Jurnal Kedokteran dan Kesehatan: Publikasi Ilmiah Fakultas Kedokteran Universitas Sriwijaya
Volume 12, No 1. 2025/DOI: 10.32539/JKK.V12i1.453
p-ISSN 2406-7431; e-ISSN 2614-0411
Page: 21-29

EFFECTIVENESS OF ANTHOCYANIN AS A HEPATOPROTECTOR: A SYSTEMATIC LITERATURE REVIEW

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ARTICLE INFO

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Kata kunci:
Antosianin
Gangguan Hati
Hepatoprotektor

Keywords:
Anthocyanin
Liver Disorder
Hepatoprotector

Original submission:
July 13, 2024
Accepted:
Nov 11, 2024
Published:
January 20, 2025

ABSTRAK

Paparan radikal bebas dapat menyebabkan terjadinya hepatotoksisitas terhadap sel hati. Hepatoprotektor diperlukan untuk mencegah radikal bebas. Senyawa antosianin golongan flavonoid yang memberikan warna ungu, biru dan merah pada banyak tumbuhan memiliki aktivitas antioksidan sebagai hepatoprotektor. Penelitian ini bertujuan untuk mengulas efektivitas berbagai tumbuhan yang mengandung antosianin sebagai hepatoprotektor dengan *systematic literature riview*. Penelusuran artikel menggunakan *Google Scholar*, *PubMed dan NCBI* dengan kata kunci seperti "*Anthocyanin compounds and Hepatoprotective effects*" yang memenuhi kriteria inklusi dan eksklusi. Hasil yang diperoleh dari 7 artikel riview menunjukkan bahwa beberapa tumbuhan mengandung antosianin seperti Bilberry dan blackberry, Rosella, Kubis ungu, bunga telang, *Aronia melanocarpa Elliot* (AMA), Red cabbage, dan lobak. Mekanisme yang terjadi pada tumbuhan mengandung antosianin sebagai hepatoprotektor yakni adanya aktivitas antioksidan, penghambatan enzim sitokrom, penghambatan peradangan, ekspresi protein, dan modulasi jalur sinyal apoptosis. Kesimpulan dari riview ini bahwa tumbuhan yang mengandung antosianin menunjukkan efektivitas sebagai hepatoprotektor alami yang efektif dengan berbagai mekanisme.

ABSTRACT

Effectiveness of Anthocyanin as a Hepatoprotector: A Systematic Literature Review. Exposure to free radicals can cause hepatotoxicity in liver cells. Hepatoprotectors are needed to prevent free radicals. The flavonoid group anthocyanin compounds, which give many plants purple, blue, and red colors, have antioxidant activity as hepatoprotectors. This study uses a systematic literature review to review the effectiveness of various plants containing anthocyanins as hepatoprotectors. Articles were searched using Google Scholar, PubMed, and NCBI with keywords such as "Anthocyanin compounds and Hepatoprotective effects" that met the inclusion and exclusion criteria. The results obtained from 7 review articles show that several plants contain anthocyanins, such as bilberry and blackberry, Rosella, purple cabbage, butterfly pea flower, Aronia melanocarpa Elliot (AMA), red cabbage, and radish. The mechanisms in plants containing anthocyanins as hepatoprotective include antioxidant activity, inhibition of cytochrome enzymes, inhibition of inflammation, protein expression, and modulation of the apoptotic signal pathway. This review concludes that plants containing anthocyanins are effective as natural hepatoprotectors with various mechanisms.

