

Antidepressant and anxiolytic-like effect of anthocyanin-containing preparations in animal models: a review

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Abstract

Depressive and anxiety disorders are two of the most life-debilitating mental health problems, affecting millions worldwide. Despite both conditions being manageable with medication, they often come with unwanted side effects. With rising attention to plant-based medications, flavonoids are one of the compounds eyed as phytochemicals that have potential antidepressant and anxiolytic properties. This review aims to summarize the results of studies exploring anthocyanin-containing preparations as antidepressants and anxiolytics in animal models

Keywords: Antidepressant, Anthocyanin-containing preparation, Anxiolytic, Mice, Rat,

Introduction

Mental health disorder is one of the most prevalent health problems, affecting 1 of 8 people in 2019 [1]. Mental health problems themselves encompass a range of diagnoses, most of which are characterized by abnormal thoughts, feelings and emotions, behaviors, and relationships with people. [2]. Among these disorders, depressive disorders are one of the most prevalent worldwide - roughly affecting 279.6 million people worldwide in 2019, causing a high health-related burden and ranked among the highest cause of years lost due to disability. Another major prevalent mental disorder that caused high health-related burdens and years lost to disability are anxiety disorders. In 2019, an estimated 301.4 million people are affected by it [3]

Even though both conditions are manageable with medications, they are often accompanied by many unwanted side effects across all classes of pharmaceuticals [4,5]. Furthermore, the efficacy of the medication is still disputed for mild and sub-threshold depression [6]. Thus, research into plant-derived flavonoids as antidepressants and anxiolytics is an ongoing subject due to its perceived less harmful side effects [7,8]

Anthocyanins are a group of pH-sensitive plant flavonoid that is well-known due to their conspicuous colors [9]. It has gained attention due to its many positive effects across multiple disease studies, both on animal models [10,11] and human subjects, which also show a profound effect on the central nervous system [12,13]. This review aimed to summarize the results of studies aiming to determine both the antidepressant and anxiolytic-like effects of anthocyanin-containing preparations in animal models with hopes of discovering new therapeutic options for both depressive and anxiety disorders alike.

Method

A literature search across Google Scholar, PubMed, and ScienceDirect was carried out with the combination of the following keywords and Boolean Operators: "(anthocyanin OR anthocyanin-rich) AND (anxiety OR anxiolytic) AND (rats OR mice OR animal model)" and "(anthocyanin OR anthocyanin-rich) AND (depression OR antidepressant) AND (rats OR mice OR animal model)". The literature search is limited to studies published within 10 years range (2012-2022) and written in English. The search is carried out from the 22nd of July to the 20th of August.

Result and Discussion

Anthocyanin

Anthocyanins are water-soluble plant metabolites that chemically belong to the polyphenol group. They produce vibrant colors that are both pH-sensitive and heavily dependent on the molecules attached to their main skeleton structure. These side structures also determined their biological activity [13].

The stability of anthocyanins depends on light, temperature, pH, and side structures – the last two that also determine their color. They're red in acidic pH and shift to blue in higher pH, but under basic conditions they easily degraded to brown oxidized compounds [14]

In plants, anthocyanins are derived from the amino acid phenylalanine [15]. It plays a wide array of protection roles, including antioxidant, a photoprotective agent, and free radical scavengers [16]

Anthocyanins have varying bioavailability as it was heavily influenced not only by their intrinsic bioavailability but also by the subject's enzymatic activities and also gut flora composition, making it vary across the population [17]

Antidepressant-Like Effect of Anthocyanin-Containing Preparations

In their 2015 study, Sacchet et al. observed that *Plinia trunciflora* fruit aqueous extract in mice showed comparable results at 800 mg/kg dosage to fluoxetine at 32 mg/kg dosage in reducing immobility time in tail suspension test (TST) [18]. A similar result was achieved by Gapski et al., whose results showed that blueberry extract at 300-400 mg/kg yielded results comparable to fluoxetine 10 mg/kg treatment in the same test [19]. Another study utilizing forced swimming test (FST) in rats shows that *Aronia melanocarpa* berry juice and imipramine both showed significantly reduced immobilization time, with a significant increase in swimming time from *Aronia melanocarpa*-treated group and climbing time from imipramine [20]. Similar outcome also showed by blueberry extract; when compared to diazepam, both showed a significant reduction in immobilization time in FST for Wistar rats [21]

Aside from TST and FST, antidepressant-like properties are also shown in rats exposed to chronic unpredictable mild stress (CUMS). In a study by Alamri [22], supplementation with *Crataegus aronia* extract on Wistar rats was able to ameliorate depressive episodes comparable to fluoxetine based on the urinary concentration of serotonin, norepinephrine, and dopamine. A similar effect was shown by purified anthocyanin from purple cauliflower; a 2020 study shows that said preparation is comparable with fluoxetine in reducing depressive-like behaviors in CUMS-exposed mice as indicated by their sucrose-preference test (SPT), FST, and elevated plus-maze test (EPM) results [23].

