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REVIEW

BIOACTIVE COMPOUNDS OF ROYAL JELLY: IMPLICATIONS AND PERSPECTIVES IN ORAL HEALTH. A REVIEW

Andreea OPRICĂ[1], Marius-Nicusor GRIGORE[2*], Cristian ROMANEC[3]

[1] Grigore T. Popa University of Medicine and Pharmacy Iasi, Romania (opricandreea15@gmail.com)
[2*] Doctoral School of Biology, Alexandru Ioan Cuza University of Iasi, Romania; (nicusor.grigore@uaic.ro)
[3] Grigore T. Popa University of Medicine and Pharmacy Iasi, Romania (cromanec@gmail.com)

Abstract. Royal jelly (RJ) is a bee product rich in biologically active compounds for example proteins, antimicrobial peptides, bioactive fatty acids, flavonoids, and polyphenols, which confer antimicrobial, antioxidant, anti-inflammatory, and regenerative properties. Due to these biological effects, RJ shows promising potential as a natural alternative in dentistry, being effective against oral pathogens involved in dental caries, fungal infections, and periodontal disease, as well as in supporting tissue healing and regeneration processes. This review aims to highlight the biologically active composition of RJ and its promising applications in oral health, emphasizing its role as a possible natural adjuvant therapy in dental medicine.

Keywords: Royal jelly, bioactive components, oral health.

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1. Introduction

Over time, natural products have held an important place in medical practice. A relevant example is apitherapy, a form of alternative medicine that uses bee products for therapeutic applications [1]. Apitherapy is described as the art and science of holistic therapy and healing process through bees and their products, involving the utilization of honey, propolis, pollen, royal jelly, and bee venom, each valued for its biological properties. In recent years, interest in bee products has significantly increased due to their antibacterial potential and beneficial health effects [2].

Royal jelly (RJ), also referred to as jellifera, is a viscous bee-derived product secreted by the hypopharyngeal and mandibular glands of worker bees of the species *Apis mellifera* (family *Apidae*) and used as food for larvae and the queen bee. It is pale yellow-white in color, has a characteristic phenolic-like odor, and an acidic pH ranging from 3.4 to 4.5. Royal jelly is recognized for its exceptional nutritional value and is considered a "superfood" due to its numerous health benefits, including antimicrobial

activity demonstrated in scientific studies like of Peykova-Shapkova et al., 2025 [3]. The protein components with significant antimicrobial potential are the main proteins of jellifera, including royalisin, jelleines, and enzymes such as glucose oxidase. These are effective against Gram-positive bacteria; jelleines are also active against Gram-negative bacteria and yeasts [4].

2. The bioactive composition of royal jelly

Royal jelly is recognized for its rich content of bioactive compounds, which confer multiple therapeutic properties. Its composition is highly complex, containing 60–70% water, approximately 18% proteins (albumin, α, β, γ globulins, glycoproteins, lipoproteins, and 23 amino acids), 15% carbohydrates (glucose, fructose, and negligible amounts of ribose, maltose, isomaltose, trehalose, neotrehalose, gentiobiose, turanose, and inositol), 3–6% lipids (sterols, glycerols, waxes, neutral fats, fatty acids, phospholipids, phenolic lipids, and free organic acids), 1.5% mineral salts, and a wide range of vitamins (B1, B2, B3, B5, B6, B7, B9, B12, E, D, A, K, and C, 336-351 mg/100 g) [3,5].

Approximately 185 organic compounds have been identified, including major RJ proteins (MRJPs), such as royalactin, that are indispensable for its biological activity, as well as peptides frequently found in RJ, like apisimin, royalisin, apidaecin, defensin, and jelleines. The major proteins of royal jelly (MRJPs) include the 350 kDa protein apisin and apisimin [6,7]. The consistent apisin composition of 3.93-4.67 g/g% may serve as a quality standard. Additionally, RJ contains biologically active substances like 10-hydroxy-2-decenoic acid (10-HDA), royalisin, polyphenolic compounds, flavonoids, phenolic acids, essential amino acids, small peptides, fatty acids, B-complex vitamins, and trace elements [8,9].

