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REVIEW

From Cardio-Kidney-Metabolic Syndrome to Periodontal Diseases: The Bio-Cellular Role of Propolis

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ABSTRACT: Cardio-kidney-metabolic (CKM) syndrome and periodontal diseases are bi-directionally linked pathologies driven by systemic inflammation, oxidative stress, and metabolic dysregulation. Identifying pleiotropic therapeutic agents targeting this axis is a major clinical priority. This review evaluates the bio-cellular role of propolis, a natural resinous hive product, in mitigating CKM syndrome and periodontal disease. Propolis exerts robust protective effects by modulating key intracellular signaling pathways. Specifically, it upregulates nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent antioxidant defenses, which subsequently interferes with redox-sensitive inflammatory triggers. Concurrently, it antagonizes pro-inflammatory signaling, including nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome cascades. Furthermore, propolis prevents tissue fibrosis and cellular apoptosis by inhibiting transforming growth factor-beta (TGF-β)/suppressor of mothers against decapentaplegic (Smad) and c-Jun N-terminal kinase (JNK)/extracellular signal-regulated kinase (ERK) pathways. By disrupting this systemic inflammatory-metabolic loop and reducing local periodontal pathogen loads, propolis emerges as a promising adjunctive therapy. Propolis represents a promising candidate adjunctive therapy, although further well-designed and standardized clinical trials are required to validate its efficacy and translational potential.

KEYWORDS: Propolis; cardio-kidney-metabolic (CKM) syndrome; periodontal diseases

1 Introduction

Cardio–kidney–metabolic (CKM) syndrome is a continuum of interconnected conditions—including obesity, type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), and atherosclerotic cardiovascular disease (CVD) that mutually amplify each other through shared mechanisms like inflammation, oxidative stress, and endothelial dysfunction [1–3]. This integrated framework emphasizes that adipose tissue, the vasculature, myocardium, and kidney form a pathophysiologic axis rather than isolated disease compartments. Clinical data indicate that individuals with metabolic syndrome or T2DM have a substantially increased risk of CKD and CVD events, and that the coexistence of renal impairment further worsens cardiovascular prognosis [4–6].

In parallel, chronic periodontitis has emerged as a low-grade inflammatory burden associated with CKM risk [7]. Severe periodontitis is characterized by a dysbiotic biofilm dominated by anaerobic Gram-negative species such as *Porphyromonas gingivalis*, persistent activation of innate immunity, and progressive destruction of tooth-supporting structures [8]. Epidemiologic and interventional studies suggest that periodontitis is associated with worse glycemic control in T2DM, accelerated CKD progression, and elevated systemic inflammatory markers such as C-reactive protein and interleukin-6 [3,9–11]. The concept of a "mouth–systemic axis" thus overlaps substantially with the CKM framework: both involve chronic inflammation, endothelial injury, oxidative stress, and innate immune activation. This axis is mediated by the systemic dissemination of periodontal pathogens and their molecular patterns (e.g., LPS), which activate pattern recognition receptors (PRRs) in distant cardiometabolic tissues, triggering a cascade of intracellular stress responses.

Propolis is a resinous product collected by bees from plant exudates and mixed with wax and salivary enzymes. It contains a complex mixture of polyphenols, flavonoids, phenolic acids and esters, terpenoids, and other minor constituents that confer broad antimicrobial, antioxidant, anti-inflammatory, immunomodulatory, and metabolic effects [12–14]. Regional botanical sources give rise to distinct chemical fingerprints, such as Brazilian green and red propolis or Taiwanese green propolis (TGP), each enriched for specific prenylated flavonoids and phenolic derivatives [15–17]. Over the past two decades, preclinical and clinical studies have examined propolis as an adjunctive or preventive agent in liver fibrosis [18], CKD [19], metabolic syndrome [20], gouty inflammation [21], and periodontal disease [22,23], often demonstrating favorable effects on oxidative stress, inflammatory mediators, metabolic indices, and tissue remodeling [18–25].

Despite this rapidly growing literature, most work remains compartmentalized within individual organ systems. A unifying analysis that connects the bio-cellular actions of propolis across CKM organs and periodontal tissues is lacking. Moreover, the direction of translation is often one-way: from bench to bedside. This integrative and bio-cellular perspective distinguishes the present review from conventional organ-specific analyses and aligns with the mechanistic focus of molecular and cellular research. Given the availability of clinical data in CKM and periodontal populations, there is now an opportunity to use human observations to refine and prioritize mechanistic hypotheses in a reverse translational manner—taking clinical signals back into cellular and animal models to dissect causal pathways and identify translatable biomarkers.