In animal disease models, anthocyanin also showed promising outcomes. Anthocyanin-containing extracts show positive anti-depressive effects in models of post-stroke depressed mice fed with maqui berry extract [24], mice with metabolic syndrome induced by high-palatable feed treated with *Vaccinium virgatum* fruit extract [25], scopolamine-induced learning and memory impaired rats fed with *Grewia asiatica* berry juice [26] and mice with neurochemical changes induced by lipopolysaccharides treated with blueberry extract [27].

Anxiolytics-Like Effect of Anthocyanin-containing Preparations

A study published in 2014 showed that anthocyanins purified from grape skin showed a significant anxiolytic effect on rats as indicated by the time spent in the open arm of EPM test [28]. This is supported by another study using *Aronia melanocarpa* berry juice, as shown by their open field test (OFT) and EPM results [20]. Similar results were also shown in tests with blueberry extract; a study done by Fernández-Demeneghi et al., showed an increase of time spent in open arms of EMP test, and a reduction of anxiety index was observed in Wistar rats [21].

This result extends to animal disease models; a 2020 study showed middle-aged rats with induced menopause via ovariectomy fed with cafeteria diet and treated with pomegranate extract also significantly spend more time in the open-arm section of EPM test by percentage [29]. Another study with scopolamine-induced learning and memory impaired rats shows that the group fed *Grewia asiatica* berry juice shows similar results to the diazepam-treated group in EPM and OFT tests [26].

However, a study published by Oliveira et al. did not show profound difference in results of OFT and EMP tests between *Vaccinium virgatum* fruit extract-treated group compared to the control group in mice with metabolic syndrome [25]. Another experiment utilizing anthocyanin-rich wheat on healthy rats even showed higher anxiety-like behavior in a study conducted in 2016. Janšáková et al., speculated that the high level of antioxidative activity from anthocyanin reduced available free radicals which disturb cell signaling, causing an increase in anxiety-like behavior [30].

Conclusion

Preparations containing anthocyanin has shown to exert antidepressant-like effect on model animals in multiple scenarios [18,19,20,21,22,23] and diseases [24,25,26,27]. While the majority of the test shows anthocyanins also have anxiolytic properties [20,21, 26, 29], some have shown no significant difference compared to the control group [25] or even outright negative results in form of higher anxiety-like behaviors [30].

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Disclosure of conflict of interest

The authors declared no conflict of interest.

References

- 1 Mental disorders [Internet]. Who.int. 2022 [cited 16 August 2022].
- 2 Diagnostic and statistical manual of mental disorders. Washington, DC: American Psychiatric Association Publishing; 2022.
- 3 Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet Psychiatry. 2022;9(2):137-150.
- 4 Khawam E, Laurencic G, Malone D. Side effects of antidepressants: an overview. Cleveland Clinic Journal of Medicine. 2006;73(4):351-353.

