examined the relationship between dietary flavonoid consumption and depression symptoms among individuals ages 45-69. In this study, 1703 participants were divided into two groups: control subjects (n = 1703) and depressed subjects (n = 487). A semi-quantitative food frequency questionnaire was used to assess daily dietary intake, including macronutrients, flavonoids and carotenoids. Depressive disorder screening was conducted using the Beck Depression Inventory-II and Center for Epidemiologic Studies-Depression Scale. As a result of the study, it was determined that individuals with depressive symptoms consumed less total flavonoids such as anthocyanins, flavonols, and isoflavonoids. While the mean consumption of Anthocyanin in the control group was 8.74 ± 0.19, this value was 7.29 ± 0.31 in depressed individuals (p=0.00). According to a multivariate regression analysis, zeaxanthin, phenolic compounds, flavones, lycopene, and anthocyanins were negatively related to depressive symptoms. The study also revealed that most flavonoids bind strongly to two important targets in depression, monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B).

Dreiseitel et. al. (23) determined the affinity of anthocyanin for MAO-A and MAO-B using in vitro evaluation method in their study. In the study, proanthocyanidins, anthocyanidin-3-glycosides, anthocyanidin- 3,5-diglucosides, 25 anthocyanidins, and phenolic metabolites were examined using a luminometric MAO assay. Anthocyanidins exhibited the highest inhibition of MAO-A as indicated by their IC50 values (Mean IC50 value is 29.2 ± 4.4), Anthocyanidin-3-glycosides (Mean IC50 value is 36.9 ± 5.8), Anthocyanidin-3,5-diglucosides (Mean IC50 value is 97.3 ± 31.0). For MAO-B, IC50 values indicated the strongest inhibition by anthocyanidins (Mean IC50 value is 32.7 ± 10.5), Anthocyanidin-3-glycosides (Mean IC50 value is 36.8 ± 5.2), Anthocyanidin-3,5-diglucosides (Mean IC50 value is 155.7 ± 84.4). As a result of the study, it was determined that anthocyanins and their aglycones can regulate neuronal activity by inhibiting MAO and provide improvements in depression-related symptoms.

Varadinova et. al. (25) investigated the pharmacological activities of anthocyanins on experimental depression parameters. Forced Swimming Test and 8-arm radial maze test were applied to Male Wistar rats weighing 270-330g. The rats were divided into two groups. While aqueous anthocyanin solution (once daily with anthocyanins extracted from red wine (Dr. Winfred Berr; 200 mg/kg p.o) was given to one group, physiological solution was applied to the another group for 24 days. They were

Table 1. Summary of studies showing the relationship between anthocyanin and symptoms of depression

Author (Year)	Participant	Material	Evaluation Scale	Results
Chang et. al. (2016) 24	Age: 36-80 y 10752 incident deppression case	Human	Total flovonoid and subclasses were evaluated by validated food- frequency questionnaires Depression symptomps were assessed by using Mental Health Index, CESD-10 and GDS-15 According to the flavonoid consumption of the participants, they were divided into 5 quintiles.	It has been determined that the risk of depression (especially late-life (>65 years) depression) decreases as the consumption of anthocyanin and proantocyanidine increases.
Park et. al. (2021) 10	Age: 45-69 y	Human	Dietary intake were assessed semi-quantitative food frequency questionnaire. Depressive disorder screening was conducted using the Beck Depression Inventory- II and Center for Epidemiologic Studies-Depression Scale.	Individuals with depressive symptoms consumed less total flavonoids such as anthocyanin, flavonols and isoflavonoids.
Dreiseitel et. al. (2009) 23	-	In vitro	Affinity of anthocyanins detected for MAO isoforms A or B. Using a luminometric MAO assay, 25 anthocyanidins, anthocyanidin-3-glycosides, anthocyanidin- 3,5-diglucosides, proanthocyanidins, and phenolic metabolites were examined.	Anthocyanins and their aglycons achieve MAO inhibition in vitro that is compatible with central nervous functionalities
Fang et. al. (2020) 19	Specific pathogen-free female mice	Animal	Purified anthocyanin from purple cauliflower (PAPC) on chronic unpredictable mild stress (CUMS) induced mice model of depression were investigated. After three weeks of CUMS induced, the mice were intragastric administration with PAPC for six weeks.	PAPC treatment significantly improved depression-like behaviors in mice following CUMS, increased monoamine neurotransmitter content and inhibited MAO in the brain. It also increased the expression of tyrosine receptor kinase B, BDNF, ERK1/2 and CREB in hippocampus.
Varadinova et. al. (2007) 25	Male Wistar rats	Animal	The rats were divided into two groups. Group 1; Aqueous anthocyanin solution (once daily with anthocyanins extracted from red wine (Dr. Winfred Berr; 200 mg/ kg p.o) for 24 days Group 2; Physiological solution was applied for 24 days. They were exposed to light stress for the first 14 days and the FST test was performed on the 15th day and the 8-arm radial maze test was performed on the 15th and 25th days.	Immobility time was significantly reduced in the anthocyanin group compared to the stress group. The results demonstrate a significant improvement in the spatial memory of the rats (is this in the 8 arm radial maze test, treated with anthocyanins. There is an important decrease in the number of errors done by the II group compared to the I group.
Shewale et. al. (2012) 26	Adult male Swiss Albino mice	Animal	Methanol extract containing anthocyanins (MHR) (30 and 100 mg/kg) and anthocyanidins (AHR) (30 and 100 mg/ kg) of Hibiscus rosa-sinensis flowers was used Mice were evaluated using behavioral tests (TST and FST).	The animals completed the TST and the FST in less time when given the extract in addition to the medicine.
Xu et. al. (2010) 27	Male ICR mice	Animal	Mice were fed with standard diet and water ad libitum and were allowed to acclimate 7 days before they were used. Mice were administered vehicle, proanthocyanidin (12.5, 25 and 50 mg/kg) or imipramine (10 mg/kg) for 1 day (Day 1) and 7 days (Day 7).	Proanthocyanidin significantly reduced immobility time in both tail suspension and forced swimming tests in a dose-dependent manner. Proanthocyanidin produced a marked increase of 5-HT levels at 25 and 50 mg/kg Proanthocyanidin exerted an antidepressant effect by affecting the monoaminergic neurotransmitter system.

