Immunomodulatory and Therapeutic Potentials of Honeybee Products: A Comprehensive Review of Their Role in Health and Disease Management

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Abstract

In this review study, we explore the therapeutic potential of bee products, including royal jelly, propolis, and honey in modulating the immune system and addressing many different health conditions. This review aims to provide a comprehensive understanding of the bioactive components of bee products and their role in enhancing human health. Products by honeybees (bee), such as propolis, royal jelly, and their bioactive ingredients, have drawn interest for their potential as treatments for a range of skin conditions because of their strong antibacterial, anti-inflammatory, regenerative, and immunomodulatory qualities. Studies have demonstrated the

ability of royal jelly and its constituent 10-hydroxy-2-decenoic acid (10-HDA) to regulate melanogenesis, offering promising avenues for treating pigmentation disorders such as melasma and skin aging by modulating key enzymes involved in melanin production. Additionally, these bee products have been shown to enhance wound healing by promoting tissue regeneration, reducing inflammation, and accelerating the closure of wounds. Royal jelly's water-soluble proteins, such as MRJP2, MRJP3, and MRJP7, stimulate epidermal cell proliferation and migration, while propolis exhibits strong antibacterial and anti-inflammatory activities, further supporting its use in treating wounds and skin infections. The combination of propolis with polymer-based wound dressings has demonstrated enhanced wound closure and accelerated healing, particularly in diabetic and burn models. These findings suggest that bee products offer a natural and effective alternative for dermatological treatments, with the potential for incorporation into tissue engineering approaches for improved wound healing. However, further clinical studies are required to validate the safety, efficacy, and mechanisms of action of these bee-derived products in human dermatology, which could ultimately lead to their integration into mainstream therapeutic strategies for skin diseases.

Keywords: Honeybee products, Royal jelly, Wound healing, Melanogenesis, Propolis.

1. Context

The human immune system plays a crucial role in defending against infections, inflammation, and disease (1). Natural bioactive compounds have gained increasing attention for their potential to modulate immune responses and improve overall health. Among these, bee-derived products have demonstrated significant immunomodulatory, antimicrobial, and anti-inflammatory properties, making them valuable for therapeutic applications (2). Honeybees produce a variety of bioactive substances, including honey, propolis, royal jelly, bee pollen, bee bread, venom, and wax (3). The health benefits, nutritional value, and medicinal properties of these bee-derived products have been recognized since ancient times, with historical documentation from Egyptian, Greek, and Chinese civilizations (4). Traditionally, these products have been utilized as dietary supplements to promote health and well-being (5). Bee products exhibit diverse biological activities, including antimicrobial, anti-inflammatory, anticancer, and antioxidant effects. Their bioactive composition includes proteins, peptides,

minerals, flavonoids, terpenes, fatty acids, and phenolic compounds, contributing to their physiological efficacy (6).

Among these, propolis, also referred to as "bee glue" or "Russian Penicillin," is a resinous, lipophilic substance synthesized by honeybees. It is composed of a mixture of plant resins (50%), waxes (30%), essential and aromatic oils (10%), pollen (5%), and other organic compounds (5%) (7). Honeybees collect resins from tree bark and leaf buds, blend them with their wax, and use the resulting substance to reinforce hive structures. Propolis possesses well-documented antibacterial, antiviral, anticancer, and anti-inflammatory properties, with evidence suggesting that it is the most potent antioxidant among bee-derived products (2). Ethanolic extracts of propolis (EEP) and its phenolic constituents have been shown to induce apoptosis in cancer cells via the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) pathway (8).

Similarly, bee venom and its major component, melittin, exhibit potent anti-inflammatory and immunomodulatory properties. Bee venom is a natural toxin synthesized by the poison and accessory glands of worker honeybees and stored in a venom reservoir within the abdominal cavity (9). It plays a crucial role in colony defence and has demonstrated anti-inflammatory, radioprotective, and antibacterial effects. Additionally, it has been investigated for its therapeutic potential in conditions such as rheumatism and cancer due to its ability to induce cytotoxic effects on malignant cells. Bee venom consists of various biologically active molecules, including melittin, apamin, adolapin, secapin, tertiapin, mast cell-degranulating phospholipase A2, and hyaluronidase (10).

