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Apiarian Bioactives in Dentistry: A Narrative Review on Pulp Preservation and Regeneration

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ABSTRACT

Vital pulp therapy (VPT) seeks to preserve the structural and functional integrity of the dental pulp following caries or trauma. While synthetic biomaterials such as calcium hydroxide, mineral trioxide aggregate (MTA), and newer calcium silicate cements have improved outcomes, limitations in terms of solubility, cost, handling, and long-term success have stimulated the search for natural alternatives. Among these, apiarian-derived bioactives, particularly propolis and royal jelly have emerged as promising candidates due to their unique combination of antimicrobial, anti-inflammatory, antioxidant, and regenerative properties.

Propolis, rich in flavonoids and phenolic acids, has demonstrated broad-spectrum antimicrobial action, modulation of inflammatory cytokines, and the ability to induce organized dentin bridge formation in pulp capping models [1,2]. Royal jelly, characterized by major royal jelly proteins and 10-hydroxy-2-decenoic acid (10-HDA), promotes fibroblast proliferation, collagen synthesis, and reparative dentinogenesis [3]. Evidence from in vitro, animal, and comparative studies suggests that their biological activity rivals or exceeds that of conventional materials in certain contexts.

This narrative review consolidates current evidence on the role of apiarian bioactives in conservative dentistry and endodontics, with emphasis on pulp preservation and regeneration. Their potential for indigenous development, affordability, and sustainability further enhance their translational value. Future perspectives include nano-enhanced formulations, hybrid biomaterials, and rigorous clinical trials to validate their integration into mainstream vital pulp therapy.

Keywords: *Vital pulp therapy, Propolis, Royal jelly, Apiarian bioactives, Pulp capping, Dentin regeneration, Conservative dentistry, Endodontics*

1. INTRODUCTION

Preservation of pulp vitality is a fundamental goal of conservative dentistry and endodontics. The pulp–dentin complex plays a vital role in tooth development, immune defense, and sensory function, and its preservation ensures long-term tooth survival. Vital pulp therapy (VPT), including direct pulp capping, indirect pulp capping, and pulpotomy, offers biologically driven alternatives to root canal treatment when the pulp remains vital despite carious or traumatic exposure [4] [5].

The choice of pulp capping material is crucial for VPT success. Calcium hydroxide, historically the gold standard, is effective but limited by high solubility, poor sealing, and porous dentin bridges [6]. Mineral trioxide aggregate (MTA) improved outcomes with superior sealing and bioactivity but remains costly and technique-sensitive[7][8]. Newer calcium silicate-based materials, such as Biodentine and TheraCal LC, address some drawbacks but still do not fully meet the criteria of an ideal agent.

These limitations have prompted interest in natural biomaterials. Among them, apiarian bioactives, particularly propolis and royal jelly have shown great promise. Propolis, rich in flavonoids and phenolic acids, demonstrates antimicrobial, anti-inflammatory, and dentinogenic properties, with studies showing continuous dentin bridge formation and reduced pulpal inflammation [9][10]. Royal jelly, a secretion containing major royal jelly proteins and the fatty acid 10-hydroxy-2-decenoic

acid (10-HDA), promotes fibroblast proliferation, collagen synthesis, and reparative dentinogenesis, with favorable outcomes in experimental pulp therapy [10,11][12].

Beyond their biological potential, propolis and royal jelly are accessible and affordable, especially in regions with established apiculture. They align with sustainable dentistry by offering natural, cost-effective alternatives to synthetic biomaterials. However, variability in composition and the lack of standardized extraction methods remain challenges, underscoring the need for further research and clinical validation.

This narrative review consolidates current evidence on propolis and royal jelly in conservative dentistry and endodontics, focusing on their composition, biological activity, applications in pulp preservation, and translational potential as natural bioactive capping agents.

2. PROPOLIS

Propolis, commonly referred to as "bee glue," is a resinous substance collected by honeybees from tree buds and plant exudates, mixed with wax and salivary enzymes [13]. Its chemical composition varies by botanical and geographical origin, but it generally contains flavonoids, phenolic acids, terpenes, aromatic esters, and trace minerals, which together account for its wide range of biological activities [14].