This review therefore aims to: (i) summarize the chemistry and major bioactive constituents of propolis with emphasis on CKM- and periodontal-relevant profiles; (ii) integrate core cellular mechanisms by which propolis modulates oxidative stress, inflammation, metabolism, and tissue remodeling; (iii) synthesize evidence for propolis in cardio–renal–metabolic conditions; (iv) examine its role in periodontal disease as both an antimicrobial and host-modulating agent; and (v) propose an integrative mechanistic model and a reverse translational research framework linking CKM syndrome to periodontal disease through the bio-cellular actions of propolis. To ensure a comprehensive and objective synthesis of the literature, a systematic search strategy was employed using PubMed, Embase, and Scopus databases for articles published up to 2026 March. The primary search terms included combinations of 'propolis', 'cardio-kidney-metabolic syndrome', 'periodontal disease', 'oxidative stress', and 'NF-κB/NLRP3'. Inclusion criteria were restricted to peer-reviewed *in vitro* studies, animal models, and human clinical trials published in English that directly investigated the bio-cellular mechanisms of propolis. Studies lacking chemical standardization of the propolis extract or those that had been retracted were excluded during the quality appraisal phase.

2 Chemistry and Bioactive Constituents of Propolis

Propolis is a chemically heterogeneous matrix whose composition is determined by bee species, local flora, season, and extraction method [25]. In general, raw propolis contains approximately 50–60% plant resins and balsams, 30–40% waxes and fatty acids, 5–10% essential oils, and 5% pollen and other minor constituents, although these proportions vary considerably between samples [16,17]. The biologically active fraction resides mainly in the resin, which is enriched in polyphenols and terpenoids. Ethanol extracts are commonly used experimentally and clinically to concentrate these constituents [25]. An overview of the botanical origin, major chemical classes, and representative bioactive constituents of propolis is summarized in Fig. 1.

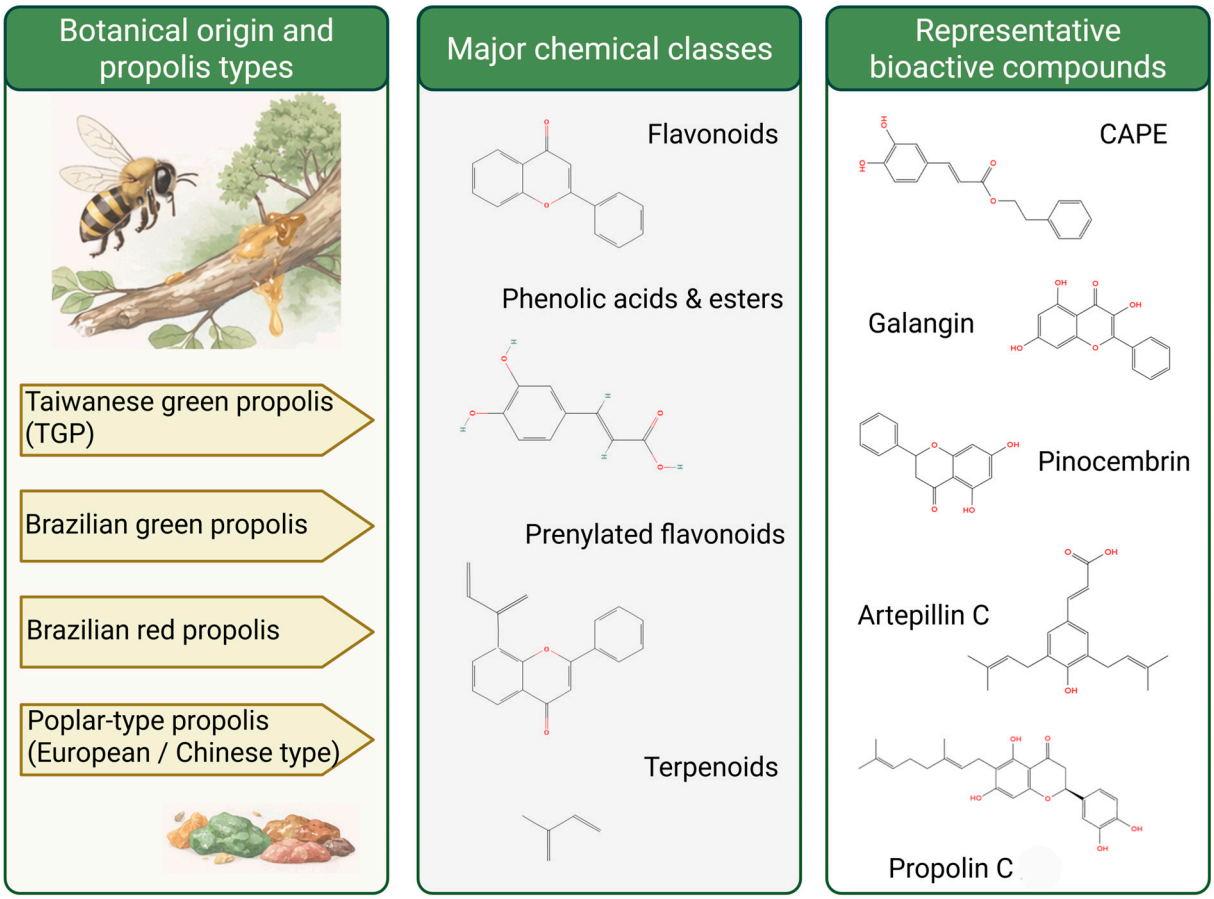

Figure 1: Botanical origin, chemical diversity, and representative bioactive constituents of propolis. Propolis is a resinous bee product derived from diverse botanical sources, giving rise to region-specific chemotypes such as Taiwanese green, Brazilian green and red, and poplar-type propolis. Its biological activities are primarily attributed to major chemical classes, including flavonoids, phenolic acids and esters, prenylated flavonoids, and terpenoids, represented by characteristic scaffolds. Representative bioactive compounds such as caffeic acid phenethyl ester (CAPE), galangin, pinocembrin, artepillin C, and propolins are highlighted. Created in https://BioRender.com (accessed on 19 December 2025).

