Review Article

Anti-neurodegenerative Activity of Anthocyanin Extract from Endemic Plant Species in the Philippines: A Systematic Review

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ABSTRACT

Introduction: Currently, neurodegeneration is increasingly prevalent and proves to be a serious health problem. Plant extraction containing phytochemical compounds that are rich in anthocyanin regulates several factors contributing to neurodegeneration-related conditions and are used to gain greater understanding of these diseases. **Aim:** Anti-neurodegenerative activity studies have been used in different kinds of anthocyanin-plant cultivated in other countries. The aim of this study was to gain an understanding of anti-neurodegenerative activity of anthocyanin-containing plants found in the Philippines and discover its neuroprotective effect. **Methods:** The related research and studies are limited within the past 5 years of the review's submission, anthocyanin-containing plant species in the Philippines, and the records are monitored thoroughly by excluding duplicates and full-text articles were assessed for eligibility. **Results:** A study showed that a dose of 24mg/kg a day of anthocyanin (ANC) for 2 weeks prevented production of reactive oxygen species (ROS) and inhibited neurodegeneration as well as neuroinflammation in mice by reversing the phosphor-c-Jun N-terminal kinase 1 (P-JNK). Evidences highlight the anthocyanin effectivity in rat models which destabilizes aβ (amyloid beta) by blocking its oligomeric structure formation. The induced metal toxicity, evidence of remyelination and neuron survival by ANC was discovered as well. The related studies reviewed showed relevant findings of anthocyanin content in Philippine plants and their impact in neuroprotection; plants like Bignay (*Antidesma bunius*) showed 436.602 mg/100 mL, Dragon fruit (*Hylocereus* spp.) noted 81.75+ 1.43 mg/100g, Rambutan (*Nephelium lappaceum* l.) Husk showed 393 mg/100g, and lastly Purple yam (*Dioscorea alata*) with 560 mg/100 g. **Conclusion:** With the gathered data, this reveals that ANC directly impacts the brain and a number of effectors, including oxidative and nitrosative stress, glial inflammation, protein aggregation, and toxicity.

Key words: Anthocyanin, Anti-neurodegenerative, Bignay, Dragon fruit, Rambutan, Purple yam.

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INTRODUCTION

All around the globe, attention is brought to the importance of leading healthy lives and maintaining a healthy lifestyle given the current coronavirus pandemic. This holds true not only for the pandemic, but also for long-known diseases whose diagnoses, treatments, and procedures are in constant state of progress.

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Neurodegeneration is one of the most damaging expressions of clinical and pathological diseases affecting the neurons of the brain. Under it are well-publicized disorders such as Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's diseases (PD), and amyotrophic lateral sclerosis (ALS) that are continually being studied extensively. In a statistical index from 2015, 300,000 Filipinos over the age of 65 have varying degrees of dementia. This number is expected to rise to 500,000 and approximately 1.15 million by 2030 and 2050 respectively.[1] This condition is associated with Alzheimer's disease and acknowledged by the World Health Organization (WHO) as one of the top 7 disabling chronic diseases— whose patient care reached $1 trillion in 2018.[2] Given the increasingly prevalent neurodegenerative disorders, anti-neurodegeneration studies become all the more crucial to combat this health problem.

In this regard, anthocyanins have arisen as promising therapeutic candidates due to their impressive anti-lipemic, cardio-protective, antioxidant, and anti-neuro inflammatory properties.[3] Anthocyanins are flavonoid compounds that appear to regulate several factors contributing to neuronal death. It is found in a high number of flowers, fruits, and vegetables and is responsible for the purple, blue, and red color in many of these species. This phytochemical compound has been used in pharmaceutical studies from treating various illnesses, including neurodegenerative diseases and can be easily incorporated into the diet through consumption of anthocyanin-rich foods and drinks or dietary supplements as well.[4]

Current evidence highlighting the anthocyanin content of Philippine plants and their impact in neuroprotection, as well as the mechanism of action of anthocyanins against neurodegeneration, will be collated in this systematic review. This collection of data will contribute to the body of knowledge on Philippine plants with anti-neurodegenerative properties and may also be used by other researchers to further their own studies, as well as advance therapy and pharmaceutics in the field of neurodegeneration.