INTRODUCTION

The liver is an organ that primarily functions in metabolism, synthesis, and detoxification.[1] The liver receives 80% of its blood supply from the circulation, which contains toxic compounds absorbed by the intestines and carried to the liver. Hence, the liver is an organ susceptible to damage caused by entering harmful substances.[2] Causes of liver damage include viruses and bacteria, metabolic disorders, excessive or inappropriate use of drugs resulting in hepatotoxicity such as paracetamol, rifampicin, hydroxyl urea, and excessive alcohol consumption in the body. One of the effects of toxic substances is that the liver experiences oxidative stress, a condition where there is an increase in free radicals that is higher than the level of endogenous antioxidants, disrupting body functions, especially the liver.[3]

Hepatoprotectors are compounds that can protect the liver from damage caused by drugs, viruses, chemical compounds, toxic substances, and other causes.[4] Disorders and oxidative stress in liver cells can be prevented by administering antioxidants, one of which is widely used, namely anthocyanin compounds. Antioxidants have hepatoprotective properties by reducing oxidative stress and increasing glutathione, thereby reducing inflammatory reactions in liver cells.[5]

Anthocyanins are included in the flavonoid group, which are water-soluble plant glucosides and food phytochemicals, have several biological functions, and act as a natural food coloring.[6] Experimental and epidemiological studies have been conducted, and anthocyanins and their metabolites have been proven to show pharmacological properties that can prevent liver damage, diabetes, cancer, and neurological and heart diseases.[7] Anthocyanin compounds are often used in the health sector because they can potentially be natural ingredients in the prevention and treatment of chronic diseases and as cosmetic ingredients.[8] Several studies have been carried out to prove that anthocyanin compounds contained in plants are hepatoprotective, namely purple cabbage which shows the results that administration of purple cabbage extract has hepatoprotective activity with average values in CCl4-induced test animal models.[9] Rosella flowers showed results that ethanol extract of rosella petals for liver disease was effective at a dose of 200-400 mg/KgBW/day.[10] Therefore, this article aims to review the effectiveness, including the mechanisms of various plants that contain anthocyanin compounds that are effective as hepatoprotectors.

METHOD

This study conducted a systematic literature review (SLR) to properly discover, extract, evaluate, and interpret data about the efficacy of different plants containing anthocyanins as hepatoprotectors. Article searches were performed through Google Scholar, PubMed, and NCBI databases, including the keywords "Anthocyanin compounds and hepatoprotective effects." Inclusion criteria are articles in Indonesian or English, in vivo experimental research design, suitability of the title, and discussion for the review, published between 2019 and 2024. Exclusion criteria were article reviews; articles did not discuss anthocyanin compounds as hepatoprotective, and articles could not be accessed in full text. The data used are research articles published in national and international journals. The results of the articles obtained will be analyzed (Figure 1).

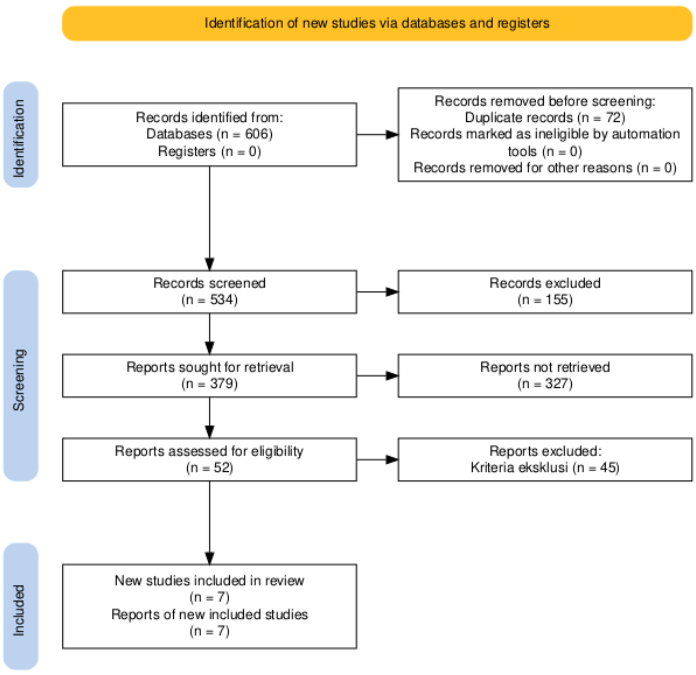

Figure 1. PRISMA Flow Diagram

Based on (figure 1), the results of a literature search using the created keywords found 606 articles that matched the keywords. The search results were then screened for articles based on the period from 2019-2024, resulting in 379 articles. Further screening based on the inclusion criteria resulted in 52 articles. Of the 52 articles, 45 were excluded because the articles were included in the exclusion criteria, namely article reviews; the articles did not discuss anthocyanin compounds as hepatoprotective, and the articles could not be accessed in full text. Seven articles that met the criteria for this systematic literature review were selected in the final article selection stage.

