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Review Article
A Comprehensive Review of the Antithrombotic Potential of Propolis: Insights into the Therapeutic Properties of Bee Glue

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Abstract

Propolis, a resinous substance produced by bees, has garnered attention for its potential as a natural antithrombotic agent due to its rich composition of bioactive compounds. This review explores the therapeutic effects of propolis, specifically focusing on its ability to inhibit platelet aggregation, promote fibrinolysis and regulate hemostatic balance. The study reviews various experimental models and clinical studies that assess the antithrombotic potential of propolis. It was found that propolis exerts significant effects by targeting multiple pathways involved in thrombus formation and clot resolution. Specifically, it inhibits excessive platelet activation, enhances fibrinolysis and maintains hemostatic balance. Additionally, the antioxidant and anti-inflammatory properties of propolis help reduce oxidative stress and systemic inflammation, both of which are linked to thrombosis. Key findings include the inhibition of platelet aggregation and enhancement of clot breakdown, supporting propolis as a promising natural alternative for thrombotic prevention and management. Propolis demonstrates significant potential as a natural adjunct to conventional antithrombotic therapies. Its multifaceted therapeutic actions, antithrombotic, antioxidant and anti-inflammatory, make it a promising candidate for reducing thrombosis risk. Propolis could become an important addition to current strategies for preventing and managing thrombotic disorders.

Key words: Propolis, blood clotting, fibrinolysis, platelet activity, bioactive compounds

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Normal blood flow through blood vessels is unobstructed. However, when capillaries are damaged, blood can leak out, including plasma and cells and excessive bleeding can be fatal. Hemostasis is the physiological process that stops bleeding by forming blood clots at the site of arterial injury. This process involves the activation of platelets and a cascade of coagulation factors[1]. The fibrinolytic system, which removes clots that are no longer needed for hemostasis, is also an integral part of the overall hemostatic system[2]. Blood clots can also form at sites where the vascular endothelium is damaged, leading to thrombus formation and other thrombotic conditions. These clots, known as thrombi, result in a condition called thrombosis[3]. Thrombi in the brain, lungs or coronary arteries can be fatal[4]. Specifically, thrombosis is a pathological clot that occurs when hemostasis is excessively triggered in the absence of bleeding.

In a healthy individual, the clotting process is regulated to prevent thrombus formation. However, individuals with risk factors such as dyslipidemia, diabetes mellitus, obesity, psychological stress, a sedentary lifestyle and cigarette smoking are more prone to developing clots in their blood vessels[5]. Atherosclerosis, characterized by fatty plaque deposits that obstruct blood vessels, further increases the risk of thrombosis[6].

In industrialized nations, where poor lifestyle choices have increased the risk of thrombotic events and the incidence of thrombosis, thrombosis prevention has become a top priority[7]. Various medications are used to combat thrombotic illnesses in these countries[8], but these medications can also disrupt the proper functioning of the hemostatic system, increasing the risk of bleeding.

Antithrombotic activity generally includes plasma's anticoagulant and antiplatelet properties and, in some cases, fibrinolytic properties[8,9]. Antithrombotic medications include fibrinolytic enzymes that directly destroy thrombi, anticoagulants that inhibit the coagulation system and prevent further clot growth and antiplatelet drugs that reduce platelet aggregation and prevent thrombus development[10]. It is essential to conduct *in vitro* and *in vivo* experiments to determine if these compounds affect blood coagulation factors, platelets and the fibrinolytic system to provide antithrombotic effects[11,12].

This review discusses the potential antithrombotic qualities of propolis and its natural ingredients. Propolis, known for its high polyphenol and flavonoid content, has been the subject of several studies investigating its potential as an anticoagulant and/or antiaggregant agent. Therefore, the main goal of the current study is to highlight evidence from previous studies that supports this belief.

METHODOLOGY

Literature search: A systematic literature search was conducted using databases like PubMed and Scopus with keywords such as propolis, antithrombotic properties, bioactive compounds, fibrinolysis and platelet aggregation.

Study selection: Studies published between (2018-2024) were included based on their focus on the chemical composition, mechanisms of action and clinical applications of propolis in thrombosis. Inclusion criteria emphasized experimental studies, clinical trials and reviews relevant to the objectives.

Data extraction: Key data were extracted on the bioactive compounds of propolis and their effects on platelet aggregation, fibrinolysis and coagulation pathways.

Categorization and synthesis: Findings were grouped into themes such as platelet aggregation inhibition, fibrinolysis promotion and antioxidative mechanisms to ensure a comprehensive understanding.

Critical evaluation: Studies were assessed for their design, outcomes and limitations to identify evidence gaps and recommend directions for future research.

Propolis

Chemical structure and biological functions: Propolis is a hive product made by bees combining resinous materials gathered from various plants or trees with their saliva[13]. While honeybee propolis is well-known and widely used, other types of bees also produce propolis[14]. Globally, propolis is utilized as a folk remedy and dietary supplement and studies have demonstrated its wide range of biological functions. Propolis contains various chemicals, typically in the following ratios: Resins and balsam (50%), beeswax (30%), pollen (5%), essential and aromatic oils (10%) and other organic components. Generally, propolis comprises polyphenols (flavonoids, phenolic acids and esters), phenolic aldehydes and ketones, among other substances[11].