Honeybee pollen, a mixture of flower pollen and nectar, serves as a crucial nutrient source for hive inhabitants. It is rich in proteins, amino acids, saccharides, vitamins, and minerals, making it one of the most nutrient-dense natural substances (11). As a result, bee pollen is widely regarded as a "superfood" and is commercially marketed as a dietary supplement (12). Another important bee product, royal jelly, is primarily used to nourish the queen bee and larvae (13). However, due to its functional bioactivity, it has also been commercially produced for use in the food and cosmetic industries. Royal jelly is an acidic emulsion composed of fats, proteins, and carbohydrates suspended in 60–70% water (7). The primary sugars present are glucose and fructose, which constitute approximately 90% of the total sugar content. Its lipid profile is unique, predominantly comprising short-chain fatty acids, particularly hydroxyl and carboxylic acids, which differ from organic acids found in other biological sources (7). Royal jelly exhibits antimicrobial, anti-inflammatory, immunomodulatory, and anti-diabetic properties, further highlighting its commercial and medicinal significance (14).

Numerous studies have documented the therapeutic potential of bee-derived products, including bee venom, royal jelly, propolis, bee pollen, and honey, in managing inflammatory and autoimmune diseases (2). However, clinical investigations on their applications remain limited. One of the key challenges is the risk of allergic reactions, including asthma and anaphylaxis, which have been reported following the consumption of royal jelly, bee venom, and bee pollen (15). These adverse reactions may restrict their widespread use despite their established health benefits. This review comprehensively examines the therapeutic potential of honeybee products, including royal jelly, propolis, and honey, in modulating immune responses and ameliorating various health disorders. It further delineates the bioactive constituents of these products and elucidates their molecular mechanisms underlying health-promoting effects, thereby providing a detailed understanding of their role in human health enhancement.

2. Evidence Acquisition

A comprehensive literature search was conducted using databases such as PubMed, Scopus, ScienceDirect, and Google Scholar to gather relevant peer-reviewed articles published between 2015 and 2025. The keywords used included “bee products,” “propolis,” “royal jelly,” “bee venom,” “immune modulation,” “bioactive compounds,” and “therapeutic potential.” Studies were selected based on relevance, scientific rigor, and focus on the immunological and therapeutic properties of bee-derived substances.

2.1. Immunomodulatory Effects of Bee Products in Diabetes

Diabetes mellitus (DM) is a chronic inflammatory and metabolic disorder characterized by immune system dysregulation, insulin resistance, and pancreatic β-cell dysfunction (16). The immune response plays a central role in the progression of diabetes, with increased levels of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), which promote immune-mediated pancreatic damage and insulin resistance (17). Bee-derived products, including propolis, bee pollen, and royal jelly, have demonstrated immunomodulatory properties that help regulate inflammatory pathways and restore immune homeostasis in diabetes models (7).

Propolis, a resinous bee product, has been shown to enhance innate immune responses in diabetic models by upregulating Toll-like receptors 2 (TLR-2) and TLR-4 (18). This activation stimulates B and T lymphocytes, promoting CCL21- and CXCL12-mediated chemotaxis, essential for immune surveillance and tissue repair. Additionally, propolis administration

restores cytokine balance by modulating the levels of IL-1β, IL-6, IL-2, IL-7, and TNF-α, thereby reducing chronic inflammation and immune dysregulation (19). In diabetic male rats, propolis treatment has been associated with a reduction in serum immunoglobulin levels (IgG, IgA, and IgE), key regulators of B and T cell proliferation, further indicating its role in immune modulation (20).

The immunoregulatory effects of bee pollen have also been explored, particularly in the context of diabetes-associated inflammation (21). The peptic bee pollen polysaccharide (RBPP-P) derived from Rosa rugosa exhibits a potent anti-inflammatory effect by downregulating TNF-α and IL-6, two cytokines known to exacerbate insulin resistance and immune dysregulation in diabetes. RBPP-P treatment has been found to reduce inflammatory cytokine levels in high-fat diet-induced diabetic mice, leading to improved insulin sensitivity and immune homeostasis (22).

