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The Antithrombotic Potential of Propolis: Acomprehensive Review

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ABSTRACT

Thrombosis, the abnormal formation of blood clots within vessels, is a major contributor to global morbidity and mortality, leading to conditions such as myocardial infarction, stroke, and venous thromboembolism. Although advancements in antithrombotic therapies have been made, conventional treatments are often associated with significant risks, particularly bleeding and other adverse effects, highlighting the need for safer, more effective alternatives. Propolis, a resinous substance produced by bees, has long been used in traditional medicine and is gaining attention for its potential antithrombotic properties. Rich in bioactive compounds like flavonoids, phenolic acids, and terpenes, propolis has demonstrated multiple therapeutic effects, including antimicrobial, anti-inflammatory, antioxidant, and antithrombotic actions. Studies show that propolis can inhibit platelet aggregation, promote fibrinolysis, and help regulate hemostatic balance, thereby preventing excessive clot formation. Additionally, propolis's antioxidant and anti-inflammatory properties may reduce the oxidative stress and inflammation that contribute to thrombosis. While promising as a natural alternative or adjunct to conventional antithrombotic drugs, the use of propolis requires further validation through large-scale, controlled clinical trials to establish its efficacy, optimal dosing, and long-term safety. Nevertheless, propolis offers a potential, low-risk approach to managing thrombotic diseases with reduced side effects.

Keywords: Propolis, Blood clotting, Fibrinolytic, Platelet activity, Coagulation tests ,Bioactive compounds

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 process by which blood clots form at wound sites in damaged arteries to stop bleeding, involving platelets and a series of coagulation factors (Favaloro et al.,2023). The fibrinolytic system, which removes clots that are no longer needed for hemostasis, is also an integral part of the overall hemostatic system (May et al.,2021).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 (Wang et al.,2018). Thrombi in the brain, lungs, or coronary arteries can be fatal (Lacey et al.,2020). 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 (Batten et al.,2023). Atherosclerosis, characterized by fatty plaque deposits that obstruct blood vessels, further increases the risk of thrombosis(Al Said et al.,2018).

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 (Makedonov et al.,2020). Various medications are used to combat thrombotic illnesses in these countries [Lunardelli et al.,2022], but these medications can also disrupt the proper functioning of the hemostatic system, increasing the risk of bleeding. Consequently, there is a preference for milder agents that cause less bleeding. Finding natural compounds and alternative medicines with antithrombotic properties is currently a major goal, and the use of such products for thrombosis prevention is anticipated (Subramani and Sathiyarajeswaran ,2022).Antithrombotic activity generally includes plasma's anticoagulant and antiplatelet properties and, in some cases, fibrinolytic properties (Lunardelli et al.,2022). 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 (Hirsh et al.,2019). 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.

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.

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 (Chuttong et al.,2023). While honeybee propolis is well-known and widely used, other types of bees also produce propolis (Campos et al.,2023). 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 (Chuttong et al.,2023)..

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 (Miłek et al.,2022). For example, propolis from Europe and North America primarily contains flavonoids, phenolic acids, and their esters (Arathi et al.,2021). Chinese propolis is highly antioxidative and rich in benzyl caffeate (Hossain et al.,2022). while Brazilian propolis is abundant in various physiologically active chemical compounds, such as artepillin C (Salatino et al.,2021). 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. Mendez-Pfeiffer et al.(2020) 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 (Barreto et al.,2022).

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 (Silva et al.,2021). 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 (Lv et al.,2021). Compelling evidence suggests that flavonoids derived from herbs like garlic and thyme may inhibit the production of vitamin K in the digestive system (Fuentes et al.,2021).Caffeic acid phenethyl ester (CAPE), a significant constituent of propolis, has been shown to exhibit dose-dependent fibrinolytic activity in human whole blood clots (Meradi et al.,2022). 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 (Lee et al.,2024). Another study highlighted the impact of extracts from the flavonoid-rich diet Rhizophora mucronata Poir on coagulation factors (Youssef et al.,2022).

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 (Oliveira et al.,2020).

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 Subramani and Sathiyarajeswaran ,2022)Research indicates that propolis may also possess antiplatelet properties (Silva et al.,2021). 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 its antiplatelet effects. Certain flavonoids found in bee pollen, including chrysin, baicalein, apigenin, luteolin, kaempferol, quercetin, and rutin, have been identified as competitive inhibitors of CYP isoenzymes (Gasmi et al.,2022). However, a separate study found no statistically significant difference between bee pollen and placebo groups in terms of antiplatelet effects. Conversely, propolis demonstrated a beneficial effect on average bleeding times in mice, unlike bee pollen, despite its adverse effects (Silva et al.,2021).This underscores the potential antiplatelet effect of propolis administration, with bleeding times measured as 102 seconds for placebo, 442 seconds for aspirin, and 310 seconds for propolis.