METHODOLOGY

Literature search

Related research and studies were gathered using an electronic database for the preliminary search on the collection of literature. Several keywords were used by the researchers such as anti-neurodegeneration, anthocyanin, antioxidant, Alzheimer's disease, and endemic plants rich in anthocyanins. The researchers used Google Drive to collect and organize the selected literature and was then imported to Microsoft Excel to tabulate the studies based on publication year, abstract, objective, methodology, results, and conclusion. Lastly, another Microsoft Excel was created indicating the full information of all articles included. The general scheme for evaluating the significance of the paper in the study was shown in Figure 1.

Eligibility criteria

To narrow and set boundaries of materials for the purposes of this review, the following criteria are set:

Inclusion criteria

The materials used must be published in the English language within the past five years of the review's submission to ensure proper understanding and documentation of the most recent findings. Studies chosen must be experimental in nature and are aligned with the extraction of anthocyanins and its measurement of activity against neurodegeneration. The studies must be taken from reputable journals and are peer-reviewed in order to guarantee its reliability.

Exclusion criteria

As the review specifies endemic anthocyanin-containing plant species in the Philippines, studies on non-Philippine endemic plants are to be excluded in this review. The materials must not be self-reported and must not come from editorial articles.

RESULTS

Plants are a significant source of nutritional and therapeutic substances that greatly contribute to treatment of conditions such as neurodegeneration. With the expansion of neurodegeneration in modern times, it is important to collate the findings on anti-neurodegenerative activity of Philippine plants with anthocyanin (ANC) content.

The use of Anthocyanin's against Neurodegenerative Diseases

Mechanism of Action of Anthocyanins in Neuroprotection

ANCs are able to cross the blood-brain barrier (BBB) through its adsorption from the stomach into the

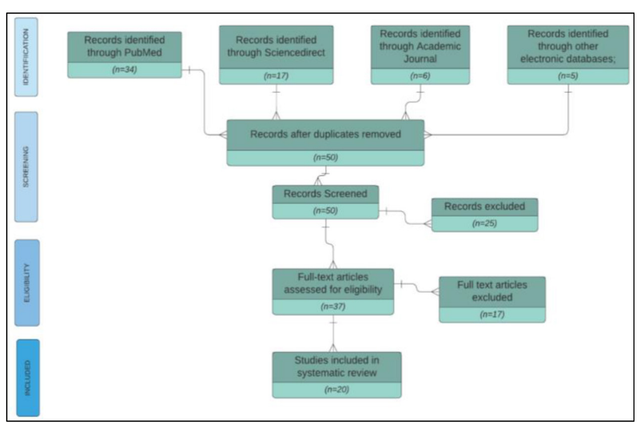

Figure 1: Flowchart for study selection.

bloodstream after ingestion, and delivery to the brain by bilitranslocase transporters present in BBB endothelial cells. This phytochemical mediates neuroprotective effects against oxidative and nitrosative stress, glial inflammation, protein aggregation, and toxicity.[4] Another study showed that a dose of 24 mg/kg a day of ANCs for 2 weeks prevented production of reactive oxygen species (ROS) and inhibited neurodegeneration as well as neuroinflammation in mice by reversing the phosphor-c-Jun N-terminal kinase 1 (P-JNK), reducing inflammatory markers like interleukin-6, lessen neuronal apoptosis, and decrease survival of beta-amyloid proteins that triggers brain inflammation leading to neuronal loss.[5] It was also proven that antioxidant properties of ANCs prevent further pathologic progress.[6]