3. Effects on oral health

3.1. Antimicrobial Activity

The growth of bacterial resistance to antibiotics has intensified research on natural compounds with antimicrobial potential (**Fig. 1**). In this context, royal jelly has attracted significant scientific interest due to its antibacterial properties and favorable safety profile, being investigated as a potential therapeutic alternative for oral bacterial infections [10]. Among the compounds responsible for this activity are royalisin and 10-hydroxy-2-decenoic acid (10-HDA), which have showed antibacterial effects against both Gram-positive and Gram-negative bacteria [7].

According to research by Otręba et al. (2021) [11], minimum inhibitory concentration (MIC) values suggest significant antibacterial potential against periodontal pathogens such as *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum*,

Tannerella forsythia, and *Treponema denticola*, while *Streptococcus pyogenes* was found to be the most resistant species. Its antimicrobial activity is correlated with its rich composition of bioactive compounds; however, variations in origin and methodology can influence results. Therefore, standardization of composition and assessment methods is essential for clinical application, especially in periodontal diseases.

In the same context, Coutinho et al. (2018) [12] demonstrated through in vitro tests for minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) using the broth dilution method that royal jelly exhibits a bactericidal effect (12.5–100 µg/mL) against *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Fusobacterium nucleatum*. *P. intermedia* and *P. gingivalis* showed higher sensitivity compared to other strains. This antibacterial activity is attributed to biologically active compounds like antimicrobial peptides (royalisin, jelleines) and also 10-HDA. Nevertheless, compositional variability necessitates product standardization and safety evaluation prior to clinical use.

Data from the study of Terada et al. (2011) [13] evidenced that the fatty acid fraction of royal jelly consists of approximately 32% 10-HDA, 24% gluconic acid, 22% 10-hydroxydodecanoic acid (HDAA), 5% dicarboxylic acids, and other minor acids. These compounds demonstrated significant inhibitory activity against oral pathogens such as *Streptococcus viridans*, *Streptococcus mutans*, *Staphylococcus aureus*, and *S. epidermidis*. Overall, RJ is a natural compound with negligible adverse effects, capable of synergistic action with other anti-plaque agents, representing a potential alternative or adjunct to synthetic antibiotics.

