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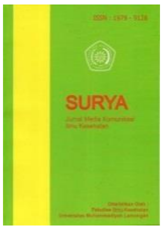


## *Article Review: In Vitro, In Vivo, And Clinical Trial Data on Proanthocyanidin Compounds*


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**ABSTRACT**

**Introduction**: Proanthocyanidins, or condensed tannins, are oligomeric flavonoids prevalent in various plant tissues such as seeds, fruits, and leaves. These compounds are recognized for their potential health benefits due to their diverse biological activities

**Methods:** This review systematically examines the health benefits of proanthocyanidins by analyzing literature from in vitro, in vivo, and clinical trials. The review utilized online databases including Google Scholar, NCBI, ScienceDirect, NIH, and PubMed, with keywords such as "in vitro," "in vivo," and "clinical trials of proanthocyanidin compounds." A total of 37 relevant articles were selected, analyzed, and summarized in tabular form to ensure a comprehensive assessment

**Results**: The analysis revealed that proanthocyanidins exhibit significant health benefits across various domains. They possess antidiabetic, antioxidant, antibacterial, immunostimulant, insomnia therapy, analgesic, and anthelmintic properties. Additionally, there is emerging evidence suggesting their potential role in the prevention and treatment of COVID-19.

**Conclusion**: Proanthocyanidins demonstrate considerable promise for therapeutic and preventive applications. Further research is warranted to fully elucidate their mechanisms and optimize their clinical use.



**Keywords**: in vivo, in vitro, clinical trials, proanthocyanidin.

## INTRODUCTION

Proanthocyanidins, a class of oligomeric flavonoids, are polyphenolic compounds that play a significant role in plant biology and human health. Often referred to as condensed tannins, these compounds consist of 2 to 50 polymer units linked by carbon chains, which are synthesized through the flavonoid pathway, rendering them resistant to hydrolysis (Kurniawan & Zahra, 2021). Proanthocyanidins are integral to pigmentation in various plant tissues, including seeds, wood, bark, and leaves (Wahjuningsih et al., 2023). In humans, these compounds exhibit substantial antioxidant activity, effectively scavenging free radicals and thus holding potential as agents for cancer prevention, visual function enhancement, and skin care. Their ability to mitigate oxidative stress highlights their significant value in promoting overall health and enhancing aesthetic qualities (Zhao et al., 2023). Due to their diverse biological activities, such as antibacterial, antiviral, anti-carcinogenic, anti-inflammatory, anti-allergic, and vasodilatory effects, proanthocyanidins have garnered significant attention in health research.

Structurally, proanthocyanidins are formed through the polymerization of flavan-3-ol units connected by C-C bonds. The structure of these compounds is determined by factors such as the type of flavan-3-ol units, the mode of linkage, the degree of polymerization, spatial configuration, and hydroxyl group substitution. Common flavan-3-ol units include catechin, epicatechin, epigallocatechin, and epigallocatechin gallate (Qi et al., 2023). Proanthocyanidins are abundantly found in natural sources such as fruits, seeds, and leaves, making them a key focus in the study of plant-based health benefits.

Fruits such as blueberries, cranberries, red grapes, apples, cherries, and plums are abundant in proanthocyanidins, providing a natural source of antioxidants that support cardiovascular health and bolster immune function (Wahjuningsih et al., 2023; Skrovankova et al., 2015). Similarly, seeds from grapes, pomegranates, and various nuts are rich in proanthocyanidins, contributing significantly to antioxidant intake and offering additional health benefits (Suter, 2021). Beverages like green and black tea, which are also high in proanthocyanidins, have been demonstrated to protect cells from oxidative damage and enhance overall health (Meccariello & D'Angelo, 2021). In addition to their health benefits, proanthocyanidins contribute to the astringent taste of certain foods and beverages and positively affect both human health and ruminant animals by increasing nitrogen content and preventing bloating (Rauf et al., 2019). Recent research has further revealed the potential of proanthocyanidins as non-antibiotic prophylactic agents against urinary tract infections (Rau et al., 2024) and highlighted their efficacy in managing non-carious cervical lesions (de Souza et al., 2020).