Hyperglycemia and dyslipidemia in diabetes contribute to oxidative stress, which further disrupts immune function by promoting excessive reactive oxygen species (ROS) generation. This oxidative stress leads to immune cell dysfunction, chronic inflammation, and tissue damage in key organs such as the liver, pancreas, and kidneys (23). Propolis, royal jelly, and bee pollen have demonstrated significant antioxidative properties, mitigating the harmful effects of oxidative stress on immune cells and restoring redox balance (24). The polyphenolic compounds in propolis, including α-amylase inhibitors, α-glucosidase inhibitors, and caffeic acid phenethyl ester (CAPE), exhibit strong anti-hyperglycemic and anti-inflammatory effects by modulating immune responses and improving glucose metabolism. Propolis has been shown to improve lipid metabolism and reduce systemic ROS levels, thereby protecting immune cells from oxidative damage and enhancing overall immune function (25).

Studies in diabetic mouse models have shown that intraperitoneal administration of a water-soluble derivative of propolis (WSDP) or (–)-epigallocatechin gallate (EGCG) (50 mg/kg/day) for seven days results in decreased lipid peroxidation in immune-related organs such as the liver, kidney, and brain (26). This reduction in oxidative stress also leads to decreased DNA damage in peripheral lymphocytes, highlighting the role of propolis in protecting immune cells from diabetes-induced oxidative stress (26). Furthermore, WSDP and ethanolic propolis extract have been shown to enhance fatty acid metabolism, leading to an overall improvement in immune function, body weight regulation, and extended lifespan in diabetic models (8).

The ability of propolis to regulate immune responses is further demonstrated in STZ-induced diabetic rats, where a four-week treatment with either 30% or 15% ethanolic propolis extract (50 mL/kg) significantly reduces hyperglycemia and protects pancreatic and renal tissues from

immune-mediated damage (27). Blood glucose levels decreased from 393 ± 192.7 mg/dL to 154 ± 28.0 mg/dL in the group treated with 30% propolis extract, and from 386 ± 141.1 mg/dL to 331.5 ± 123.74 mg/dL in the 15% propolis-treated group. Histological analysis revealed reduced immune cell infiltration and improved tissue integrity in propolis-treated groups compared to controls (28). The immunoprotective effects were further supported by the inhibition of α-amylase (IC50: 0.62 ± 0.00 μg/mL) and α-glucosidase (IC50: 40.40 ± 0.09 μg/mL), with CAPE and chrysin identified as the dominant phenolic immunoregulators (28).

Bee pollen and date palm pollen have also demonstrated immunomodulatory effects in diabetic conditions. A four-week administration of bee pollen suspension (100 mg/kg) in STZ-induced diabetic Wistar rats resulted in improved immune responses, reduced systemic inflammation, and enhanced antioxidant defence (29). This was evidenced by decreased levels of nitric oxide (NO) and lipid peroxidation (LPx), both key markers of immune-driven oxidative stress. Additionally, bee pollen supplementation enhanced the activity of crucial antioxidant enzymes such as glutathione (GSH), glutathione-S-transferase (GSH-ST), glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD), which are essential for maintaining immune cell function under oxidative stress conditions (29).

2.2. Immunomodulatory Effects of Bee Products in Cancer

Cancer development is closely linked to immune system dysregulation and chronic inflammation, with nearly 20% of cancers attributed to inflammatory processes (30). Inflammation plays a pivotal role in tumor initiation, progression, invasion, and metastasis by modulating immune responses and altering the tumor microenvironment (31). The concept of chemoprevention involves using natural or synthetic compounds to suppress mutagenesis, carcinogenesis, tumor proliferation, and metastasis, thereby harnessing immune modulation as a strategy for cancer prevention and treatment (32).

Bee-derived products, particularly honey, propolis, and royal jelly, contain bioactive compounds with strong immunomodulatory, anti-inflammatory, and anticancer properties (3). The polyphenolic constituents of honey—pinobanksin, pinocembrin, luteolin, galangin, chrysin, and quercetin—have been shown to enhance immune responses while exerting anti-proliferative and anti-metastatic effects (34). These compounds regulate immune signaling pathways, induce apoptosis, and exhibit antioxidative activity against various cancer types. A key immune regulator in cancer progression is the tyrosine-phosphorylated signal transducer and transcription 3 activator (p-STAT3), which is heavily involved in lung and breast cancer pathogenesis. Manuka honey (MH) has demonstrated inhibitory effects on p-STAT3 in the triple-negative breast cancer cell line MDA-MB-231 and the non-small cell lung cancer cell

line A549. MH suppresses immune evasion by targeting the IL-6 receptor α chain (IL-6Rα), preventing its binding to IL-6 by approximately 60%. This inhibition reduces glycoprotein 130 (gp130) and tyrosine-phosphorylated JAK2 levels, both of which are critical components of IL-6-mediated immune suppression. Flavonoid compounds such as galangin, chrysin, quercetin, and luteolin in MH contribute to this immune regulatory effect by blocking IL-6Rα–IL-6 interaction by 34.3%, 31.8%, 29.2%, and 22.4%, respectively, at 50 μM concentrations (35).