One of the most extensively studied properties of propolis is its antimicrobial activity. It exhibits inhibitory effects against cariogenic microorganisms such as *Streptococcus mutans* and *Lactobacillus acidophilus*, as well as resilient endodontic pathogens including *Enterococcus faecalis*. This antimicrobial effect is largely attributed to flavonoids and caffeic acid phenethyl ester (CAPE), which disrupt bacterial membranes, inhibit glucosyltransferases, and reduce biofilm formation [15]. Such properties make propolis particularly valuable in vital pulp therapy, where microbial contamination at the exposure site is one of the main causes of treatment failure.

In addition to its antibacterial role, propolis demonstrates anti-inflammatory and antioxidant effects. It modulates the immune response by downregulating pro-inflammatory mediators such as COX-2, TNF-α, and IL-1β, thereby reducing pulpal inflammation [16]. Kantrong et al. (2023) reported that Thai propolis extract significantly suppressed IL-1β–induced inflammatory responses in human pulp cells via inhibition of the NF-κB signaling pathway [10]. Its antioxidant capacity, mediated by flavonoids and phenolic compounds, reduces oxidative stress and protects pulp cells from free radical induced damage, creating a microenvironment favorable for healing.

Beyond infection control and inflammation modulation, propolis also exerts a regenerative effect. It has been shown to enhance fibroblast proliferation and stimulate the differentiation of dental pulp stem cells into odontoblast-like cells. Parolia et al. (2010) demonstrated that teeth capped with ethanolic extract of propolis in animal models developed continuous dentin bridges with minimal pulpal inflammation, outcomes comparable to those obtained with MTA and superior to calcium hydroxide [9]. Histological studies consistently reveal more organized reparative dentin with propolis compared to $Ca(OH)_2$, which often induces porous bridges with tunnel defects.

Further comparative studies highlight propolis's potential as a viable pulp capping material. Pribadi et al. (2020) reported that propolis produced lower solubility and better sealing ability compared to calcium hydroxide, along with a broader antimicrobial spectrum [17]. Additionally, in vitro assays suggest that propolis not only protects pulp tissue but also promotes odontogenic gene expression, supporting true biological regeneration rather than simple reparative calcification.

Clinically, propolis's appeal lies not only in its biological performance but also in its accessibility and cost-effectiveness. Unlike MTA or Biodentine, which are expensive and technique-sensitive, propolis can be locally sourced and formulated into cost-effective preparations, particularly in regions with established apiculture. This makes it attractive for resource-limited settings where advanced synthetic biomaterials may not be routinely available.

However, the clinical translation of propolis faces challenges. Its chemical composition varies significantly depending on the plant sources available to bees, leading to inconsistency in biological activity between different batches or regions. Furthermore, standardization of extraction and formulation methods is essential to ensure reproducible clinical outcomes. While preclinical evidence is promising, large-scale randomized clinical trials are still lacking, and regulatory approval will depend on addressing these concerns.

In summary, propolis embodies the characteristics of an ideal pulp capping agent: antimicrobial, anti-inflammatory, biocompatible, and regenerative. It provides outcomes comparable to or better than calcium hydroxide and, in certain models, approaches the performance of MTA. Combined with its accessibility and affordability, propolis represents a strong candidate for integration into vital pulp therapy. However, standardization and clinical validation remain the critical steps toward its adoption in mainstream endodontic practice.

3. ROYAL JELLY

Royal jelly is a milky secretion produced by the hypopharyngeal and mandibular glands of worker bees, primarily used to nourish queen bees and larvae. It is a nutrient-rich substance containing water, proteins, sugars, lipids, vitamins, amino acids,

and trace minerals. A distinctive feature of royal jelly is its major royal jelly proteins (MRJPs), which constitute more than 80% of its protein content, and its unique fatty acid, 10-hydroxy-2-decenoic acid (10-HDA), considered responsible for many of its biological properties[11].