However, the composition and biological activity of propolis are significantly influenced by the location of the bees, the time of year the resins are collected and the plants from which the resins are derived[15]. For example, propolis

from Europe and North America primarily contains flavonoids, phenolic acids and their esters[16]. Chinese propolis is highly antioxidative and rich in benzyl caffeate[17], while Brazilian propolis is abundant in various physiologically active chemical compounds, such as anti pilling C[18]. This chemical heterogeneity of propolis is thus understandable, with the region of production greatly affecting its properties.

Seasonal changes also impact the quality of propolis. Salatino *et al.*[19] documented seasonal variations in the antioxidant activity of Argentinean propolis, noting that samples collected in November, had the highest level of antioxidant activity, which correlated with flavonoid concentration. In Brazilian propolis, the contents of Mg, Fe, Na, Ca and Cu fluctuate seasonally. Additionally, the dry and wet seasons distinctly affect the antibacterial activity and chemical composition of Brazilian red propolis. As a result, the quality of propolis varies seasonally even within the same location[20].

Propolis contribution in hemostasis

Clinical evidence: Platelet function disorders, a category of bleeding disorders closely linked to oxidative stress, involve abnormalities in platelet activity. Inhibitors of platelet aggregation play a crucial role in various stages of the clotting cascade by preventing clot formation and inhibiting platelet adhesion. Medications such as aspirin and other antiplatelet agents are effective in preventing clot formation by inhibiting platelet aggregation[21]. Anticoagulants, commonly referred to as blood-thinning medications, also reduce or prevent blood clotting by extending clotting time, in addition to antiplatelet drugs.

In addition to exploring anticoagulant and antiplatelet medications, research has investigated natural compounds with inhibitory properties due to their flavonoid content[11,22]. Compelling evidence suggests that flavonoids derived from herbs like garlic and thyme may inhibit the production of vitamin K in the digestive system[23]. Caffeic acid phenethyl ester (CAPE), a significant constituent of propolis, has been shown to exhibit dose-dependent fibrinolytic activity in human whole blood clots[24]. *In vitro* studies using coagulation assays such as prothrombin time (PT), thrombin time (TT) and Activated Partial Thromboplastin Time (aPTT) have demonstrated the antithrombotic effects of flavonoids like rutin and hesperetin[25]. Another study highlighted the impact of extracts from the flavonoid-rich diet *Rhizophora mucronata* Poir on coagulation factors[26].

While, these individual medications and naturally occurring compounds rich in polyphenols show promising results, their combined use may pose risks due to potential interactions or adverse effects. Therefore, individuals on blood thinners should exercise caution and be mindful of their dietary choices[22].

Anticoagulant activity of propolis: Propolis, widely used in apitherapy, is a natural supplement rich in phenolic acids and flavonoids which contribute to its significant antioxidant, anti-inflammatory and antibacterial properties. However, high-concentration propolis extracts may pose risks when taken concurrently with blood thinners like aspirin and warfarin[9]. Research indicates that propolis may also possess antiplatelet properties[19]. Despite extensive studies on the impact of various plant extracts on blood coagulation, research specifically focusing on propolis remains limited.

The diversity of flavonoids in bee pollen may contribute to these effects[19]. For instance, quercetin, a commonly known flavonoid in propolis, has been shown to affect platelet aggregation[27]. Additionally, flavonoid-rich plant extracts, including propolis, have been linked to fibrinolytic activity[3]. The CAPE, for example, has been found to exhibit notable fibrinolytic activity, as shown by thrombolysis assays[28].

Furthermore, propolis flavonoids demonstrate inhibitory effects on clotting factors. It is essential to conduct studies examining the concentrations and combinations of propolis-derived compounds to better understand their effects on the hemostatic system[5].

Antiplatelet activity of propolis: Platelets play a crucial role in blood clotting by aggregating at the site of blood vessel injury. However, excessive platelet aggregation can lead to thrombus formation and subsequent cardiovascular events such as heart attacks and strokes. Propolis has demonstrated significant antiplatelet activity in various studies of Salatino *et al.*[19]. Youssef *et al.*[26] examined the effects of propolis on platelet aggregation *in vitro*, finding that propolis extracts significantly inhibited platelet aggregation induced by adenosine diphosphate (ADP). The active compounds in propolis, such as flavonoids and phenolic acids, were identified as key contributors to this antiplatelet effect.

In addition to inhibiting platelet aggregation, propolis has been shown to reduce the production of Thromboxane A2 (TXA2), a potent platelet activator[28]. This reduction in TXA2 synthesis is thought to be a critical mechanism by which propolis helps prevent excessive platelet aggregation. Furthermore, Fouad *et al.*[29] demonstrated that the flavonoid-rich extracts from Brazilian red propolis not only inhibit platelet aggregation but also exhibit a dose-dependent effect on reducing platelet activation.