Propolis, which is rich in polyphenolic compounds, has been widely recognized for its chemopreventive, tumor-inhibitory, and immunoprotective effects. These bioactive constituents modulate immune responses by inducing apoptosis, inhibiting matrix metalloproteinases, and regulating gene methylation (36). Propolis also exerts anti-inflammatory and anti-angiogenic activities against urothelial and bladder cancer. The water-soluble derivative of propolis (WSDP), along with its key polyphenolic compounds caffeic acid (CA) and caffeic acid phenethyl ester (CAPE), plays a crucial role in immune modulation and tumor suppression. When administered intravenously (50–150 mg/kg) in mammary carcinoma-bearing mice, WSDP, CA, and CAPE significantly reduced tumor colony formation (37). Additionally, subcutaneous administration inhibited tumor growth and prolonged survival. The proposed mechanism involves phenolic compounds activating macrophages, which block metastasis and increase hydrogen peroxide production—an essential factor in lymphocyte activation and immune response modulation. This aligns with findings that CA enhances spleen cell responses to polyclonal mitogens such as phytohemagglutinin (PHA), concanavalin A (ConA), pokeweed mitogen (PWM), and lipopolysaccharide (LPS) in treated mice, further highlighting its immune-stimulating potential (65). WSDP also suppresses IL-1, a key cytokine involved in B and T cell proliferation, thereby limiting immune-mediated tumor progression (8).

Another powerful bee product, royal jelly, has high anti-inflammatory and immunomodulatory properties that are effective against cancer cells. By preventing the synthesis of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-8, its active ingredient, 10-hydroxy-2-decenoic acid (10-HDA), controls immunological responses in human colon cancer cells (Collazo et al., 2021). 10-HDA promotes the synthesis of IL-1 receptor antagonist (IL-1ra) in WiDR human adenocarcinoma cells (BCRC 60157), which inhibits the growth-promoting effects of IL-1 and IL-8, which are both linked to the development of colon and pancreatic cancer. By inhibiting the self-renewal process of breast cancer stem cells (bCSCs) and limiting CD44-mediated clonal growth, CAPE, another important immunoregulatory drug, has been

demonstrated to specifically target bCSCs, lowering the risk of immune evasion and malignant transformation (38).

2.3. Immunomodulatory and Cardioprotective Effects of Bee Products in Hypertension

A significant risk factor for cardiovascular illnesses (CVDs), including myocardial infarction, heart failure, and cerebral stroke, hypertension is intimately associated with immunological dysregulation and chronic inflammation. The regulation of blood pressure and the inflammatory processes linked to hypertension and CVDs are mostly controlled by the renin-angiotensin system (RAAS). Modulating RAAS activity and controlling hypertension are popular uses of pharmacological therapies, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers, and direct renin inhibitors (39). Nonetheless, natural substances with antihypertensive and immunomodulatory qualities present encouraging supplementary strategies for vascular health and blood pressure management (40).

Products made from honeyhoneybees, especially royal jelly and bee pollen, have potent anti-inflammatory, antioxidant, and immunoregulatory properties that can control hypertension (33). Angiotensin-converting enzyme (ACE), a crucial RAAS enzyme that stimulates vasoconstriction and the production of inflammatory cytokines, has been demonstrated to be inhibited by polyphenolic chemicals found in bee pollen. A preclinical investigation found that supplementing C57BL6 mice with bee pollen extract (0.1 and 1 g/kg for 16 weeks) substantially decreased the levels of ACE and angiotensin II brought on by high-fat diets. The modulatory effect of bee pollen on RAAS and its possible role in decreasing blood pressure through immune-mediated pathways were demonstrated by the enhanced endothelial function that resulted from this decrease (41).