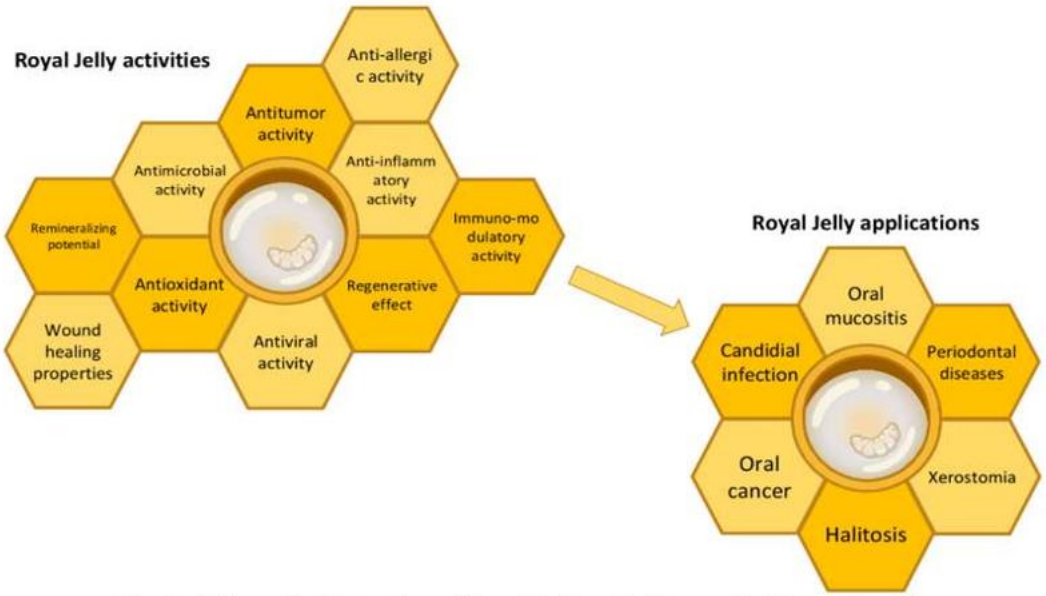

Fig. 1. Schematic illustration of Royal Jelly activities applied in oral health

3.2. Antiviral Activity

Similar to other bee products, royal jelly may exert antiviral effects directly (by inhibiting viral entry or replication) or indirectly (by stimulating the immune response) [14]. Experimental studies by Hashemipour et al. (2014) [15] suggest that RJ can reduce replication of Herpes simplex virus type 1 (HSV-1) through bioactive proteins, antimicrobial peptides, and 10-HDA, indicating potential as a natural treatment for oral herpetic lesions. Clinical studies are, however, required to confirm safety and efficacy for oral or topical use.

3.3. Antioxidant Activity

Antioxidant activity is associated with the capacity to counteract oxidative stress, as a result of the imbalance between reactive oxygen species production and antioxidant mechanisms. In royal jelly, antioxidant activity is primarily attributed to MRJP proteins and peptides derived from proteolysis, which demonstrate increased efficiency against lipid peroxidation [6]. The research of Guo et al. (2009) [16] highlighted that short peptides (2–4 amino acids) exhibit high hydroxyl radical scavenging capacity. Enzymatic treatment further enhances antioxidant activity (assessed by DPPH assay) without altering freshness or 10-HDA content, while increasing free amino acids and reducing allergenic potential via degradation of major proteins. Antioxidant capacity varies with the time of collection and the age of larvae. Samples collected within the first 24 hours show superior antioxidant activity, reducing power, and more effective inhibition of lipid peroxidation compared to later collections, differences associated with variations in polyphenol and protein content.

In addition, Liu et al. (2008) [17] found that royal jelly harvested in the first 24 hours exhibits higher antioxidant activity (DPPH assay), greater reducing power, and more effective inhibition of linoleic acid peroxidation, but lower SOD activity compared to samples collected at 48 and 72 hours. Additionally, the decline in antioxidant activity after 24 hours was correlated with decreased total polyphenol and protein content.

3.4. Anti-inflammatory, immunomodulatory, anti-allergic activities and regenerative effects

Inflammation is a complex cellular and molecular response initiated by tissue injury, infection, or various pathological conditions. It represents a protective defense mechanism activated by various pathogenic factors such as infectious agents, toxins, chemicals, and mechanical trauma and it plays an essential role in restoring normal physiological functions, with macrophages acting as key regulators of the immune response [18]. The major fatty acids in royal jelly,10-hydroxydecanoic acid (10-HDA), trans-10-hydroxy-2-decenoic acid

(10-H2DA), and dicarboxylic acids have been investigated for their anti-inflammatory activity and effects on inflammatory gene expression in mouse experiments (Peykova-Shapkova et al., 2025) [3].

Literature indicates the viability of periodontal ligament cells (PDL) on root surfaces, which is essential for maintaining the long-term viability of replanted teeth following avulsion, as these cells are necessary for PDL tissue regeneration. In a study by Sricholpech and Srisupabh (2015) [19], RJ was tested on periodontal ligament fibroblasts (PDLF) in an in vitro tooth avulsion model. Results showed that RJ solutions maintained PDLF viability in a dose-dependent manner compared to HBSS ($p<0.05$), comparable to skim milk at concentrations of 500 and 900 μg/mL. RJ solutions also stimulated proliferation of surviving PDLFs, demonstrating potential as a transport medium for avulsed teeth.

Moreover, Yanagita et al. (2011) [20] analyzed the impact of royal jelly on periodontal ligament cells (MPDL22 line) using cultures stimulated with *Porphyromonas gingivalis* lipopolysaccharide, analyzing mineralization (alizarin red staining), osteoblastic gene marker expression (RT-PCR), and inflammatory mediator secretion (ELISA). The study showed that royal jelly treatment substantially increased mineralized nodule formation and expression of osteoblast markers (osteopontin, osteocalcin, osterix) while reducing IL-6, CXCL10, and CD54, demonstrating osteoinductive and anti-inflammatory effects with potential in periodontal regeneration and therapy.