2.1 Polyphenols and Flavonoids

Flavonoids are among the best-characterized antioxidant compounds in propolis [24,25]. They include flavones (apigenin, chrysin, luteolin), flavonols (galangin, kaempferol, quercetin), flavanones (pinocembrin, naringenin, pinobanksin), and their glycosides and prenylated derivatives [24,25]. These molecules exhibit

potent antioxidant activity through direct scavenging of reactive oxygen and nitrogen species, metal chelation, and modulation of endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase [25–30]. Many flavonoids also interfere with key inflammatory signaling pathways, including NF-κB, MAPK, and JAK/STAT, and modulate cellular processes such as apoptosis, proliferation, and differentiation in immune, endothelial, hepatic, and adipose cells [31–33].

TGP and other Pacific-type propolis are particularly rich in prenylated flavanones termed propolins (A–J) [34], which confer strong antioxidant and anti-inflammatory activity and have been implicated in metabolic regulation [20], inflammasome inhibition [21], antifibrotic [18,19], antidiabetic [17–25,33,35,36], and anticancer effects [17–25,33,35,36] in preclinical models. Brazilian green propolis contains artepillin C, a prenylated cinnamic acid derivative with pronounced anti-inflammatory and anti-angiogenic properties, while Brazilian red propolis is enriched in isoflavonoids and phenolic acids with notable antimicrobial and cytotoxic activity against tumor cells [15,16]. A research study confirmed that Brazilian propolis helps prevent hyperglycemia by increasing glucose uptake in skeletal muscle cells through the translocation of the GLUT4 transporter [37]. This process involves the activation of both the PI3K and AMPK signaling pathways, with the polyphenol kaempferide identified as a key active compound responsible for lowering postprandial blood glucose levels.

2.2 Phenolic Acids and Esters

Phenolic acids (e.g., caffeic, *p*-coumaric, ferulic, cinnamic) and their esters represent another major bioactive class [24,25]. Caffeic acid phenethyl ester (CAPE), one of the most intensively studied constituents, exerts strong antioxidant and anti-inflammatory actions, partly via inhibition of NF-κB activation, suppression of inducible nitric oxide synthase and cyclooxygenase-2 expression, and modulation of apoptosis and cell-cycle regulators [38–40]. CAPE and related phenolics also affect cell signaling transduction pathways, including AMP-activated protein kinase (AMPK), AKT, MKK4, mitophagy, and autophagy, and have been shown to alter metabolism of iron [38,41–44], lipid [38,41–44], and inflammatory disease [38,41–44] in various studies. In addition to these canonical pathways, CAPE modulates broader signaling networks beyond NF-κB. CAPE suppresses CDK1 and AKT activity, leading to reduced phosphorylation of key regulatory residues (e.g., Ser81 and Ser213) and thereby destabilizing downstream targets such as the androgen receptor [45]. Based on these molecular events, CAPE appears to act as a kinase-directed modulator that interferes with the ATP-binding pocket or disrupts the docking of upstream kinases to their substrates, thereby dampening signal amplification. This kinase-directed modulation highlights how phenolic acids can influence not only inflammatory and metabolic pathways but also protein stability and transcriptional programs central to cell survival and stress responses.

Diverse phenolic compounds contribute to the immunomodulatory and antimicrobial properties of propolis, including interference with bacterial quorum sensing, disruption of microbial membranes, reducing the biofilm adherence in the oral cavity [45], inhibition of viral replication, bacterial and fungal growth [46–49]. From a CKM perspective, phenolic acids and CAPE are central candidates for mediating vasoprotective, cardioprotective, renoprotective, and metabolic actions. While in the oral cavity, they likely underlie both direct antibacterial effects and modulation of host responses in gingival and periodontal tissues.

2.3 Terpenoids and Other Constituents

In addition to polyphenols, propolis contains various mono-, sesqui-, and triterpenes, as well as sterols, long-chain hydrocarbons, and minerals [50,51]. Terpenoids can exhibit antimicrobial, anti-inflammatory, and cytotoxic activities, and may synergize with flavonoids and phenolic acids. Certain triterpenes and

sterols may interact with nuclear receptors or influence membrane microdomains, potentially contributing to the modulation of lipid metabolism, steroidogenesis, and cell signaling [42,52,53].