Oxidative damage is prevented by ANCs oxygen radical absorption capacity (ORAC) to scavenge ROS and RNS. This interrupts free radical chain reactions by donating hydrogen ions, thus forming flavonoid radicals that stop oxidation by free radicals. This can be done not only to active oxygen species but also hydrogen peroxide, superoxide, singlet oxygen, and OH and peroxyl radicals. Xanthine oxidase (XO), an enzyme in nucleic acid degradation, is also inhibited by the action of ANCs when sugars replace OH in its structure and when double bond conjugations between C2 and C3 positions leads to saturation and destruction of its coplanarity.[4,7] ANCs analogues having catechol groups are associated with chelating metal ions and its ferrous-dependent mechanism, leading to prevention of LDL oxidation.[4,7]

Evidence of Anthocyanin Effectivity in Rat Models

Several studies demonstrated a reduction in lipid peroxidation, cognitive deficit prevention, and CNS injury restriction in rat models. Stimulation of pro-inflammatory proteins were induced through injection with lipopolysaccharide (LPS), while ANCs acted to attenuate nitric oxide, tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) as well as reduced the expression of cyclooxygenase-2.[4,8,9] Moreover, JNK, Akt, p38-mitogen activated protein kinase, and extracellular signal-regulated kinase 1/2 are reduced significantly.[5]

The total ANC content and method of extraction for Philippine plants found to enhance neuroprotection are listed in Table 1. Each is based on at least two different sources, with direct correlation to anti-neurodegenerative processes. All are intensively examined and assessed by the researchers based on the 'Eligibility Criteria' found in the review.

Another neurodegenerative process, the formation of amyloid beta (aβ) toxicity and aggregation, was found to be hindered by ANC. ANC destabilizes aβ by blocking its oligomeric structure formation.

Induced metal toxicity in rat models was countered by ANC through elevated expression of antioxidant enzymes, reduction of oxidative stress and lipid peroxidation, and decreasing cholinesterase activity. Evidence of remyelination and neuron survival by ANC was also discovered.

Findings on anthocyanin content of Philippine plants and their impact in neuroprotection

Bignay (*Antidesma bunius*)

Bignay trees are able to produce hundreds of kilograms of its fruit per year and is thus considered a potential raw material for fruit juice production. In an experiment conducted by Hardinasinta *et al.*, the total ANC content of bignay juice was found to be 436.602 mg/100 mL.[10] The high amount of antioxidant properties found in most berries that are proved to prevent the progression of neurological disorders are also found in bignay fruit. Hence, this indicates that bignay contains health-promoting chemical compounds and can be used as a natural source of ANC and can act as an alternative that compromises toxic neurological activity.[11]

Dragon Fruit (*Hylocereus* spp.)

Ali *et al.*, experiment used dragon fruit (*Hylocereus polyrhizus)* peel and were pureed with 100 g of the whole fruit

Table 1: Total anthocyanin content of Philippine plants.

Philippine plants rich in ANCs	Total anthocyanin content	Methods of Extraction	References
Bignay (*Antidesma bunius*)	436.602 mg/100 mL	pH differential method	(Hardinasinta *et al*., 2020) & (Manalo *et al*., 2019)
Dragon fruit (*Hyocereus* spp.)	81.75+ 1.43 mg/100g	Rossi and Singleton method	(Ali *et al*., 2017), (Fan *et al*., 2020) & (Moccia *et al*., 2018)
Rambutan (*Nephelium lappaceum* l.) Husk	393 mg/100g	Amberlite XAD-16, Folin Ciocalteu methods	(Hernandez *et al*., 2017) & (Zhuang *et al*., 2017)
Purple yam (*Dioscorea alata*)	560 mg/100 g	pH differential method	(Adnyana, 2020) & (Adnyana *et al*., 2018)