Abrevations: CESD: Center for Epidemiologic Studies Depression; GDS: Geriatric Depression Scale; MAO: monoamine oxidases; BDNF: Brain-derive neurotrophic factor; ERK1/2: Extracellular-regulated kinase ½; CREB: cAMP-responsive binding element; TST: Tail suspension test; FST: Forced swim test

exposed to light stress for the first 14 days and the FST test was performed on the 15th day and the 8-arm radial maze test was performed on the 15th and 25th days. The results demonstrated a significant improvement in the spatial memory of the rats (is this in the 8 arm radial maze test), treated with anthocyanins. There was an important decrease in the number of errors done by the II group compared to the I group.

Shewale et. al. (26) evaluated the anti-depressant activity of methanol extract of Hibiscus rosa-sinensis flowers containing anthocyanins (MHR) (30 and 100 mg/kg) and anthocyanidins (AHR) (30 and 100 mg/kg) using adult male Swiss Albino mice. Behavioral tests such as tail suspension test (TST) and forced swim test (FST) associated with depressive symptoms were administered to mice. As the study group received imipramine (10 mg/kg) (It is a tricyclic antidepressant used to treat depression) as a positive control, the results showed similar results to those found in the imipramine group, with a significant reduction in immobility time in TST and FST. The extract significantly decreased TST and FST by reducing the effects of Haloperidol, a D2-like dopamine receptor antagonist, prazosin, an α-adrenoceptor antagonist, and p-chlorophenyl alanine, a serotonin synthesis inhibitor. Anthocyanin has been demonstrated to regulate depression-related behaviors by affecting dopaminergic, noradrenergic, and serotonergic systems.

Xu et. al. (27) administered 12.5, 25, and 50 mg/kg of proanthocyanin or 10 mg/kg imipramine to male ICR mice and monitored depression-related behaviors using behavior tests. They also measured 5-hidroksitriptamin levels in different parts of the brain. Both tail suspension and forced swimming tests were significantly reduced by oral administration of proanthocyanidin at doses of 25 and 50 mg/kg for 7 days. Furthermore, proanthocyanidin produced a marked increase in 5-HT levels when administered at

25 and 50 mg/kg. Based on the findings of the study, proanthocyanidin could exert antidepressant effects by affecting monoaminergic neurotransmitters.