RESULT

The analysis of 7 papers demonstrates the anthocyanin content in these plants, which provides hepatoprotective properties (Table 1). The reviewed articles employed various toxic substances and doses, including CCl4 induction, high-fat feed, alcohol, paracetamol, and acetaminophen. The test parameters assessed were alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), liver histopathology, and bilirubin levels. Therefore, each article yields distinct research findings.

Table 1. Results Review of Articles on Plants Containing Anthocyanins as Hepatoprotectors

Title	Author	Method	Result
Hepatoprotector Cabbage Extract Activity Test *(Brassica oleracea* var. Capitata L.) on Animal Rabbit Trials (*Oryctolagus cuniculus*)	Suriani *et al*, 2019[9]	In vivo; Induced CCL4; Treatment concentration dosis 2%, 4%, dan 6% b/v.	The administration of purple cabbage extract at doses of 2%, 4%, and 6% b/v can maintain normal levels of ALT and AST so that purple cap extract is

Induced by Carbon Tetrachloride (CCl4).			potentially hepatoprotective.
Effective Dose of Rosella Calyx Extract (*Hibiscus sabdariffa* L.) against Liver Marker Enzymes and Liver Histopathological of High-Fat Feed-Induced Rats	Hidayat, *et al*, 2019[10]	In vivo; High Fat Induced; Treatment concentration 200, 400, 600 mg/KgBB/hr.	The effective Rosella Calyx Extract dose for liver disease based on the histopathological picture of the liver, ALT, and GGT in male Wistar rats induced by PTL is a dose of 200-400 mg/KgBB/hr.
Polyphenolic Composition, Antiradical And Hepatoprotective Activities Of Bilberry And Blackberry Pomace Extracts	J. Canadanovi c-Brunet, *et al*, 2019[11]	In vivo; Induced CCL4; Treatment concentration 0.1, 0.5, or 2 mL kg−1 b.w.	The best results in neutralizing oxidative stress caused by CCl4 were observed for 2 mL berry extract pomace kg^{-1} b.w.
The Effects And Mechanism Of *Aronia melanocarpa Elliot* (AMA) Anthocyanins On Hepatic Fibrosis	J. Yang, *et al*, 2020[12]	In vivo; Induced CCL4; Treatment concentration 20 mg/kg, 40 mg/kg.	AMA at a 40 mg/kg dose has a specific therapeutic effect on liver fibrosis caused by CCl4. It can significantly reduce the liver injury index of mice with liver fibrosis and return it to a state close to normal mice.
Anthocyanin-rich extract of Red Cabbage (RCE) Attenuates Advanced Alcohol Hepatotoxicity in Rats in Association with Mitochondrial Activity Modulation	Buko *et al,* 2022[13]	In vivo; Alcohol-induced; Treatment concentration 11 mg RCE/kg dan 22 mg RCE/kg.	The hepatoprotective effectiveness of RCE is dose-dependent, and the administration of higher doses of polyphenols (22 mg/kg) indicates better results.
Hepatoprotective Activity of Ethanol Extract of Butterfly Pea Flower (*Clitoria ternatea* L.) in White Rats Induced by Paracetamol	Pebiansyah, *et al*, 2022[14]	In vivo; Induced Paracetamol; Treatment Concentration 123 mg/200 g BB, 247 mg/200 g BB dan 370 mg/200g BB.	Only two doses (247 mg/200 g BB) showed hepatoprotective activity equivalent to positive control.
Hepatoprotective Effects of Radish (*Raphanus sativus* L.) on Acetaminophen-Induced Liver Damage via Inhibiting Oxidative Stress and Apoptosis	Hwang, *et al.,* 2022[15]	In vivo; Acetaminophen Induced; Treatment concentrations were 500 mg/kg and 1000 mg/kg.	A concentration of 1000 mg/kg of both extracts equally provides hepatoprotective, antioxidant, and antiapoptotic effects.