Resins increase hardness, but beeswax supplies flexibility and acts as a binder, producing the sticky, workable texture of propolis [50]. Waxes and fatty acids are generally considered less bioactive but influence physical properties, bioavailability, and formulation behavior. Other components may also contribute vitamins, amino acids, and enzymes, although their role in systemic CKM or periodontal effects is less clear [42,50–53].

2.4 Variability, Standardization, and Implications for CKM–Periodontal Research

The pronounced geographic and botanical variability of propolis complicates direct comparison between studies but also offers a "natural library" of chemotypes with differential bioactivity profiles. For example, TGP rich in propolins has shown robust anti-inflammatory, antifibrotic, and metabolic effects in models of obesity [18–23], gouty inflammation [18–23], liver fibrosis [18–23], kidney injury [18–23] and gingivitis [18–23], whereas Brazilian green propolis enriched in artepillin C has been more extensively studied in cardiometabolic and oncologic contexts [12–16,42,50–54].

Standardization strategies have therefore begun to focus not only on total polyphenol content but also on quantifying key marker compounds such as CAPE, artepillin C, and individual propolins. For reverse translational work, the choice of propolis chemotype and extraction method should be closely aligned with the targeted CKM and periodontal pathways. Studies that clearly define chemical composition and relate it to specific mechanistic outcomes will be critical to move from descriptive efficacy toward rational design of propolis-based interventions. A summary of major propolis chemotypes, their characteristic constituents, and reported biological activities relevant to CKM and periodontal research is provided in Table 1.

Table 1: Summary of major propolis types and their key chemical constituents. Variations in prenylated flavonoids, artepillin C, phenolic acids, and isoflavonoids contribute to differences in their biological activities.

Propolis Type	Key Chemical Constituents	Representative Bioactive Molecules	Characteristic Bioactivities	References
Taiwanese Green Propolis (TGP)	Rich in *prenylated flavonoids*, especially **Propolin A–J**; flavanones; polyphenols	Propolin C, Propolin G	Strong antioxidant activity; NF-κB/JNK suppression; NLRP3 inhibition; anti-fibrotic (↓Smad2/3); metabolic regulation	[18,21–23,35]
Brazilian Green Propolis	Artepillin C–rich; cinnamic acid derivatives; flavonoids	Artepillin C, Baccharin, Dihydrokaempferide	Anti-inflammatory; anti-angiogenic; antimicrobial; metabolic modulation	[15,16,42,54]
Brazilian Red Propolis	Isoflavonoids; phenolic acids; terpenoids	Formononetin, Pinobanksin derivatives	Strong antimicrobial and cytotoxic activities; anti-inflammatory	[15,16,55]
Poplar-Type Propolis (European/Chinese)	Flavonoids (pinocembrin, galangin, chrysin); phenolic acids (caffeic, ferulic)	CAPE, Pinocembrin, Galangin	Antioxidant; NF-κB inhibition; anti-microbial; wound healing	[12,40,56]
Mediterranean Propolis	Terpenoids; flavonoids; aromatic acids	Thymol, Carvacrol, Apigenin	Strong antimicrobial; antioxidant; anti-inflammatory	[56,57]
Stingless Bee Propolis (Meliponini)	High terpenoids; unique phenolic profiles	Prenylated phenolics, triterpenes	Potent antimicrobial; anti-biofilm; antioxidant	[52,58]

Note: ↓ indicates a decrease or inhibition in the corresponding biological activity. Full names of abbreviations: NF-κB, nuclear factor-kappa B; JNK, c-Jun N-terminal kinase; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; Smad2/3, suppressor of mothers against decapentaplegic 2/3. Bold text indicates key characteristic bioactivities that are particularly prominent or well-documented for each propolis type.

3 Core Cellular Mechanisms Linking Propolis to CKM and Periodontal Pathobiology

The core cellular mechanisms by which propolis modulates oxidative stress, inflammation, metabolic reprogramming, fibrotic signaling, and periodontal host responses across CKM and oral tissues are summarized in Fig. 2.