to extract the total ANC content by using a spectrophotometer. Dragon fruit and its peel were then crushed and added to 30% maltodextrin. The concentration of ANCs was determined by applying the Lambert-Beer law. Using a UV-28O2 diode array spectrophotometer where spectra are recorded (UNIC, USA) which is measured at 25°C and 530 nm against the solvent and 10 mm quartz cells were used. The test further examined the phenolic content by using Rossi and Singleton method and HPLC by column chromatography with some modifications which resulted from having 81.75±1.43 mg/100 g of ANCs.[12] On the other hand, Fan *et al*., experiment made use of three *Hylocereus* spp. cultivars such as Da Hong, Fen Rou, Bai Rou, found that ANCs were more concentrated in the Da Hong cultivar and has identified five ANC compounds, including Cyanidin 3-glucoside, Cyanidin 3-rutinoside, Delphinidin 3-rutinoside, Delphinidin 3-O-(6-O-malonyl)-beta-glucoside-3-O-beta-glucoside and Delphinidin 3-O-beta-D-glucoside 5-O-(6-coumaroyl-beta-D-glucoside).[13] In addition, the flavonoids and anthocyanin of the dragon fruit have neuroprotective potential, probably related to their ability to modulate, the inflammatory responses involved in neurodegenerative diseases, as both phenolic molecules have the ability to reduce the expression of pro-inflammatory cytokines (COX-2, TNF-α, IL-6, and IL-1β), down-regulate inflammatory markers and prevent neural damage.[14]

Rambutan (*Nephelium lappaceum* L.) husk

Hernandez *et al*., studied the polyphenols from the dried rambutan husk (20g). The total phenolic content was determined to be 582 mg/g of dried rambutan husk, with two forms of ANC reported.[15]

Meanwhile, in a study conducted by Zhuang *et al*., the rambutan peel phenolic (RPP) extracts were purified and the main phenolic compounds were identified. The results significantly showed that RPP provided protective effects against H_2O_2- induced oxidative damage in HepG2 cells and against D-galactose induced aging in mice. RPP also decreased intracellular ROS levels and increased SOD activity in H2O2-induced HepG2 cells. Hence, it could improve oxidative stress defense, inhibit cell apoptosis, and decreased D-gal-induced oxidative stress in mice by regulating T-AOC, SOD, GSH-Px and MDA levels of serum as well.[16]

Purple Yam (*Dioscorea alata*)

Adnyana *et al*., experiment shows purple yam contains 560 mg of ANC/100 g of tuber, which is higher than the ANC contents of other root crops.[17] Purple yam has antioxidant effects by suppressing the production of malondialdehyde (MDA) *in vivo* and inducing endogenous antioxidants The ANC extracted from Balinese cultivar of purple yam was administered to Wistar rat models with induced ischemic stroke.

The activities of anti-apoptotic (Bcl-2), pro-apoptotic (cytochrome c, caspase-3) molecules, and apoptosis rate were evaluated as well. This study demonstrated higher anti-apoptotic expression in the treatment compared with the control group. On the other hand, the pro-apoptotic cytochrome c and caspase-3 levels were found to be significantly lower in the treatment as opposed to the control group. Moreover, the apoptosis rate was found markedly lower among treatment than control groups.

The results indicated a significant neuroprotective effect of anthocyanin derived from Balinese cultivar of purple yam because ANCs was able to increase and reduce anti-apoptotic and pro-apoptotic protein levels, resulting in a lesser cellular apoptotic rate.[18]

DISCUSSION

Several studies regarding the phytochemical component of various berries, fruit and leaf extracts containing ANC have been proved to be effective against the delay of neurodegenerative disorders.

In recent studies regarding the analysis of different colorful berry fruits such as blackberry (*Rubus* spp.), black raspberry (*Rubus occidentalis*), blueberry (*Vaccinium corymbosum*), cranberry (*Vaccinium macrocarpon*), and red raspberry (*Rubus idaeus*) containing natural antioxidants which are proved as a valuable resource in the fight against therapeutic neuro interventions.[19] However, these fruits are not widely crafted in the Philippines, hence, finding a plant that is rich in ANCs and widely available in the country may lead to the preparation of a more sustainable and cost-effective natural anti-neurodegenerative dietary supplements.