DISCUSSION

The liver is an organ with the most complex functions in the body, such as producing plasma proteins, phagocytosis of microorganisms and erythrocytes, leukocytes, the center of protein, fat and carbohydrate metabolism, the detoxification center of toxic substances in the body, producing bile, storing various substances such as minerals, vitamins, glycogen and various toxic substances that cannot be removed from the body.[16] Damaged liver function is characterized by yellow skin and mucous membranes and increased concentrations of bilirubin, ALT, ALP, GGT, and other parameters in the blood. Types of liver disease include hepatitis, liver cirrhosis, jaundice, Wilson's disease, Reye's syndrome, and liver tumors.[17]

Factors that cause liver disorders include consuming alcoholic drinks at a particular time and in specific quantities so that digestive enzymes oxidize the alcohol to become saturated, resulting in increased blood alcohol levels;[18] Smoking can cause lipid peroxidation and damage to liver cell membranes, thereby increasing ALT and AST levels;[19] Hepatitis virus infection which is an inflammatory liver disease that can be transmitted;[20] Drugs are one of the causes of liver damage or hepatotoxicity by involving direct hepatotoxic mechanisms and adverse immune reactions; Cholestasis (failure of production and excretion of bile) and Jaundice (excess bilirubin in the blood and accumulation of bile pigments on the skin, mucous membranes, and eyeballs.[21]

Antioxidants help protect the liver from damage caused by free radicals. Antioxidants are compounds that can prevent or eliminate oxidative damage to core molecules. The body produces endogenous antioxidants to deal with free radicals; however, exogenous antioxidants are required as free radicals increase.[22] Previous research stated that bilberries and blackberries, purple cabbage, Rosella, red cabbage, butterfly pea flowers, purple corn, and radishes contain high levels of antioxidants, including flavonoid compounds such as anthocyanins. These flavonoids are thought to function as hepatoprotectors, protecting the liver from chemicals or drugs that can damage the liver. The mechanism of action of anthocyanin compounds as hepatoprotectors is based on their activity as antioxidants. Among the anthocyanin pigments, cyanidin-3-glucoside is the main anthocyanin found in most plants.[23]

The induction used in previous research to cause liver damage can be the use of CCl4, high fat, and other foods, which then enter the body and are metabolized by the liver, causing the formation of free radicals and damaging liver cells. According to Slater TF (1985), CCl4 is used to induce acute liver loss. CCl4 is a multifactorial toxic agent involved in free radical production, lipid peroxidation, gene expression changes, macromolecular binding, and loss of calcium homeostasis. Parameters that are visible when the liver is damaged include ALT, AST, ALP, GGT, superoxide dismutase (SOD) and others.[24]

In Cui's (2022) research, purple corncob anthocyanins induced by CCl4, anthocyanin activity was able to repair chronic liver damage caused by CCl4 by regulating oxidative stress and the liver hepatocyte apoptosis pathway. This study explains the mechanism of anthocyanins in preventing liver damage, which can be seen in (Figure 2).[25]