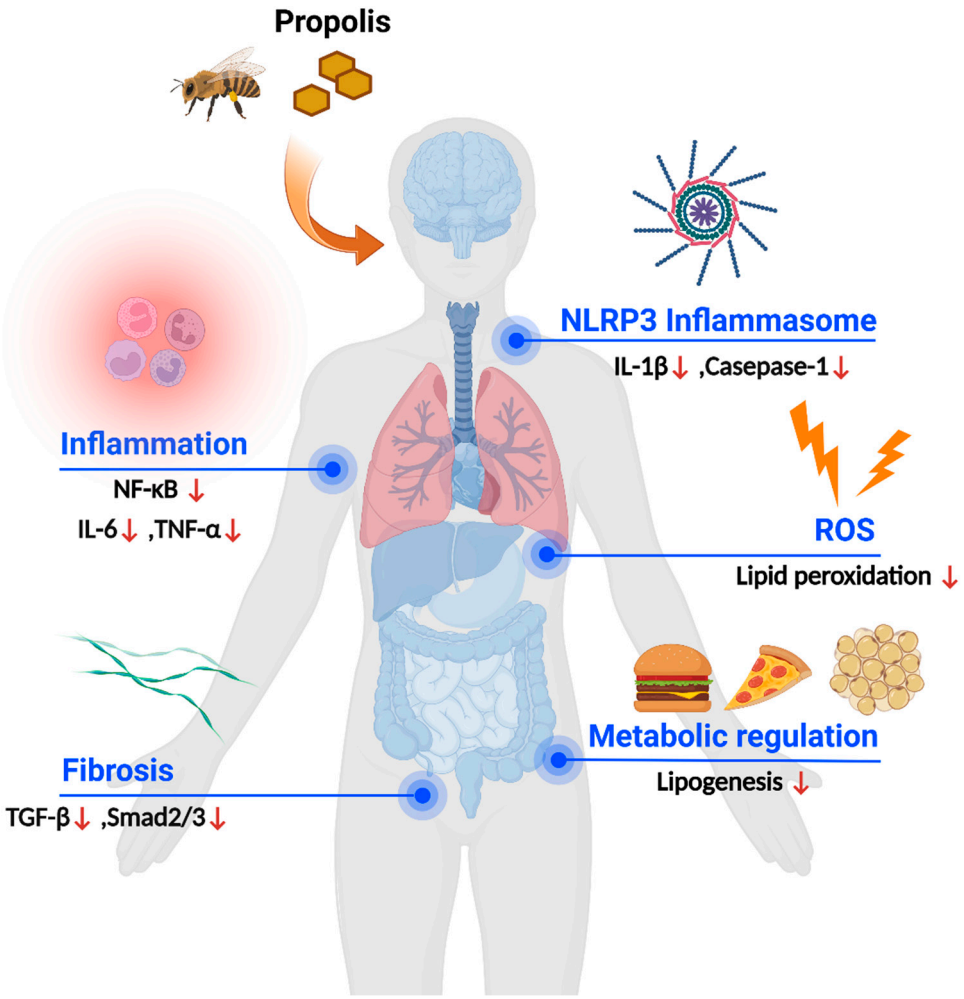

Figure 2: A molecular-level mechanistic summary illustrating the intracellular signaling targets of propolis, specifically highlighting the inhibition of the NF-κB/NLRP3 inflammasome and TGF-β/Smad pathways. Propolis modulates several key pathways across metabolic and inflammatory systems, including: (1) inhibition of systemic inflammation (NF-κB↓, IL-6↓, TNF-α↓); (2) suppression of NLRP3 inflammasome activation (IL-1β↓, Caspase-1↓); (3) reduction of oxidative stress (ROS↓ and lipid peroxidation); (4) anti-fibrotic signaling (TGF-β↓, Smad2/3↓); and (5) metabolic regulation (lipogenesis↓). These pathways represent interconnected intracellular signaling networks rather than isolated cascades. Created in https://BioRender.com (accessed on 09 December 2025).

3.1 Modulation of Oxidative Stress and Redox Signaling

Oxidative stress is a central driver of CKM syndrome and periodontal breakdown, promoting endothelial dysfunction, insulin resistance, adipose tissue inflammation, mitochondrial impairment, and osteoclast activation [59,60]. Propolis and its major constituents consistently attenuate oxidative stress across multiple models by combining direct radical scavenging with upregulation of endogenous antioxidant systems [61,62].

In animal models, propolis protects rats from CCl4-induced liver and kidney toxicity by enhancing antioxidant defenses and reducing oxidative stress, including lowering liver enzymes and increasing antioxidant agents like glutathione [63]. Moreover, propolis upregulates Nrf2 signaling by facilitating its nuclear translocation, where it binds to the Antioxidant Response Element (ARE) in the promoter regions of cytoprotective genes. This increases transcription of detoxifying enzymes, including heme oxygenase-1, glutathione peroxidase, catalase, and superoxide dismutase [64–66]. At the cellular level, activation of the Nrf2/HO-1 axis not only enhances antioxidant defense but also suppresses NF-κB-mediated inflammatory transcription through redox-sensitive signaling cross-talk. In diabetic and obese models, propolis reduces malondialdehyde accumulation, restores glutathione levels, and attenuates ROS generation in blood, pancreas, liver, spleen, and kidney [67]. These actions protect mitochondrial integrity, preserve insulin signaling, and mitigate oxidative tissue injury associated with CKM progression.

Within the periodontal environment, propolis protects gingival fibroblasts, periodontal ligament cells, and dental pulp cells from oxidative stress through antimicrobial activity, ROS scavenging, and modulation of redox-sensitive signaling pathways, including activation of the Nrf2/HO-1 pathway and suppression of NF-κB signaling–mediated NLRP3 inflammasome activation, thereby preserving cell viability and reducing apoptosis under bacterial or hyperglycemic conditions [23,68]. Collectively, these mechanisms converge on a shared upstream redox driver linking CKM organ damage and periodontal breakdown.