In vitro investigations have shown that caffeic acid phenethyl ester (CAPE), a major component of propolis, exhibits dose-dependent fibrinolytic activity (Rodríguez et al.,2022). Previous studies in rats have reported lower fibrinogen levels but prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT) following CAPE administration (Pérez et al.,2023). However, these studies used pure CAPE, neglecting the matrix effect caused by polyphenols in propolis. Flavonoids, the largest molecular subclass of phenolic compounds, have been shown to inhibit several Cyt-P450 enzymes and influence the coagulation cascade (Oliveira et al.,2020).

ANTIPLATELET CAPACITY OF PROPOLIS

Platelets play a crucial role in hemostasis and the pathogenesis of cardiovascular and cerebrovascular diseases by aggregating and forming thrombi on injured blood vessel surfaces (Stegner et al.,2019). Managing platelet activation is critical in treating thrombosis, cardiovascular diseases, and cerebrovascular disorders, despite the bleeding risks associated with current antiplatelet medications used clinically.

Caffeic acid phenethyl ester (CAPE), found in propolis from Europe, the Far East, and New Zealand, has been extensively studied both in vivo and in vitro, revealing its diverse biological actions . CAPE is attributed with anticancer, antioxidant, immunomodulatory, antibacterial, antiviral, anti-inflammatory, neuroprotective, hepatoprotective, and cardioprotective properties (Olgierd et al.,2021). Studies suggest that CAPE influences platelet activation, with Chavda et al. (2023) demonstrating its inhibitory effect on collagen-induced platelet activation in human platelets.

CAPE (25 μM) has also been shown to inhibit platelet aggregation induced by α2β1 integrin

agonist aggretin and glycoprotein VI agonist convulxin. Additionally, CAPE inhibits thromboxane A2 (TXA2) formation, v-Akt murine thymoma viral oncogene (AKT) phosphorylation, and other pathways associated with collagen-induced platelet activation (Chavda et al.,2023). Furthermore, a CAPE analog (CAPE-NO2) demonstrated inhibition of collagen-induced platelet aggregation, possibly through upregulation of cyclic guanosine monophosphate (cGMP) and nitric oxide (NO) and downregulation of thromboxane B2 (TXB2), cyclooxygenase 1 (COX-1), and serotonin (5HT) (Khoshandam et al.,2023).

Studies have demonstrated that aqueous propolis extract inhibits platelet aggregation in a dose-dependent manner when induced by agonists such as collagen, thrombin receptor activator peptide, and adenosine diphosphate (Bhargava et al., 2021). Specific propolis constituents, including galangin, apigenin, quercetin, kaempferol, ferulic acid, rutin, chrysin, pinostrobin, and pinocembrin, were identified as key contributors to this effect. These findings suggest that propolis components, including CAPE, may offer therapeutic potential for thrombotic disorders, though clinical validation remains necessary. In vivo studies have also shown that CAPE (5 mg/kg) significantly delays platelet plug formation in mice (Silva et al., 2021).

Recently, Bhargava et al. (2021) demonstrated through whole-blood platelet aggregation experiments that ethanolic extracts of propolis inhibit ADP-induced platelet aggregation . Their study confirmed the antiplatelet activity of propolis ethanolic extracts at low micromolar concentrations in whole blood samples. Additionally, oral administration of propolis (65 mg/kg/day) extended tail bleeding time in mice, mirroring the in vivo platelet aggregation activity observed with oral aspirin (10.4 mg/kg). These results indicate potential beneficial effects of propolis supplementation in vivo, though further research is needed to confirm these findings.

PROPOLIS APPLICATION TO THROMBOSIS PREVENTION AND THERAPY

The potential of propolis to prevent and treat thrombosis is gaining attention, although studies investigating its effects on thrombosis are scarce. It is crucial to disseminate the potential antithrombotic effects of propolis to encourage further research in this area. As mentioned earlier, propolis's antithrombotic effects are bolstered by its ability to inhibit platelet aggregation and plasminogen activator inhibitor-1 (PAI-1) formation.Research using whole blood has

demonstrated that even small amounts of propolis (5 μg of flavonoids) incorporated into whole blood can inhibit platelet aggregation . Oral propolis (65 mg/kg/day) significantly prolongs tail bleeding duration, indicating in vivo platelet aggregation activity (Bt Hj Idrus et al.,2020). Moreover, propolis dietary supplementation (0.5% ethanol extract) inhibits PAI-1 production in mice (Kitamura et al.,2019). While propolis's antithrombotic properties have yet to be extensively studied in clinical settings, the propolis concentrations utilized in these studies provide valuable insights for future investigations.