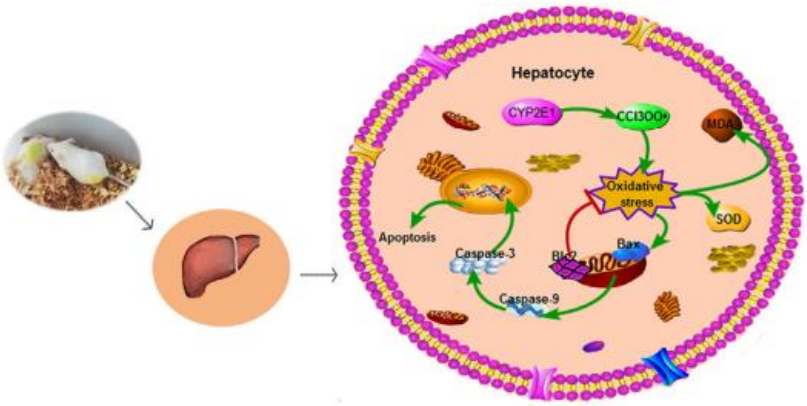

Figure 2. Protective mechanism of pure purple corn cob anthocyanin on chronic liver injury in mice.[25]
This mechanism acts to modulate SOD and MDA activity, upregulating Bcl-2 expression and downregulating caspase-3, Bax, and CYP2E1 expression to reduce oxidative stress and hepatocyte apoptosis.

In (figure 2) describe a hepatoprotective mechanism that occurs, namely that the antioxidant compounds contained inhibit oxidative stress by inhibiting CYP2E1 activity which is responsible for the metabolism of CCl4 into free radicals, resulting in a decrease in MDA concentration, an increase in SOD activity, an increase in regulation of Bcl-2 protein expression, and downregulation of caspase-3 and Bax protein expression and thus can modulate cell apoptosis.[25]

In line with Hwang's research results, K-A. (2022) that extracts of Ganghwa radish (RG) and Jeju radish (RJ) showed hepatoprotective effects measured through expression factors involved in the antioxidant pathway, Nrf2/HO-1 and BCL-2/BAX, namely the increase in upstream and downstream regulatory factors of Nrf2 HO-1, which is an antioxidant-related factor so that GM and RJ radishes can increase antioxidant enzyme activity. In addition, it can regulate mitochondria-dependent apoptosis through BCL-2 and Bax and inhibit proteolytic activity and apoptosis by inhibiting caspase three and caspase 9. These results are believed to be caused by the components contained in both radish extracts, namely antioxidants such as anthocyanins, glucosinolates, phenyl isothiocyanate, and sulforaphane.[15]

The administration of purple cabbage extract to CCl4-induced experimental animals showed that purple cabbage extract had a defense against ALT and AST at a concentration of 6%, which was closest to the results of the positive control. The results are likely due to antioxidant compounds, namely anthocyanins as hepatoprotectors. The mechanism by which anthocyanins protect the liver from hepatotoxicity is by increasing glutathione reserves and reducing oxidative DNA damage. So, the results indicate that the activity of purple cabbage extract can maintain the ALT and AST values as an indication of hepatoprotector.[9]

The reactive metabolite CCl4, when it reacts with polyunsaturated fatty acids, transforms into saturated fatty acids that compromise cell membrane permeability. These toxic substances can have a detrimental effect on liver mitochondria and significantly inhibit enzymatic activity. However, the administration of bilberry extract and blackberry pomace has shown promise in reducing the toxic effects of CCl4. This prevents liver fibrosis and the accumulation of membrane lipid peroxidation in the liver and significantly improves mitochondrial ultrastructure. This research underscores the potential benefits of bilberry and blackberry extracts, which are rich in polyphenols, particularly anthocyanins, in reducing the effects of exposure to chemicals that can cause cell injury

through metabolic reactive oxygen species (ROS), a type of harmful oxygen molecule produced during normal metabolism.[11]

Research on *Aronia Melanocarpa Elliot* (AMA) with CCl4 induction shows that anthocyanins are essential biologically active substances because they have strong antioxidant properties and specific preventive and therapeutic effects on liver fibrosis. AMA is a polyphenolic compound obtained from Aronia melanocarpa Elliot and has potent antioxidants. The TGF-B/Smad signaling pathway achieves the mechanism of AMA in liver fibrosis therapy. Therefore, AMA can potentially alleviate liver fibrosis, and natural plant active ingredients have positive effects in preventing and treating liver injury diseases.[12]