Fibrinolytic activity of propolis: Fibrinolysis is the process by which blood clots are dissolved after they have fulfilled their role in hemostasis[30]. It is essential for maintaining the balance between coagulation and clot dissolution. Several studies have highlighted the fibrinolytic activity of propolis. Lai *et al*.[31] found that propolis extracts enhanced fibrinolysis by increasing the activity of plasminogen protein involved in clot breakdown. Furthermore, propolis' ability to stimulate the release of tissue plasminogen activator (tPA), which converts plasminogen to plasmin, further supports its role in promoting fibrinolysis[9].

The impact of propolis on fibrinolytic pathways suggests its potential as an adjunctive treatment for conditions like deep vein thrombosis and pulmonary embolism, where the body fails to dissolve clots adequately[2]. However, more clinical studies are necessary to fully assess the therapeutic potential and safety of propolis for fibrinolysis.

Propolis and antioxidant activity: Oxidative stress plays a significant role in the pathogenesis of thrombosis. Free radicals can damage the endothelial cells lining blood vessels, making them more susceptible to clot formation. Propolis, with its high antioxidant content, has the potential to mitigate oxidative stress and reduce the risk of thrombus formation. Studies have shown that propolis exhibits significant free radical scavenging activity, primarily due to its flavonoid and polyphenol content[32]. The antioxidants in propolis neutralize free radicals, thereby protecting the blood vessel walls from oxidative damage and preventing the initiation of thrombosis.

Lunardelli *et al*.[8] found that propolis extracts, particularly from the Brazilian red variety, showed strong antioxidant activity in both *in vitro* and *in vivo* models. This activity was linked to the reduction of malondialdehyde (MDA) levels, a marker of oxidative stress. Additionally, propolis was shown to increase the levels of endogenous antioxidants like superoxide dismutase (SOD) and catalase, further enhancing its protective effect against oxidative damage.

Mechanisms of action of propolis in thrombosis prevention: The mechanisms by which propolis prevents thrombosis are multifaceted and involve both direct and indirect pathways. The primary bioactive compounds in propolis, including flavonoids, phenolic acids and terpenes, have been shown to affect key processes in hemostasis and thrombosis prevention.

One of the most important mechanisms is the inhibition of platelet aggregation. As previously mentioned, flavonoids in propolis, such as quercetin and kaempferol can block the activation of platelets, thus preventing the formation of thrombi[19]. Additionally, propolis ability to reduce TXA2 production plays a key role in its antiplatelet effect.

Propolis also exerts anticoagulant effects by interacting with various coagulation factors, potentially prolonging clotting times[5]. Studies have demonstrated that propolis can significantly reduce the activation of factors like thrombin and factor Xa both of which are critical in the coagulation cascade. This anticoagulant effect further supports propolis as a potential natural alternative to conventional anticoagulants.

Moreover, propolis promotes fibrinolysis by enhancing the activity of plasminogen and stimulating the release of tPA. These effects contribute to the breakdown of blood clots and prevent the formation of pathological thrombi[24].

The antioxidant activity of propolis also plays a crucial role in thrombosis prevention by protecting the endothelial cells from oxidative damage, a key factor in the initiation of thrombosis[33].

Clinical implications and future directions: While studies on the antithrombotic properties of propolis are promising, clinical evidence is still limited and further research is needed to confirm its efficacy and safety. Large-scale clinical trials are necessary to determine the optimal dosage and treatment duration for propolis, as well as its potential interactions with conventional blood-thinning medications. Additionally, future studies should explore the synergistic effects of propolis with other natural anticoagulants and antiplatelet agents.

In animal studies, propolis has been investigated for its role in improving clotting function in animals with conditions such as hemophilia, thrombocytopathy or those undergoing major surgeries. By modulating platelet aggregation, enhancing vascular integrity and reducing excessive bleeding, propolis could offer an adjunctive or alternative treatment to conventional therapies, particularly in cases where synthetic anticoagulants may pose risks of adverse effects[33,34].

Given the growing interest in natural products and the increasing demand for alternative therapies, propolis represents a promising candidate for thrombosis prevention and management. However, more rigorous studies are required to fully understand its therapeutic potential in clinical practice.

CONCLUSION

Propolis, with its rich composition of bioactive compounds, has demonstrated significant potential as an antithrombotic agent. Its antiplatelet, anticoagulant and fibrinolytic properties, combined with its antioxidant activity,

make it a promising natural alternative to conventional thrombosis medications. However, more clinical studies are needed to better understand its safety and efficacy and to establish guidelines for its use in thrombosis prevention and management. The exploration of propolis as a natural remedy for thrombosis could potentially lead to the development of safer, more effective therapies for patients at risk of thrombotic events.

SIGNIFICANCE STATEMENT

This comprehensive review emphasizes the significant antithrombotic potential of propolis, detailing its ability to modulate key pathways involved in platelet aggregation, fibrin formation and clot resolution. The review highlights the bioactive compounds in propolis, such as flavonoids and phenolic acids, which exhibit strong antithrombotic effects by inhibiting thrombus formation and enhancing fibrinolysis. This positions propolis as a promising natural agent for preventing and managing thrombotic disorders, suggesting its potential as a complementary therapy in cardiovascular disease management. However, further clinical studies are necessary to confirm its efficacy and safety in humans.

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