Bioactive peptides found in royal jelly have strong immunomodulatory and antihypertensive effects. It has been demonstrated that Protease N-treated royal jelly (Pro-RJ), which contains peptides such Ile–Tyr (IY), Val–Tyr (VY), and Ile–Val–Tyr (IVY), has potent inhibitory effect against ACEIs. Significant antihypertensive effects were obtained after 28 days of oral treatment of these peptides, either alone or in combination. Cardiovascular protection is further enhanced by the immune-regulating qualities of royal jelly proteins, especially major royal jelly protein 1 (MRJP1). Vascular smooth muscle cells (VSMCs), which are essential for blood vessel contraction and relaxation, are the target of MRJP1's antihypertensive effect. It prevents vascular constriction and enhances blood flow control by inhibiting aberrant VSMC proliferation, migration, and contraction (42).

2.4. Immunomodulatory and Regenerative Potential of Bee Products in Skin Diseases

The creation of melanin is essential for protecting the skin from ultraviolet (UV) rays, but too much melanin build-up can result in hyperpigmentation conditions such nevi, melasma, and age-related skin discolouration (43). Preclinical research has shown that substances obtained from honeybees have anti-melanogenic properties through the modification of important regulatory mechanisms in the formation of melanin.

Tyrosinase is a crucial enzyme in the formation of melanin, and royal jelly has been demonstrated to inhibit melanogenesis in B16F1 mouse melanocytes by downregulating its mRNA transcription. Intracellular melanin levels are significantly decreased as a result. Furthermore, a significant fatty acid found in royal jelly, 10-hydroxy-2-decenoic acid (10-HDA), has demonstrated anti-pigmentation properties in vivo. By inhibiting microphthalmia-associated transcription factor (MITF), a crucial regulator of melanogenesis, 10-HDA suppresses the expression of (44). These results underscore the potential of royal jelly as a natural remedy for pigmentation disorders and skin-brightening treatments.

The skin, which serves as the body's main barrier of defence, is continuously subjected to external stresses, wounds, and infections. Because of their antibacterial, anti-inflammatory, and regenerative qualities, bee products—such as propolis and royal jelly—have long been used in dermatology. The bioactive proteins in royal jelly, such as the major royal jelly proteins (MRJP2, MRJP3, and MRJP7), promote keratinocyte migration, differentiation, and proliferation, speeding up wound closure. Royal jelly also stimulates the production of collagen and reduces inflammation by regulating cytokine activity. By inhibiting pro-inflammatory cytokines including interleukin (IL)-1 and IL-6, the immunoregulatory chemicals found in royal jelly, including 10-HDA, defensin-1, and MRJP3, reduce excessive inflammation without compromising macrophage function (25). Royal jelly is a potential treatment for wound care and tissue regeneration because of these qualities.

Another substance produced by honeybees, propolis, has anti-inflammatory, antioxidant, and antibacterial qualities that make it essential for wound healing. Caffeic acid phenethyl ester (CAPE), one of its bioactive flavonoids, inhibits inflammatory mediators such as prostaglandins, proteinases, and cyclooxygenases (COX-1 and COX-2) (46). Topical propolis administration dramatically decreased levels of IL-1β, IL-6, matrix metalloproteinase-9 (MMP9), and tumour necrosis factor-alpha (TNF-α) in diabetic wound models, improving wound healing. Propolis has also been demonstrated to speed up keratinocyte migration, increase fibroblast activity, and promote collagen deposition, all of which shorten the time it takes for rats to heal wounds (46).

Propolis from various geographic locations has shown synergistic antibacterial and anti-inflammatory properties, especially against Candida albicans, Staphylococcus aureus, and Escherichia coli. Propolis is a promising option for wound care applications because of this integrated strategy, which markedly enhanced re-epithelization, oxidative stress reduction, and tissue regeneration (47).

3. Conclusion

In the fields of melanogenesis, wound healing, and inflammation, bee products such as royal jelly, propolis, and their bioactive components have great potential as therapeutic agents. Royal jelly and propolis are excellent candidates for treating conditions like pigmentation disorders, burns, chronic wounds, and inflammatory skin diseases because of their capacity to control melanin production, encourage tissue regeneration, and alter immune responses. Research has emphasised the ways in which these bee products work, such as by suppressing important enzymes, lowering inflammatory cytokines, and promoting cell migration and proliferation. Furthermore, it has been shown that adding propolis to polymer-based wound dressings improves wound healing results. Although these results provide credence to the medicinal potential of bee products, more clinical research is required to confirm their safety and effectiveness in dermatological applications involving humans. New, natural remedies for skin conditions may be made possible by the use of bee-derived products into clinical skincare.

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