3.5. Antitumor Activity

Although chemotherapy, radiotherapy, and surgery are effective, they may induce significant adverse effects. RJ is not an independent anticancer treatment but may be used as an adjuvant, enhancing chemotherapy efficacy and reducing genotoxicity [21]. In vivo and in vitro studies show that RJ administration can inhibit metastasis development and support antitumor effects in experimental animal models [22]. Key bioactive compounds responsible for antitumor activity include polyphenols (especially flavonoids) and 10-HDA, suggesting a connection between antioxidant, anti-inflammatory, and anticancer properties of royal jelly [8].

3.6. Remineralizing potential

Recent studies [23] highlight royal jelly as a promising biomaterial in conservative dentistry and endodontics due to its antimicrobial, anti-inflammatory, antioxidant, and regenerative properties. When applied in pulp capping, it not only inhibits cariogenic bacteria like *Streptococcus mutans* and diminishes pulpal inflammation but also supports remineralization and dental tissue regeneration, maintaining pulp vitality and promoting natural dentin repair.

In liner restorations under restorative materials, royal jelly may improve biocompatibility and pulp protection, reducing the risk of cellular damage. Although less studied than propolis in endodontic therapy, it offers antioxidant effects and support for tissue regeneration, contributing to decreased periapical inflammation and accelerated repair. On the other hand, in another study, Turbatmath and Sharma (2025) [24] analyzed the antimicrobial efficacy of 4% RJ with 2% CHX and 2% $Ca(OH)_2$ against *Streptococcus mutans* using agar diffusion and biofilm inhibition tests. RJ demonstrated the highest antibacterial activity, followed by CHX and $Ca(OH)_2$, with no significant differences between the latter two. The outcomes suggest the ability of royal jelly as a natural alternative in pulp therapy, though further studies on dosage, safety, and long-term clinical efficacy are needed.

3.7. Wound healing properties

Preclinical researches indicate that royal jelly and its bioactive derivatives support wound healing by stimulating cell proliferation and migration and through anti-inflammatory, antioxidant, and antimicrobial effects. Wound healing progresses gradually through hemostasis, inflammation, granulation tissue formation, re-epithelialization, and extracellular matrix remodeling [25]. Formulations containing RJ, such as collagen gels, promote tissue regeneration, stimulate stem cell migration, and inhibit bacterial biofilms, accelerating wound closure and repair [26]. Clinical studies also suggest that topical application can significantly improve healing and repair processes [27].

4. Applications of royal jelly in oral diseases

4.1. Oral mucositis

Currently, oral mucositis represents a common and challenging side effect of chemotherapy and head-and-neck radiotherapy, but it may be alleviated due to the pharmacological characteristics of royal jelly, which provides symptomatic support and potential healing effects [28]. Based on Erdem et al. (2014) study, [29] topical administration of royal jelly extract notably diminished the severity and healing time of oral mucositis compared to the control group. Patients receiving treatment exhibited faster lesion remission, regardless of severity, with the effect more pronounced in the early stages of the condition. These data suggest the potential of royal jelly as an effective and safe adjuvant therapeutic option in managing oral mucositis, contributing to symptom relief and improved clinical outcomes.

4.2. Candidal infection

Denture stomatitis is a chronic inflammation commonly associated with denture wearing, where poor hygiene promotes biofilm development and *Candida spp.* proliferation, the primary pathogen involved. When hygiene measures and biofilm control are insufficient, fungal susceptibility testing and appropriate antifungal treatment are essential. Prolonged antifungal use, however, can lead to treatment resistance [30]. Research by Jareemit et al. (2017) [31] evaluated the influence of royal jelly extract on samples of heat-polymerized acrylic resin, self-polymerizing resin, and tissue-conditioning materials, using nystatin as a control. Royal jelly demonstrated the ability to inhibit *Candida albicans* adhesion at concentrations of 25–50 mg/mL, comparable to 23 mg/mL nystatin, suggesting that RJ may be a potential alternative antifungal agent.