3.2 Anti-Inflammatory and Immunomodulatory Actions

Chronic low-grade inflammation is the second major axis connecting CKM syndrome and periodontitis. Pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, with chemokines and acute-phase reactants, drive insulin resistance, endothelial activation, vascular remodeling, and bone resorption in the human body [3,69]. Propolis exerts multi-layered anti-inflammatory and immunomodulatory effects in innate and adaptive immune cells as well as in parenchymal tissues [70].

At the transcriptional level, propolis inhibits NF-κB activation by preventing IκBα degradation and p65 nuclear translocation, and attenuates phosphorylation of upstream kinases such as IKK, JNK, and p38 MAPK. These findings are often observed in macrophages, monocytes, and endothelial cells stimulated with lipopolysaccharide or crystalline damage-associated molecular patterns [71]. This leads to reduced expression of IL-1β, IL-6, TNF-α, MCP-1, and COX-2, and decreases the production of prostaglandins and nitric oxide [62]. These effects reflect a coordinated suppression of both the priming and activation phases of inflammatory signaling, positioning NF-κB as a central upstream regulator modulated by propolis across multiple cell types. This also highlights the role of NF-κB as a key priming signal required for subsequent NLRP3 inflammasome activation.

Propolis also modulates inflammasome signaling, specifically the NLRP3 inflammasome, which plays an important role in gouty inflammation, CKD progression, and potentially in periodontal bone loss. At the cellular level, NLRP3 inflammasome activation is tightly regulated by mitochondrial ROS production, potassium efflux, and lysosomal destabilization, all of which are key upstream signals targeted by propolis. In models of monosodium urate crystal–induced inflammation, propolis and specific propolins reduce NLRP3 expression and interfere with the NLRP3 inflammasome assembly by inhibiting the oligomerization of ASC and the subsequent cleavage of pro-caspase-1. This reduces ASC speck formation, inhibits caspase-1 activation, and diminish IL-1β maturation, partly via limiting mitochondrial damage, ROS production, and lysosomal disruption, and partly via induction of autophagy [21]. These actions directly target a convergent node of CKM and crystal-driven joint disease.

In adaptive immunity, propolis influences T-cell and B-cell responses, promoting regulatory T-cell phenotypes in some settings and modulating antibody production [72]. Although data remain limited in CKM models, such immunoregulatory effects may help restrain chronic vascular and renal inflammation and shape the periodontal immune microenvironment. Together, these inflammatory and inflammasome-modulating effects constitute a central arm of the mechanistic framework illustrated in Fig. 2.

3.3 Metabolic Reprogramming: Insulin Sensitivity, Adipose Tissue, and Hepatometabolic Effects

From a CKM perspective, a key question is whether propolis exerts direct metabolic effects beyond generalized antioxidant and anti-inflammatory actions. Several lines of preclinical and clinical evidence suggest that it does. In diet-induced obesity and T2DM models, propolis supplementation improves glucose tolerance and insulin sensitivity, reduces fasting glucose and insulin levels, and attenuates hepatic steatosis and dyslipidemia [73,74]. These changes are accompanied by alterations in adipose tissue biology: propolis decreases adipocyte hypertrophy and macrophage infiltration in white adipose depots, downregulates pro-inflammatory adipokines, and upregulates genes associated with mitochondrial function and thermogenesis. Some studies demonstrate increased expression of uncoupling protein-1 and browning markers in white adipose tissue, as well as preserved brown adipose tissue morphology and non-shivering thermogenesis, suggesting that propolis promotes a more oxidative and energy-dissipating adipocyte phenotype [75]. At the cellular level, these metabolic effects are associated with enhanced mitochondrial function, improved insulin receptor signaling, and reduced intracellular lipid accumulation in hepatocytes, adipocytes, and skeletal muscle cells.

Hepatic effects include reduced *de novo* lipogenesis, enhanced β-oxidation, and attenuation of lipotoxicity-related stress pathways, which together improve lipid and glucose homeostasis. At the molecular level, propolis and CAPE have been reported to influence AMPK, AKT, and PPAR signaling. Specifically, the activation of the AMPK/AKT pathway by propolis facilitates the translocation of GLUT4 to the plasma membrane, thereby enhancing glucose uptake in skeletal muscle and adipose cells [76,77]. AMPK activation further promotes mitochondrial biogenesis and fatty acid oxidation, while AKT signaling enhances glucose uptake and cell survival, indicating that propolis directly regulates intracellular metabolic signaling networks.

Renal and vascular tissues also exhibit metabolic reprogramming under propolis exposure, with improved endothelial nitric oxide bioavailability, reduced accumulation of uremic toxins, and attenuation of lipid accumulation in renal tubules and the arterial wall [19,55]. Collectively, these mechanisms converge on a phenotype characterized by improved insulin sensitivity, more favorable adipose and hepatic metabolism, and protection of cardio–renal structures from metabolic injury. Together, these findings indicate that propolis exerts direct intracellular metabolic regulation beyond its antioxidant and anti-inflammatory properties.