Royal jelly exhibits notable antimicrobial activity, attributed to bioactive peptides such as royalisin and jelleines, along with 10-HDA [18–20]. These compounds inhibit the growth of cariogenic and endodontic pathogens including *Streptococcus mutans* and *Porphyromonas gingivalis* [21,22][21]. Li et al. (2021) demonstrated that MRJP-derived peptides significantly reduced bacterial adhesion and biofilm formation, indicating its potential in preventing secondary infection at pulp exposure sites [12].

Beyond antimicrobial activity, royal jelly also provides strong anti-inflammatory and antioxidant effects, which are crucial in pulp preservation. By modulating cytokine release and scavenging free radicals, it reduces pulpal inflammation and oxidative stress. Studies suggest that 10-HDA inhibits the production of pro-inflammatory mediators, creating a favorable environment for pulp healing. This modulation of inflammation, combined with its antioxidative properties, positions royal jelly as a promising agent for promoting controlled healing in exposed pulps.

A key aspect of royal jelly in dentistry is its regenerative capacity. It has been shown to stimulate fibroblast proliferation, increase collagen synthesis, and accelerate tissue repair. In pulp therapy, these properties translate into enhanced odontogenic differentiation and reparative dentin formation. In animal studies, teeth treated with royal jelly showed well-organized dentin bridges with minimal pulpal inflammation, outcomes comparable to those achieved with calcium hydroxide and, in some cases, superior in terms of tissue organization. These findings suggest that royal jelly promotes not only reparative calcification but also supports the biological processes underlying true pulp regeneration.

Royal jelly also influences stem cell behavior. Research indicates that its proteins and fatty acids enhance the differentiation of dental pulp stem cells into odontoblast-like cells, promoting deposition of mineralized matrix. This effect is believed to be mediated by activation of signaling pathways linked to odontogenesis, such as BMP and TGF-β signaling cascades. Such bioinductive potential highlights the ability of royal jelly to go beyond symptomatic pulp protection, instead actively guiding tissue regeneration.

From a clinical standpoint, royal jelly has advantages similar to propolis: it is biocompatible, natural, and relatively inexpensive compared to synthetic materials like MTA and Biodentine. Its ready availability in regions with apiculture supports its use in sustainable dentistry, particularly in resource-constrained environments. Its multifunctionality combining antimicrobial, anti-inflammatory, and regenerative properties aligns with the biological objectives of vital pulp therapy.

Nevertheless, challenges remain. The chemical composition of royal jelly can vary with seasonal and geographic conditions, which may affect its biological activity. Lack of standardization in harvesting and processing further complicates its consistent clinical application. Moreover, while preclinical evidence supports its efficacy, clinical trials remain sparse. Without robust human studies and regulatory standardization, the translation of royal jelly into mainstream pulp therapy remains limited.

In summary, royal jelly is a multifunctional apiarian bioactive with significant potential in vital pulp therapy. By inhibiting bacterial growth, modulating inflammation, and promoting odontogenic differentiation, it mirrors many of the qualities sought in an ideal pulp capping material. Experimental findings suggest it can achieve reparative outcomes comparable to conventional agents while offering the added benefits of accessibility and cost-effectiveness. However, as with other natural products, clinical validation and standardization are essential before it can be fully integrated into routine endodontic practice.

4. APPLICATIONS IN CONSERVATIVE DENTISTRY AND ENDODONTICS

The therapeutic potential of apiarian bioactives such as propolis and royal jelly extends directly to the core goals of conservative dentistry and endodontics namely, the preservation of pulp vitality and the prevention of reinfection. Their multifunctional biological properties have positioned them as promising alternatives or adjuncts to conventional pulp capping materials.