4. Discussion

Mental diseases have a greater burden on health, social and economic, and cause negative effects on the health of the individual by causing disability. Depression has a broad spectrum among mental illnesses. However, relatively few longitudinal studies are available to evaluate dietary factors that may play a significant role in depression's etiology (28). In both cross-sectional and longitudinal studies, the Mediterranean diet and a diet rich in anti-inflammatory and antioxidant nutrients have been associated with a reduction in depression risk (29–31). Inflammation may develop as a result of oxidative stress. Increasing oxidative stress causes the oxidation of proteins, DNA, lipids, and many molecules in the body and triggers neuron degeneration, especially in brain cells. In brain tissues, ROS can regulate synaptic and non-synaptic communication between neurons, resulting in neuroinflammation and cell death (32). It is known that the increase in proinflammatory cytokine levels causes pathologies in neurotransmitter metabolism. There are several different mechanisms of inflammation caused by oxidative stress. One of these is the mechanism by which increased ROS as a result of decreased tripeptide glutathione (GSH), an intracellular thiol antioxidant, can lead to immune response imbalances and inflammation (33). The release of PRDX2, an intracellular enzyme, is also induced by inflammation. Upon release, it acts as an inflammatory mediator redox-dependently, stimulating macrophages to produce and release tumor necrosis factor-alpha (TNF-alpha) (34). Kim et al. (31) found that there was an increase in blood circulation of tumor necrosis factor-α, interleukin-6, interleukin-1β, and other acute phase proteins in depressed individuals. Similarly, Howren et al. (35) as a result of their meta-analysis, found that many studies in the literature emphasized increased proinflammatory cytokine levels in individuals with depression. Here, it can be thought that an important mechanism is a pathway mediated by the endothelial dysfunction that develops with the release of proinflammatory cytokines (36). Endothelial cells are cells that secrete BDNF. It is emphasized that endothelial dysfunction results from inflammation that causes inhibition of BDNF expression and this causes neuronal dysfunction (37). BDNF is effective in the proper functioning of many neuronal mechanisms. It is involved in the neurogenesis, differentiation, and maturation of neurotransmitters; A major effect of this substance is the modulation of synaptic plasticity and the proper functioning of the central and peripheral nervous systems (38). Depression is associated with decreased BDNF levels in the blood samples, prefrontal cortex, and hippocampus (39–41). Impairments in tryptophan metabolism as a result of increased levels of proinflammatory cytokines is the second mechanism in the increase of depressive symptoms due to inflammation. As an essential amino acid, tryptophan plays a major role in the production of serotonin. While some of the tryptophan is metabolized in the liver via kynurenine, the remaining tryptophan is used for 5-HT synthesis. In cases where pro-inflammatory cytokines increase, tryptophan can be oxidized, which impairs serotonergic neurotransmission in the brain (42). As we emphasized in our previous review, 5-HT enters the serotonin synthesis pathway in the presence of pyridoxal 5 phosphate. During stress and inflammation, instead of serotonin release from tryptophan, tryptophan 2,3-dioxygenase and indoleamine 2,3-dioxygenase enzymes induce kynurenine synthesis (43). By causing deterioration in neurotransmitter pathways and a decrease in BDNF levels in the brain, the metabolic pathways we highlighted above suggest that oxidative stress can increase depression symptoms. It is concluded that a diet rich in antioxidant nutrients can regulate the symptoms of depression.

In addition to acting as antioxidants, anthocyanins also increase the activity of the antioxidant enzymes super superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). In a study by Bakuradeze et al. (44) individuals consumed anthocyanin-rich fruit juice for 8 weeks, and an increase in SOD levels was observed as a result of the study. They also found a reduction in CAD enzyme levels in their study. On the contrary, according to Kuntz et al. (42) the intake of anthocyanin-rich juices or smoothies increases plasma SOD and CAT activities, but does not affect SOD activity in erythrocytes after 14 days. In one study, after consuming 160 mg of anthocyanins twice daily for 24 weeks, plasma levels of oxidative stress biomarkers (8-iso-prostaglandin F2α (8-iso-PGF2α), 13-hydroxyoctadecadienoic acid (13-HODE)) were significantly reduced ($p<0.05$). Several studies have demonstrated that anthocyanin activates the endogenous antioxidant system in diabetics in order to scavenge excess free radicals and reduce oxidative damage (45). In another study, one group received a placebo while the other three groups received 40, 80, and 320 mg of anthocyanins per day, respectively. At week 12, serum IL-6 and TNF-α and urine 8-iso-PGF2α were moderately decreased in the group receiving 40 mg/day anthocyanin supplementation and were significantly reduced in the group receiving 80 mg/day anthocyanin supplementation. The group receiving 320 mg/day anthocyanins showed greater improvement in reducing serum IL-6 and TNF-α, MDA and urinary 8-iso-PGF2α, 8-OHdG compared to those receiving 80 mg and 40 mg daily. Morever, supplementation with anthocyanin at 320 mg/day for six weeks significantly improved T-SOD ($p<0.05$), although no other cytokines were significantly improved. Results from these studies demonstrated that anthocyanin induces anti-inflammatory and antioxidative effects in a dose-dependent manner (46).

5. Conclusion

In conclusion, in the light of the literature, the mechanism of inflammation caused by oxidative stress and the deterioration in neurogenesis due to this was mentioned above. It is emphasized that increased proinflammatory cytokine levels in depression may be a trigger for depressive symptoms. As a consequence, it is hypothesized that an anti-inflammatory nutrient-rich diet may help patients suffering from depression to achieve a better outcome. This review has demonstrated that anthocyanins have high anti-inflammatory effects in humans, animals, and in vitro studies, and may be effective in reducing symptoms associated with depression. It is thought that in individuals suffering from depression, anthocyanin has been shown to provide both preventative and therapeutic benefits.

6. Contribution to the Field

In this review, it has been revealed in the light of various human, animal and in vitro studies that anthocyanins

have high anti-inflammatory effects and may be effective in reducing symptoms associated with depression. Anthocyanin is thought to provide both preventive and therapeutic benefits in individuals suffering from depression. Anthocyanin's importance in depression is clear, but studies are limited. Therefore, we think that this review will shed light on future studies.

Conflict of Interest

There is no conflict of interest regarding any person and/or institution.

Authorship Contribution

Concept: GA, EK; **Design:** GA, EK; **Supervision:** GA, EK; **Funding:** GA, EK; **Materials:** GA, EK; **Data Collection/ Processing:** GA, EK; **Analysis/Interpretation:** GA, EK, AHD; **Literature Review:** EK, GA; **Manuscript Writing:** EK, GA, FY, SUH, AHD; **Critical Review** EK, GA.

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