3.4 Antifibrotic and Tissue-Remodeling Effects

Fibrosis of the liver, kidney, heart, and vasculature is a central determinant of CKM progression and adverse outcomes. Propolis interferes with profibrotic signaling in multiple cell types, including hepatic stellate cells [78], renal tubular cells [78], and cardiac fibroblasts [78].

In TGF-β–driven models of liver and kidney fibrosis, propolis and specific constituents such as propolin G inhibit Smad2/3 phosphorylation and nuclear translocation. By preventing the binding of phosphorylated Smad complexes to the promoters of profibrotic genes, propolis effectively suppresses the expression of α-smooth muscle actin and type I and IV collagens, thereby limiting extracellular matrix deposition [18,79]. At the molecular level, inhibition of Smad2/3 phosphorylation prevents their nuclear translocation and transcriptional activation of fibrosis-related genes, thereby suppressing myofibroblast differentiation and

extracellular matrix production. Non-Smad pathways such as JNK and ERK are also downregulated, further dampening fibrogenic responses [19]. These signaling cascades are functionally interconnected, with MAPK signaling potentiating TGF-β–driven fibrotic responses through transcriptional regulation, underscoring the multi-level antifibrotic effects of propolis at the cellular level. These effects translate into reduced histologic fibrosis, lower fibrosis-associated biomarkers, and better preservation of organ function *in vivo*. Similar antifibrotic tendencies have been observed in cardiac and vascular tissues, where propolis diminishes fibroblast proliferation and matrix synthesis in hypertensive and metabolic stress models, although the literature here remains more limited [80]. In the periodontal context, propolis appears to favor a reparative rather than fibrotic phenotype in gingival fibroblasts and pulp cells, supporting wound healing while avoiding excessive scar formation [81].

3.5 Antimicrobial, Anti-Biofilm, and Host-Modulating Actions in Periodontal and Oral Cells

Propolis exhibits potent antimicrobial and anti-biofilm activity against key oral pathogens, including *P. gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, *Cariogenic streptococci*, and *Candida* species [82]. Ethanol extracts and isolated compounds such as artepillin C, baccharin, and ursolic acid disrupt bacterial membranes, increase permeability, and cause rapid bactericidal effects in *P. gingivalis*, while exerting relatively milder effects on commensal streptococci [83]. Propolis also inhibits biofilm formation and can reduce the viability of established biofilms on dentin and implant surfaces, suggesting potential applications in both preventive and therapeutic oral care products [58].

Beyond direct antimicrobial action, propolis modulates the host response in periodontal tissues. *In vitro*, it reduces the production of IL-1β, IL-6, TNF-α, and matrix metalloproteinases by gingival fibroblasts and epithelial cells stimulated with bacterial products, while enhancing anti-inflammatory cytokines such as IL-10 in monocyte-derived cells [84,85]. Furthermore, propolis modulates the RANKL/OPG ratio to maintain alveolar bone homeostasis. At the molecular level, it suppresses the induction of c-Fos and NFATc1, which are the master transcriptional switches for osteoclastogenesis [86]. By blocking RANKL-mediated MAPK and NF-κB pathways, propolis effectively prevents the cellular commitment to bone resorption while concurrently upregulating Runx2 to promote osteoblast differentiation [87].

These mechanisms—antioxidant, anti-inflammatory, antifibrotic, antimicrobial, and pro-resolving—overlap substantially with the pathways implicated in CKM syndrome. This mechanistic convergence provides a rationale for viewing propolis not merely as a local oral agent or a systemic nutraceutical, but as a bridge between the CKM axis and periodontal tissues, as discussed in the following sections. These antimicrobial and host-modulating actions complete the mechanistic spectrum depicted in Fig. 2, linking local periodontal effects with systemic CKM-related pathways.

Collectively, these mechanisms illustrate that propolis exerts coordinated regulatory effects across multiple intracellular signaling pathways rather than acting on isolated targets, providing a mechanistic basis for its systemic effects across cardio–kidney–metabolic and periodontal tissues.

4 Propolis in Cardio-Kidney-Metabolic Syndrome

Accumulating evidence indicates that propolis exerts pleiotropic biological effects across multiple components of CKM syndrome. By concurrently modulating oxidative stress, inflammatory and inflammasome signaling, metabolic pathways, and fibrotic responses, propolis impacts a broad spectrum of CKM-related phenotypes, including obesity and metabolic syndrome [20,88], type 2 diabetes mellitus [20,88], chronic kidney disease [20,88], gouty inflammation [20,88], and CVD [78]. An overview of the major biological effects of propolis across CKM components and their representative mechanisms is summarized in Table 2,

which provides a systems-level framework to contextualize the disease-specific evidence discussed in the following subsections.

Table 2: Integrated biological effects of propolis across cardio-kidney-metabolic (CKM) systems and related mechanisms. Propolis modulates oxidative stress, inflammation, metabolic signaling, and fibrotic pathways, contributing to improvements in obesity, diabetes, metabolic dysfunction-associated steatotic liver disease (MASLD), chronic kidney disease (CKD), gout-related inflammasome activation, and cardiovascular disease (CVD).