The most widely studied application is in direct and indirect pulp capping. In direct pulp capping, where the pulp is exposed, propolis has been shown to provide antimicrobial protection while promoting the formation of a continuous dentin bridge with minimal pulpal inflammation [23]. Animal and in vitro studies confirm that its performance is comparable to MTA and superior to calcium hydroxide, particularly in terms of dentin bridge quality and reduced inflammatory cell infiltration [9]. Royal jelly has similarly demonstrated favorable outcomes in pulp capping models, where its bioactive fatty acid 10-HDA and major royal jelly proteins promote odontoblastic differentiation, fibroblast proliferation, and collagen synthesis. This results in organized reparative dentinogenesis and improved pulp healing compared to calcium hydroxide.

In indirect pulp capping, where carious dentin is left intentionally to avoid pulp exposure, both propolis and royal jelly offer advantages through their antimicrobial and anti-inflammatory actions. Their ability to suppress cariogenic bacteria such as *Streptococcus mutans* and modulate cytokine expression reduces the risk of residual infection while allowing the pulp to recover. Propolis's superior sealing and lower solubility compared to $Ca(OH)_2$ provide additional protection against

microleakage, improving the predictability of outcomes.

Another area of exploration is the use of apiarian products as intracanal medicaments in endodontic therapy. Propolis, in particular, has demonstrated strong antimicrobial activity against *Enterococcus faecalis*, a pathogen commonly associated with root canal failures and resistant to many conventional intracanal medicaments. Its ability to penetrate dentinal tubules and disrupt biofilms enhances its potential in root canal disinfection. Although royal jelly has been less extensively studied as an intracanal agent, its antioxidant and anti-inflammatory properties suggest a supportive role in reducing periapical inflammation and promoting healing following endodontic therapy.

Additionally, both propolis and royal jelly have been investigated as components of restorative liners and adjuncts. Their incorporation beneath restorative materials has been shown to reduce bacterial penetration, enhance pulp protection, and promote biocompatibility. Experimental formulations of liners containing propolis have demonstrated good sealing ability and minimal cytotoxicity, while royal jelly's regenerative properties support pulp tissue repair beneath restorations placed in deep cavities.

Collectively, these applications highlight the relevance of apiarian bioactives in conservative dentistry and endodontics. Their capacity to combine antimicrobial, anti-inflammatory, and regenerative effects aligns closely with the biological principles underlying pulp preservation strategies. While their efficacy has been confirmed in numerous preclinical models, translation to clinical practice requires standardization of formulations and validation through well-designed randomized controlled trials.

Table 1. Evidence for Propolis and Royal Jelly in Vital Pulp Therapy

Study Type	Findings on Propolis	Findings on Royal Jelly
In vitro	Suppresses IL-1β–induced COX-2 and PGE_2 expression in pulp cells; inhibits NF-κB activation; enhances fibroblast proliferation and odontogenic differentiation.	MRJP-derived peptides and 10-HDA inhibit *S. mutans* and *P. gingivalis* growth; stimulate fibroblast proliferation, collagen synthesis, and odontogenic differentiation.
Animal models	Direct pulp capping with ethanolic extract of propolis induces continuous dentin bridges with minimal inflammation, comparable to MTA and superior to $Ca(OH)_2$.	Animal pulp capping studies show organized dentin bridge formation and minimal pulpal inflammation, with outcomes similar to calcium hydroxide and in some cases more favorable.
Comparative studies	Demonstrates lower solubility, better sealing, and broader antimicrobial spectrum compared to $Ca(OH)_2$; effective against resistant *E. faecalis*.	Comparable reparative dentinogenesis to $Ca(OH)_2$; enhances odontogenic differentiation and tissue repair in pulp exposures.

Evidence from laboratory and preclinical studies strongly supports the use of propolis and royal jelly as bioactive pulp capping agents. In vitro experiments highlight their capacity to suppress inflammatory cytokine expression, enhance pulp cell viability, and stimulate odontogenic gene expression. Propolis, in particular, has shown strong antimicrobial efficacy against both cariogenic and endodontic pathogens, including *Enterococcus faecalis*, a species resistant to many conventional intracanal medicaments. Royal jelly, through its unique fatty acid 10-HDA and major proteins, enhances fibroblast proliferation and collagen deposition, supporting dentinogenesis at pulp exposure sites.