To date, there has been no comprehensive review encompassing in vitro, in vivo, and clinical trials involving proanthocyanidins. This review article addresses this critical gap in the literature by consolidating and analyzing existing research on these compounds. The objective is to provide an in-depth examination of the biological activities and health benefits of proanthocyanidins, synthesizing data from various study types to enhance our understanding and guide future research efforts.

The review aims to elucidate the diverse roles of proanthocyanidins in health, focusing on their potential applications in both dietary and therapeutic contexts. By integrating findings from in vitro, in vivo, and clinical studies, this review seeks to highlight the broad spectrum of effects exhibited by proanthocyanidins and underscore the need for further research. Such research is essential to fully explore and harness the potential of proanthocyanidins in promoting health and preventing disease.

## METHODS

The methodology for this article involved a systematic literature review to compile comprehensive data on proanthocyanidin compounds. We performed a descriptive analysis using literature from the past ten years to ensure the relevance and timeliness of the data. Data collection was conducted through online databases, including Google Scholar, NCBI, ScienceDirect, NIH, and PubMed, employing the search keywords “in vitro, in vivo, and clinical trials of proanthocyanidins.” The inclusion criteria were limited to articles published between 2014 and 2024 in both national and international journals, focusing specifically on studies addressing in vitro, in vivo, and clinical trials involving proanthocyanidin compounds. This method ensured a thorough and up-to-date selection of literature for detailed analysis.

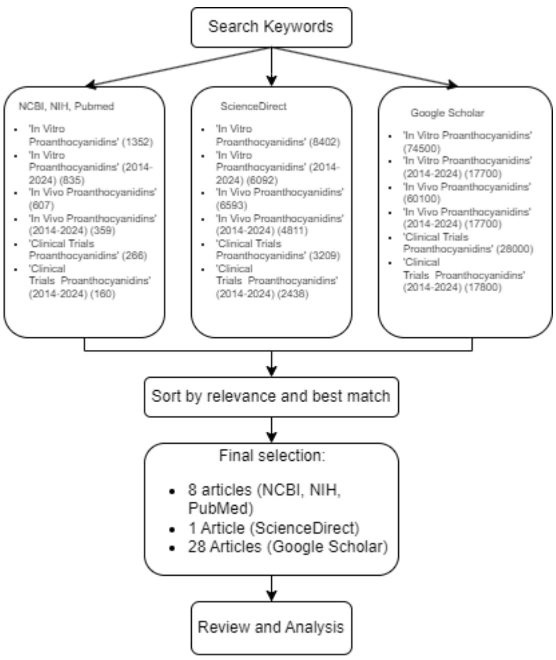


Figure 1. Flowchart of the Literature Search Methodology

## RESULTS

The results of this review indicate that proanthocyanidins possess several beneficial properties, including antioxidant (Nawrot-Hadzik et al., 2021), immunostimulant (Rauf et al., 2019), antidiabetic (Frengki et al., 2023), and antibacterial (Fauziyyah et al., 2023) effects. The pharmacological mechanisms of proanthocyanidins have been investigated through various types of research: in vitro, in vivo, and clinical trials.

In vitro studies involve experiments conducted outside of a living organism, typically using cell-based assays, and are performed using tools such as test tubes, involving isolated tissues, organs, or cells. This approach is commonly referred to as “in glass” by the World Health Organization (WHO). In contrast, in vivo studies, meaning “in living,” use whole living organisms to test compounds, focusing on minimizing the use of animal models and human cultures to reduce animal cruelty (Pangestu et al., 2023). Clinical trials are conducted to evaluate the efficacy and safety of compounds in humans (Widjaja & Aini, 2023).

Proanthocyanidins, as polyphenolic compounds found in nature, are characterized by their significant antioxidant and antibacterial properties. Dietary consumption of proanthocyanidins can influence biochemical and epigenetic mechanisms within the body, including the modulation of microRNAs in cells (Bladé et al., 2016). This interaction suggests that proanthocyanidins have the potential to address various metabolic issues. A more detailed examination of their in vitro, in vivo, and clinical trial activities is presented in the following sections.