Several studies have also demonstrated a neuroprotective effect of ANC plant extracts with preclinical models of neurodegenerative diseases by use of multiple mechanisms. Bignay, dragon fruit, rambutan, and purple yam are plants that are reported to contain high amounts of ANCs. This ANC inhibits intracellular calcium overload— the leading cause of excitotoxicity and progression of neurodegenerative disorders.[20] In addition, ANCs also push the oxidative stress and inflammatory mediator, iNOS activation lipid peroxidation, pushing the apoptotic factors in the cortex, an area involved in memory and cognition.[8] Furthermore, ANCs are proved to prevent the onset and progression of neurodegenerative disorders by improving the learning and memory of aging mice models using ANC-rich fruit extracts that elevates proapoptotic B cell lymphoma 2 (Bcl-2) and reducing anti-apoptotic B cell lymphoma protein associated with X (Bax) in apoptotic mechanisms.[4] Thus, consumption of plants that are rich in ANC are associated with reduced risk of Alzheimer's disease and other neurological disorders.

CONCLUSION AND RECOMMENDATIONS

As part of the flavonoid family that produces a blue, red, or purple pigmentation in plants and fruits, the gathered data reveals that ANCs directly impact the brain and a number of its effectors, including oxidative and nitrosative stress, glial inflammation, protein aggregation, and toxicity. The paper combines known data related to both ANCs and plant species in the Philippine setting. As well as to highlight the pharmaceutical-therapeutic potential of several Philippine plants that also contain significant amounts of ANCs that will further help in the field of anti-neurodegenerative activity— namely, bignay, dragon fruit, rambutan, and purple yam.

Further research must be conducted to deepen the knowledge of Philippine plants with ANC content and their activity in neuroprotection that will help propel ANC-rich plant extracts progress as treatment and supplements. Additionally, clinical laboratory parameters should be set and standardized to enhance the methods used in the related studies. Studies on the absorbance, metabolism, segregation, and characterization of different ANCs will allow further understanding of its prospects in anti-neurodegeneration.

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CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the study of this paper.

Authors' Contribution

The authors of this study contributed to the following parts of the study; Buenaventura, Jan Lance and Male, Reianna Mae designed the flowchart needed for the methodology. Asis, Sophia Yvonne and Olandez, Joaquin managed the literature studies needed to build a solid background information. Bulanhagui, Angelic Mizpah Chaste, Maniquis, Kristel Faith, Samulde, Keneth Dayle was responsible for the first and second draft of the manuscript, editing and revisions needed. All authors read and approved the final manuscript. Ms. Laarni Hannah C. Lacorte and Mr. John Sylvester B. Nas, supervised the whole writing of the manuscript.

SUMMARY

Acknowledged by the World Health Organization as an increasingly prevalent and expensive disabling chronic condition, anti-neurodegeneration is a crucial subject for research and development. Phytochemical compounds that are rich in anthocyanin are said to regulate several factors that gain greater understanding in contributing to neurodegenerative diseases. With reports of its neuroprotective effects, ANC-rich plants and fruits are both a healthy and accessible option to combat brain disorders. Research shows several Philippine plants that contain significant amounts of ANCs— namely, bignay, dragon fruit, rambutan, and purple yam. Furthermore, a study showed that anthocyanin effectivity in rat models destabilizes aβ (amyloid beta) by blocking its oligomeric structure formation. It also revealed that a dose of 24mg/kg a day of anthocyanin for 2 weeks prevented production of reactive oxygen species (ROS) and inhibited neurodegeneration as well as neuroinflammation in mice by reversing the phosphor-c-Jun N-terminal kinase 1 (P-JNK).

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