4.3. Oral Cancer

Oral cancer ranks as the six most frequently reported cancers worldwide. Pathologically, the most common type is oral squamous cell carcinoma (OSCC), accounting for 84–97% of cases [6]. An in vitro experiment by Kul Köprülü et al. (2025) [32] demonstrated that royal jelly (RJ) may increase the sensitivity of OSCC cells to the chemotherapeutic agent paclitaxel (PAX). The combination of RJ with PAX enhanced antiproliferative and antimigratory effects on OSCC cells while decreasing glycolytic capacity and the expression of genes playing a role in the cell cycle and DNA replication. Simultaneously, RJ reduced PAX cytotoxicity on healthy gingival fibroblasts, suggesting a possible adjuvant role in oral cancer therapy.

4.4. Halitosis

Halitosis (bad breath) has become increasingly recognized as a factor affecting interpersonal interactions and can be managed by cleaning the tongue with bacterial plaque via tooth brushing, tongue scrapers, oral prophylaxis, and antimicrobial mouthwashes [6]. In this context, Meto et al. (2017) [33] carried out a comparative evaluation of the antimicrobial efficacy of royal jelly versus chlorhexidine activity against *Enterococcus faecalis*, *Staphylococcus aureus*, *Streptococcus mutans*, *Escherichia coli*, and *Candida albicans*. Results indicated that royal jelly exhibits antimicrobial efficacy comparable to 0.2% chlorhexidine.

4.5. Xerostomia

Xerostomia (dry mouth) refers to the subjective sensation of oral dryness, usually due to reduced salivary flow (hyposalivation) [34]. In a crossover study with randomizationand bliding, Mochizuki et al. (2023) [35] evaluated 15 adults

with normal salivary flow but subjective dry mouth who received 800 mg/day of enzymatically treated royal jelly or placebo for 12 weeks. Dry mouth sensation, anxiety, and social dysfunction were assessed using the VAS (Visual Analogue Scale), HADS (Hospital Anxiety and Depression Scale), and GHQ-12 (General Health Questionnaire-12). Results showed significant improvements in VAS, HADS, and GHQ-12 scores in the royal jelly group compared to placebo, indicating that daily dosing of royal jelly effectively reduces dry mouth symptoms and associated psychological distress.

4.6. Periodontal diseases

Periodontal disease is a chronic multifactorial condition initiated by subgingival microbiome dysbiosis, characterized by a reduction in beneficial microorganisms and an increase in pathogenic species, disrupting the host immune response and leading to destruction of supporting tooth tissues and bone resorption [36]. Non-surgical periodontal therapy (NSPT), primarily through scaling and root planing, is the standard therapy for periodontitis. Its goal is to remove deposits from root surfaces and modify subgingival microbial flora to control disease progression, although residual biofilm or persistent inflammation may limit effectiveness [37]. Subgingival irrigation is one effective NSPT technique for plaque control. More than that, Rudhra et al. (2023) [38] carried out a randomized clinical research evaluating royal jelly as an irrigation agent in chronic periodontitis treatment. Thirty patients were separeted into three groups treated with scaling and root planing (SRP) combined with RJ, saline, or distilled water. After 45 days, the RJ group indicated notable improvements in plaque index, gingival index, and probing pocket depth, performing as effectively as saline and better than distilled water, suggesting its potential as an irrigation agent due to antimicrobial, antioxidant, and anti-inflammatory characteristics.

Conclusions

(1) Royal jelly is a complex bee product rich in biologically active compounds (antimicrobial peptides, major proteins, specific fatty acids, and phenolic compounds), which confer multiple therapeutic properties, including antimicrobial, antiviral, antioxidant, anti-inflammatory, immunomodulatory, and regenerative effects.

(2) These properties support its potential in oral health by contributing to the prevention and management of conditions such as oral mucositis, candidal infections, halitosis, xerostomia, and periodontal diseases, as well as promoting tissue remineralization and regeneration and possibly serving as an adjuvant in oral cancer therapy.

(3) However, variability in composition and the limited number of clinical studies restrict its widespread use, highlighting the need for further research and randomized clinical trials to standardize the product and confirm its efficacy and safety, positioning royal jelly as a promising natural biomaterial for future dental applications.

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