A study investigating the effects of alcohol-induced red cabbage treatment with a dosage of 22 mg polyphenols/kg found that the extract effectively decreased hepatic steatosis, reduced the size of lipid droplets in hepatocytes, and decreased lymphocytic infiltration. Administration of red cabbage extract significantly and in appropriate doses can protect against alcohol-induced liver injury by reducing the accumulation of serum ALT, alkaline phosphatase, and bilirubin. Polyphenols in red cabbage, especially anthocyanins, can treat alcohol-induced liver damage due to their broad biological activity and potential to modulate mitochondrial function. Red cabbage extract as a hepatoprotective can reduce the accumulation of neutral lipids in serum and liver, showing an intense anti-inflammatory action, assessed by reducing the levels of pro-inflammatory cytokines (TNFα and IL-6) in blood serum.[13]

The ethanol extract of rosella petals was researched with the induction of high-fat feed. The study's results indicated that the administration of the extract at a dose of 200 mg/KgBW/day could significantly reduce ALT enzyme levels, cloudy swelling, and steatosis. Additionally, the extract doses of 400 and 600 mg/KgBW/day lowered ALT levels and GGT. The mechanism that occurs in this extract as a hepatoprotection is by reducing the ALT enzyme, namely through antioxidant activity, which reduces oxidative stress and mitochondrial dysfunction by decreasing the expression of Bcl-2-associated-x protein (Bax) and truncated Bcl2 Interacting Domain (tBID) in the liver, so that a decrease in liver enzymes such as ALT, AST, and ALP. Based on liver histopathology, the effective dose of GGT and ALT extract for liver disease is 200-400 mg/KgBW/day.[10,26]

The research on paracetamol-induced butterfly pea flower extract has revealed its potential as a hepatoprotective agent. The ethanol extract of butterfly pea flower, with a 247mg/200grBB concentration, demonstrated hepatoprotective activity comparable to the positive control. It effectively inhibited the release of ALT and AST enzymes in the blood, as indicated by lower levels of ALT and AST compared to the positive control. This extract's ability to prevent liver damage is attributed to its secondary metabolites of flavonoids and anthocyanins, which can donate electrons to stabilize free radicals that cause liver damage. Moreover, flavonoid compounds can interfere with oxidation reactions in cells, protect cells against oxidative stress, and increase endogenous antioxidants, thereby reducing the risk of liver damage.[14, 27]

According to the reviewed publications, anthocyanin compounds have hepatoprotective properties due to their antioxidant activity. This activity helps decrease oxidative stress and counteract free radicals in liver cells, preventing damage to liver cells and tissue. The inflammation inhibition mechanism, namely anthocyanins, inhibits the production and activity of pro-inflammatory such as TNFα and IL-6 to reduce inflammation, and anthocyanins can protect liver cells from further damage. The mechanism of cytochrome enzyme inhibition, namely anthocyanins, can inhibit the activity of cytochrome P450 enzymes such as CYP2E1, which are involved in drug metabolism and detoxification so that they can help protect the liver from the toxic effects of

chemical compounds. The regulatory mechanism for protein expression, namely anthocyanins, can influence the expression of proteins related to liver cell damage, such as tBid and Bax. Anthocyanins can reduce cell death or apoptosis caused by oxidative stress and liver inflammation by modulating signaling pathways associated with apoptosis. The mechanism in each plant is different; several possibilities, such as the inducing agent, the hepatotoxic induction mechanism, and the location of the damage in the liver, can cause this. Thus, the mechanism of anthocyanin compounds in protecting the liver will be different.

CONCLUSION

Based on the results of a systematic literature review, it was concluded that plant extracts such as bilberry and blackberry, Rosella petals, purple cabbage, Aronia melanocarpa Elliot, Red Cabbage, butterfly pea flower, and radish contain anthocyanins with mechanisms of antioxidant activity, inflammation inhibition, cytochrome enzyme inhibition, protein expression, and modulation of apoptosis-related signaling pathways as hepatoprotection. The results in each study are different because the plants, induction substances, doses, and test parameters used are different.

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