Propolis's antithrombotic qualities, like its other biological characteristics, are closely tied to its chemical composition, which varies based on local flora, pollen collection season, harvesting methods, and bee species. Further research on propolis's active ingredients and their impact on platelets, the fibrinolytic system, and blood coagulation factors is essential before clinical use. Validation and quality control of propolis's antithrombotic properties are imperative for its therapeutic applications.

IMPACT OF PROPOLIS ON THE FIBRINOLYTIC SYSTEM

Fibrinolysis plays a critical role in healing vascular injuries by breaking down clots. By removing fibrin from the vascular system, fibrinolysis prevents the formation of pathological thrombotic clots, thereby averting blood vessel obstruction (May et al.,2021). Enhancing fibrinolysis is therefore essential for reducing the risk of thrombosis.The process of fibrinolysis is controlled by plasminogen activator (PA) and plasminogen activator inhibitor-1 (PAI-1) (Keasey et al.,2022).PAI-1 is synthesized by various tissues including the liver, adipose tissue, muscle, bone, and hematopoietic cells. It inhibits tissue plasminogen activator during blood fibrinolysis. Elevated plasma PAI-1 levels hinder clot dissolution, contributing to thrombosis. Individuals with metabolic syndrome, such as obesity and diabetes, often exhibit higher plasma PAI-1 levels, indicating a predisposition to thrombosis due to metabolic imbalances (Lai et al.,2023)

Obesity and related disorders are exacerbated by chronic low-grade inflammation (Longo et al.,2019). Increased plasma PAI-1 levels in adipose tissues of obese individuals are closely associated with this chronic inflammation. Thus, reducing PAI-1 elevation linked to chronic low-grade inflammation may help mitigate thrombosis associated with lifestyle-related diseases. In an animal model, chronic low-grade inflammation induced a propensity for thrombosis, which was alleviated by oral ethanol extract of Brazilian propolis, suppressing the elevation of plasma PAI-

1 (Kitamura et al.,2019). Moreover, Brazilian propolis ethanol extract reduced PAI-1 production in cultured HUVEC cells stimulated with inflammatory TNF-α, a cytokine known to induce PAI-1 release into the media (Khoshandam et al.,2023).Chrysin, a compound found in Brazilian propolis albeit in relatively low concentrations, was identified as the most potent inhibitor of TNFα-induced PAI-1 secretion from HUVEC cells (Ismail et al.,2021).Further research is needed to elucidate how propolis influences PAI-1 synthesis and to identify specific components in Brazilian propolis that effectively inhibit PAI-1 production.The following table (1) summarizes the actions of propolis on blood clotting, including its effects at various stages and underlying mechanisms.

CONCLUSION

In summary, propolis exhibits significant anti-thrombotic activity, largely determined by its intricate chemical composition, which is influenced by various factors such as local flora, the timing of pollen collection, and the specific bee species involved. This natural product has the potential to serve as an innovative therapeutic agent for the management of thrombotic disorders due to its ability to modulate platelet function, enhance fibrinolytic activity, and influence coagulation pathways. However, the journey towards integrating propolis into clinical practice requires a robust foundation of scientific inquiry.

To unlock its full therapeutic potential, comprehensive research is essential to identify and characterize the bioactive compounds responsible for its anti-thrombotic effects. Understanding the molecular mechanisms underlying these actions will not only elucidate how propolis functions at a biochemical level but also guide the development of targeted therapies. Additionally, it is imperative to conduct pharmacokinetic studies that explore the absorption, distribution, metabolism, and excretion of propolis, alongside investigations into potential interactions with established anticoagulant medications. Such studies are crucial to assess the safety and efficacy of propolis, particularly in populations with varying health profiles.The establishment of rigorous validation processes, standardization of chemical constituents, and the implementation of strict quality control measures are vital to ensure that propolis can be reliably used as a therapeutic agent. These steps will enhance reproducibility and safety, providing confidence to healthcare practitioners and patients alike.

Moreover, future clinical trials must be designed to evaluate the efficacy of propolis in a clinical setting, determine optimal dosages, and define its role within the broader context of anti-thrombotic therapy. By systematically addressing these challenges, propolis could emerge as a valuable alternative or complementary option in the treatment of thrombotic disorders, potentially transforming the landscape of thromboembolic management and contributing to the advancement of natural products in modern medicine.In conclusion, while the promise of propolis as an anti-thrombotic agent is evident, a concerted effort in research and clinical evaluation is essential to fully realize its benefits for patient care and public health.

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The author designed the article, searched the literature, wrote the first draft, reviewed the revised draft of the manuscript, completed the manuscript, and approved the submitted version.

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CONFLICT OF INTEREST

The author declare that they have no conflict of interest.

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