## DISCUSSIONS

### In vitro data on proanthocyanidin compounds

In a study evaluating the antioxidant activity of proanthocyanidin compounds from cocoa beans using rat urine (Table 1), the cocoa beans were extracted via maceration. The study involved 20 rats divided into five groups, receiving doses of 50 mg/kg BW, 100 mg/kg BW, and 200 mg/kg BW. The results indicated that the proanthocyanidin compounds in the cocoa bean extract effectively scavenged free radicals, leading to a reduction in 8-OHdG levels by 21.20%, 31.34%, and 35.28%, respectively (Iflahah et al., 2016).

Table 1. A number of in vitro data from natural products containing proanthocyanidins

| Natural Products | Results | In Vitro Activity |
|---|---|---|
| Cocoa Beans | The n-butanol fraction, administered at doses of 50 mg/kg BW, 100 mg/kg BW, and 200 mg/kg BW, resulted in reductions in urinary 8-OHdG levels in rats of 21.20%, 31.34%, and 35.28%, respectively (Iflahah et al., 2016) | Antioxidant |
| Kamboja leaves | It produced an average inhibition zone of 1.307 cm, compared to the standard tetracycline (30 µg), which produced an inhibition zone of 1.637 cm (Ikrom et al., 2014). | Antibacterial |
| Grape peels | In a rat model with a high-cholesterol diet, the extract administered at a dose of 100 mg/175 g/kg BW significantly reduced plasma MDA levels (Nurhidayati et al., 2020). | Antioxidant |
| Pakis Tangkur Roots | Proanthocyanidin dosages of 2.78 µg/50 µL and 3.7 µg/50 µL demonstrated high antioxidant activity. Notably, 3.7 µg/50 µL of proanthocyanidin exhibited greater antioxidant effectiveness than α-tocopherol at an equivalent dosage (Subarnas & Indrayati, 2006). | Antioxidant |

Table 2**.** A number of in vivo data from natural products containing proanthocyanidins

| Natural Products | Animal Models | Results | In Vivo Activity |
|---|---|---|---|
| Avocado leaves (*Persea americana* Mill) | Male Wistar Rat (*Rattus norvegicus*) | The 70% methanol extract of avocado leaves, administered at doses of 100 mg/200 g BW, 150 mg/200 g BW, and 200 mg/200 g BW, significantly reduced blood sugar levels in rats induced with alloxan (Handayani et al., 2016). | Antidiabeti c |
| Bambo apus leaves (*Gigantochloa apus*), bambo petung leaves (*Dendrocalamus asper*), and bamboo legi leaves (*Gigantochloa atter*) | Goat | Proanthocyanidins, with concentrations of 8.81% w/w, 4.84%, and 3.19%, demonstrate potential as anthelmintics (Nurcahyo & Prastowo, 2017). | Anthelmint ic |

Table 3. A number of clinical trials data from natural products containing proanthocyanidins

| Natural Products | Results | Clinical Activity |
|---|---|---|
| Cranberry (*Vaccinium macrocarpon*) | Consuming 250 ml of cranberry juice twice daily for 35 and 90 days significantly reduces *H. pylori* colonization (Cires et al., 2017). | Antibacterial |
| Cherry | Cherry juice improves sleep duration and efficiency, reduces the serum kynurenine-to-tryptophan ratio, lowers serum PGE2 levels, decreases inflammation, and inhibits indoleamine 2,3-dioxygenase by reducing tryptophan degradation (Losso et al., 2018). | Anti-insomnia |
| Grape seeds, red grapes, cranberries, blueberries | Certain natural materials exhibit antioxidant, anti-cholesterol, and immunostimulant activities, and are effective in moisturizing the skin and enhancing cognitive function (Wang et al., 2022). | Potential in the prevention and treatment of COVID-19 |
| Dried petals of Roselle flower (*Hibiscus sabdariffa*) | Daily administration of roselle petal extract, providing 9.6 milligrams of anthocyanins, for a duration of 4 weeks significantly reduced hypertension (Diana & Adiesti, 2016). | Anti- hypertension |

In a separate study on Plumeria leaves, which are rich in proanthocyanidins with antibacterial properties, the extract was tested against *Aeromonas hydrophila*. The results showed an inhibition zone with an average diameter of 1.307 cm, which was comparable to the inhibition zone produced by a disk containing 30 µg of tetracycline, which measured 1.637 cm (Ikrom et al., 2014).