Animal studies reinforce these findings, consistently demonstrating that both agents induce continuous dentin bridge formation with minimal pulpal inflammation. Outcomes with propolis are often reported as equivalent to MTA and superior to calcium hydroxide, while royal jelly produces reparative dentin comparable to $Ca(OH)_2$, with improved tissue organization. Comparative studies further highlight advantages such as reduced solubility and better sealing with propolis, suggesting enhanced long-term reliability.

Taken together, the evidence indicates that apiarian bioactives not only protect the pulp from microbial and inflammatory insults but also actively stimulate regenerative processes. While current data remain largely preclinical, the consistency of outcomes across in vitro and animal studies underscores their translational promise in vital pulp therapy.

5. INDIGENOUS DEVELOPMENT ASPECT

A major advantage of apiarian bioactives such as propolis and royal jelly is their potential for indigenous development. In many regions, particularly in countries with well-established apiculture, these products can be locally sourced and formulated into cost-effective dental biomaterials. This reduces dependence on costly imports such as MTA and Biodentine, which often limit access to advanced pulp therapy in resource-constrained settings.

Local sourcing also promotes sustainability, as apiarian products are renewable and environmentally friendly. However, variability in chemical composition due to geographic, seasonal, and botanical differences presents a significant challenge. For example, propolis collected in tropical regions may differ substantially in its flavonoid and phenolic content compared to propolis from temperate climates, leading to inconsistencies in biological performance. Similarly, the concentration of bioactive components such as 10-HDA in royal jelly varies with bee species and environmental conditions.

To address these issues, standardization in harvesting, extraction, and formulation is essential. Establishing pharmacological profiles and defining minimum bioactive concentrations would help ensure consistency and reproducibility across clinical applications. Indigenous development, combined with standardized production, has the potential to provide affordable, accessible, and reliable bioactive materials for vital pulp therapy worldwide.

6. DISCUSSION

The progression of vital pulp therapy materials has shifted from synthetic to natural bioactives in pursuit of the ideal pulp capping agent. While calcium hydroxide and MTA have provided predictable outcomes, their limitations such as porous dentin bridges, cost, handling issues, and esthetic drawbacks highlight the need for alternatives. Apiarian bioactives such as propolis and royal jelly offer a natural solution that combines antimicrobial, anti-inflammatory, antioxidant, and regenerative properties.

Comparative evidence suggests that propolis induces dentin bridge formation of comparable quality to MTA and superior to $Ca(OH)_2$, while royal jelly enhances pulp healing through fibroblast proliferation, collagen deposition, and odontogenic differentiation. Both agents consistently demonstrate minimal pulpal inflammation and good biocompatibility in experimental models. Their affordability and accessibility further enhance their translational relevance, particularly in resource-limited settings.

Nonetheless, important challenges remain. The variability of composition between regions, the absence of standardized extraction protocols, and the lack of robust randomized clinical trials limit their immediate clinical application. Addressing these challenges is essential for moving apiarian bioactives from promising experimental agents to accepted mainstream biomaterials.

7. FUTURE PERSPECTIVES

Future research on apiarian bioactives should focus on nanoformulations to enhance stability, penetration, and controlled release, as well as hybrid systems combining propolis or royal jelly with calcium silicate cements for added mechanical strength. Standardization of extraction methods and dosage is essential to overcome variability in composition. Most importantly, clinical trials are needed to validate preclinical findings and establish evidence-based protocols before routine clinical adoption.

8. CONCLUSION

Propolis and royal jelly combine antimicrobial, anti-inflammatory, and regenerative effects, making them strong candidates for vital pulp therapy. Evidence shows outcomes comparable to or better than conventional agents like calcium hydroxide and MTA, with the added benefits of affordability and sustainability. However, issues of standardization and lack of clinical validation remain barriers. With further research, apiarian bioactives could become reliable, natural alternatives for pulp preservation and regeneration.

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