- 5 Guaiana G, Barbui C, Cipriani A. Hydroxyzine for generalised anxiety disorder. Cochrane Database of Systematic Reviews. 2010.
- 6 Cameron I, Reid I, MacGillivray S. Efficacy and tolerability of antidepressants for sub-threshold depression and for mild major depressive disorder. *Journal of Affective Disorders*. 2014;166:48-58.
- 7 Khan H, Perviz S, Sureda A, Nabavi S, Tejada S. Current standing of plant derived flavonoids as an antidepressant. *Food and Chemical Toxicology*. 2018;119:176-188.
- 8 Sarris J, McIntyre E, Camfield D. Plant-Based Medicines for Anxiety Disorders, Part 2: A Review of Clinical Studies with Supporting Preclinical Evidence. *CNS Drugs*. 2013;27(4):301-319.
- 9 Holton T, Cornish E. Genetics and Biochemistry of Anthocyanin Biosynthesis. *The Plant Cell*. 1995;:1071-1083.
- 10 Choirotussanijjah C, Notopuro H, Qurnianingsih E. Effects of Ethanol Extract of Rosa damascene on HbA1c Level and NF- κ B Expression in Diabetic Rats. *Indonesian Journal of Medical Laboratory Science and Technology*. 2021;3(2):146-157.
- 11 Itishom R, Wafa I, Budi D, Pratama N. Oral Delivery of Purple Sweet Potato (*Ipomoea batatas* L.) Extract-Loaded Carboxymethyl Chitosan and Alginate Nanocapsule in Streptozotocin-induced Diabetic Mice. *Indian Journal of Pharmaceutical Education and Research*. 2021;55(3):709-714.
- 12 Tsuda T. Dietary anthocyanin-rich plants: Biochemical basis and recent progress in health benefits studies. *Molecular Nutrition & Food Research*. 2011;56(1):159-170.
- 13 Riaz M, Zia-Ul-Haq M, Saad B. Introduction to Anthocyanins. *Anthocyanins and Human Health: Biomolecular and therapeutic aspects*. 2016;:21-33.
- 14 Mattioli R, Francioso A, Mosca L, Silva P. Anthocyanins: A Comprehensive Review of Their Chemical Properties and Health Effects on Cardiovascular and Neurodegenerative Diseases. *Molecules*. 2020;25(17):3809.
- 15 Taiz L, Zeiger E, Møller I, Murphy A. Fundamentals of plant physiology. New York: Oxford University Press; 2018.
- 16 Gould K. Nature's Swiss Army Knife: The Diverse Protective Roles of Anthocyanins in Leaves. *Journal of Biomedicine and Biotechnology*. 2004;2004(5):314-320.
- 17 Eker M, Aaby K, Budic-Leto I, Rimac Brnčić S, El S, Karakaya S et al. A Review of Factors Affecting Anthocyanin Bioavailability: Possible Implications for the Inter-Individual Variability. *Foods*. 2019;9(1):2.
- 18 Sacchet C, Mocelin R, Sachett A, Bevilacqua F, Chitolina R, Kuhn F et al. Antidepressant-Like and Antioxidant Effects of *Plinia trunciflora* in Mice. *Evidence-Based Complementary and Alternative Medicine*. 2015;2015:1-9.
- 19 Gapski A, Gomes T, Bredun M, Ferreira-Lima N, Ludka F, Bordignon-Luiz M et al. Digestion behavior and antidepressant-like effect promoted by acute administration of blueberry extract on mice. *Food Research International*. 2019;125:108618.
- 20 Tomić M, Ignjatović Đ, Tovilović-Kovačević G, Krstić-Milošević D, Ranković S, Popović T et al. Reduction of anxiety-like and depression-like behaviors in rats after one month of drinking *Aronia melanocarpa* berry juice. *Food & Function*. 2016;7(7):3111-3120.
- 21 Fernández-Demeneghi R, Rodríguez-Landa J, Guzmán-Gerónimo R, Acosta-Mesa H, Meza-Alvarado E, Vargas-Moreno I et al. Effect of blackberry juice (*Rubus fruticosus* L.) on anxiety-like behaviour in Wistar rats. *International Journal of Food Sciences and Nutrition*. 2019;70(7):856-867.
- 22 Alamri H. Evaluation of the antidepressant-like activity of the aqueous extract of *Crataegus aronia*. *Pharmacognosy Magazine*. 2022;18(77):128.
- 23 Fang J, Luo Y, Jin S, Yuan K, Guo Y. Ameliorative effect of anthocyanin on depression mice by increasing monoamine neurotransmitter and up-regulating BDNF expression. *Journal of Functional Foods*. 2020;66:103757.
- 24 Di Lorenzo A, Sobolev A, Nabavi S, Sureda A, Moghaddam A, Khanjani S et al. Antidepressive effects of a chemically characterized maqui berry extract (*Aristotelia chilensis* (molina) stuntz) in a mouse model of Post-stroke depression. *Food and Chemical Toxicology*. 2019;129:434-443.

- 25 Oliveira P, Gazal M, Flores N, Zimmer A, Chaves V, Reginatto F et al. *Vaccinium virgatum* fruit extract as an important adjuvant in biochemical and behavioral alterations observed in animal model of metabolic syndrome. *Biomedicine & Pharmacotherapy*. 2017;88:939-947.
- 26 Imran I, Javaid S, Waheed A, Rasool M, Majeed A, Samad N et al. *Grewia asiatica* Berry Juice Diminishes Anxiety, Depression, and Scopolamine-Induced Learning and Memory Impairment in Behavioral Experimental Animal Models. *Frontiers in Nutrition*. 2021;7.
- 27 Spohr L, Luduvico K, Soares M, Bona N, Oliveira P, de Mello J et al. Blueberry extract as a potential pharmacological tool for preventing depressive-like behavior and neurochemical dysfunctions in mice exposed to lipopolysaccharide. *Nutritional Neuroscience*. 2020;25(4):857-870.
- 28 Gutierrez J, Carvalho F, Schetinger M, Agostinho P, Marisco P, Vieira J et al. Neuroprotective effect of anthocyanins on acetylcholinesterase activity and attenuation of scopolamine-induced amnesia in rats. *International Journal of Developmental Neuroscience*. 2013;33(1):88-97.
- 29 Estrada-Camarena E, López-Rubalcava C, Ramírez-Rodríguez G, Pulido D, Cervantes-Anaya N, Azpilcueta-Morales G et al. Aqueous extract of pomegranate enriched in ellagitannins prevents anxiety-like behavior and metabolic changes induced by cafeteria diet in an animal model of menopause. *Neurochemistry International*. 2020;141:104876.
- 30 Janšáková K, Bábíčková J, Havrlentová M, Hodosy J, Kraic J, Celec P et al. The effects of anthocyanin-rich wheat diet on the oxidative status and behavior of rats. *Croatian Medical Journal*. 2016;57(2):119-129.