Additionally, in vitro studies on grape peels revealed notable antioxidant activity attributed to proanthocyanidins. Research conducted by Nurhidayati et al. (2020) demonstrated that grape skin extract, administered to rats on a high-cholesterol diet at a dose of 100 mg/175 g/kg BW, significantly reduced plasma malondialdehyde (MDA) levels. MDA, a marker of oxidative stress, reflects an imbalance between reactive oxygen species (ROS) and antioxidants, indicating the effectiveness of grape skin extract in counteracting oxidative damage (Amalia & Ikeu, 2014).

**In vivo data on proanthocyanidin compounds**

In an in vivo study evaluating the analgesic effects of tangkur fern root (Table 2), male Swiss Webster mice were treated with an extract of tangkur fern root combined with aspirin at a dosage of 50 mg/kg BW. The treatment resulted in a significant reduction in the average total writhing count to 119.25 ± 2.16 following induction with 0.7% acetic acid, reflecting a 68.62% decrease compared to the control group, with statistical significance at $p < 0.05$ (Nurul, 2022). Additional research supports the analgesic efficacy of proanthocyanidins through the inhibition of COX-2 in prostaglandin synthesis (Suwandi et al., 2021).

In studies on antidiabetic activity, avocado leaves (*Persea americana* Mill) were shown to contain condensed tannins with significant antidiabetic effects. Administration of a 70% methanol extract of avocado leaves at doses I (100 mg/200 g BW), II (150 mg/200 g BW), and III (200 mg/200 g BW) led to substantial reductions in blood sugar levels in male

Wistar rats induced with alloxan (Handayani et al., 2016). Furthermore, research by Nurcahyo & Prastowo (2017) identified that apus bamboo leaves (*Gigantochloa apus*) contain 8.81% w/w condensed tannins (proanthocyanidins), petung bamboo leaves (*Dendrocalamus asper*) contain 4.84%, and legi bamboo leaves (*Gigantochloa atter*) contain 3.19%. These findings suggest potential anthelmintic properties of these bamboo leaves.

**Clinical trials on proanthocyanidin compounds**

Clinical trial data (Table 3) reveal that cranberry (*Vaccinium macrocarpon*) contains proanthocyanidins with significant antibacterial activity. In a study involving 189 adults, the consumption of 250 ml of cranberry juice twice daily for 35 and 90 days resulted in a notable reduction in *H. pylori* colonization (Cires et al., 2017). Additionally, proanthocyanidins have been shown to prevent bacterial infections by inhibiting bacterial adhesion to cellular surfaces and biomaterials, and by disrupting the motility of pathogens such as *Pseudomonas aeruginosa*, Escherichia coli, and Proteus mirabilis (Maisuria et al., 2016).

Cherry fruit, which is rich in condensed tannins, has demonstrated efficacy as a therapy for insomnia. Cherry juice has been found to improve sleep duration, enhance sleep efficiency, lower the serum kynurenine-to-tryptophan ratio, reduce serum PGE2 levels, decrease inflammation, and inhibit indoleamine 2,3-dioxygenase, thereby reducing tryptophan degradation (Losso et al., 2018).

Furthermore, condensed tannins have shown potential in the prevention and treatment of COVID-19. Consuming grape seeds, red grapes, cranberries, and blueberries, all rich in condensed tannins, can benefit COVID-19 patients by boosting immune function, improving skin hydration, and enhancing cognitive function. These substances also exhibit antioxidant and anti-cholesterol properties (Wang et al., 2022).

## CONCLUSION

Proanthocyanidins, as condensed tannins, have demonstrated extensive therapeutic potential across various health domains, including their antioxidant, antibacterial, antidiabetic, and immunostimulant properties. The findings from this comprehensive review, which includes in vitro, in vivo, and clinical trial data, emphasize the significant role these polyphenolic compounds can play in health promotion and disease prevention. However, the current body of research is still evolving, and further studies are necessary to fully elucidate the mechanisms of action of proanthocyanidins and to optimize their clinical applications. Future research should focus on detailed mechanistic studies, dose-response relationships, and long-term safety assessments to better integrate proanthocyanidins into preventive and therapeutic health strategies. Additionally, expanding clinical trials to include diverse populations and health conditions will be crucial in confirming the wide-ranging benefits of these compounds

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