CKM Component	Key Effects of Propolis	Representative Mechanisms
Obesity/Metabolic Syndrome	Improves lipid profile; reduces visceral fat; enhances adipose remodeling	↓ NF-κB/JNK, ↓ ROS, ↑ Browning genes, ↑ modulation of gut microbiota
Type 2 Diabetes Mellitus	Lowers fasting glucose; improves insulin sensitivity	↑ AMPK/AKT signaling, ↓ oxidative stress, β-cell protection
Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD)	Reduces steatosis and inflammation	↓ TGF-β/Smad2/3, ↓ lipogenesis, ↑ β-oxidation
Chronic Kidney Disease (CKD)	Decreases fibrosis and uremic toxin retention	↓ Smad2/3, ↓ JNK/ERK, ↓ EMT, ↓ PCS/IS levels
Gout/Hyperuricemia (NLRP3-driven)	Attenuates gouty inflammation	↓ NLRP3, ↓ ASC, ↓ Caspase-1, ↓ IL-1β
Cardiovascular Disease (CVD)	Improves endothelial function, reduces oxidative injury	↑ NO bioavailability, ↓ ROS, ↓ COX-2

Note: ↓: decrease; ↑: increase; AKT, Protein kinase B; AMPK, AMP-activated protein kinase; ASC, Apoptosis-associated speck-like protein containing a CARD; COX-2, Cyclooxygenase-2; EMT, Epithelial-mesenchymal transition; ERK, Extracellular signal-regulated kinase; IL-1β, Interleukin-1 beta; IS, Indoxyl sulfate; JNK, c-Jun N-terminal kinase; NF-κB, Nuclear factor-kappa B; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NO, Nitric oxide; PCS, p-Cresyl sulfate; ROS, Reactive oxygen species; Smad2/3, Suppressor of mothers against decapentaplegic 2/3; TGF-β, Transforming growth factor-beta.

4.1 Cardiovascular Protection

In the context of CKM syndrome, the cardiovascular protective effects of propolis are primarily driven by the preservation of endothelial function, the active suppression of vascular inflammation, and the prevention of adverse cardiac remodeling. Recent comprehensive reviews emphasize that propolis and its bioactive constituents serve as potent countermeasures against a broad spectrum of core cardiovascular risk factors, including obesity, hypertension, dyslipidemia, and atherosclerosis [85,86]. Specifically, bioactive polyphenols such as CAPE actively protect vascular endothelial cells by upregulating endothelial nitric oxide synthase (eNOS) activity [78]. Propolis enhances endothelial nitric oxide synthase (eNOS) activity specifically through the PI3K/AKT-dependent phosphorylation of eNOS at Ser1177. This precise molecular event increases nitric oxide (NO) bioavailability and restores endothelial function within the CKM-vascular axis [86]. Furthermore, propolis exerts potent anti-atherosclerotic effects by stabilizing lipid plaques, inhibiting macrophage apoptosis, and reducing vascular smooth muscle proliferation, highlighting its translational value in CVD management [85].

4.2 Cardiovascular Remodeling

Beyond vascular endothelial protection, propolis exerts direct anti-fibrotic effects within the myocardium and surrounding stromal tissues. Following ischemic events such as myocardial infarction, flavonoid extracts from propolis have been demonstrated to inhibit structural cardiac fibrosis by upregulating the SIRT1 pathway, thereby mitigating pathological ventricular remodeling [80]. Additionally, specific propolis compounds directly interfere with profibrotic signaling cascades by inhibiting TGF-β1/SMAD activation in human fibroblasts, limiting excessive extracellular matrix deposition [79].

By coupling these anti-inflammatory vascular actions with robust myocardial anti-fibrotic mechanisms, propolis effectively delays the progression of atherosclerosis and cardiac stiffness, offering profound systemic protection against the macrovascular complications inherent to the CKM continuum.

4.3 Metabolic Syndrome and Obesity

Multiple animal and human studies indicate that propolis favorably influences key components of metabolic syndrome, including central obesity, dyslipidemia, glucose intolerance, and low-grade inflammation. In diet-induced obesity models, supplementation with standardized propolis or chemically defined TGP attenuates weight gain, improves serum triglyceride and cholesterol profiles, reduces visceral fat accumulation, and decreases hepatic steatosis [20,35,89]. These effects are accompanied by improved glucose tolerance and insulin sensitivity, reduced fasting glycemia, and lower circulating insulin levels [90].

At the tissue level, TGP has been shown to remodel white adipose tissue by reducing adipocyte hypertrophy, suppressing inflammatory signaling (NF-κB, JNK) and ROS production, and promoting browning with increased thermogenic gene expression [23,42]. Brown adipose tissue morphology and function are preserved, with augmented non-shivering thermogenesis in response to cold exposure [75]. Simultaneously, alterations in gut microbiota composition have been described, with an increase in beneficial, SCFA-associated taxa and a reduction in potentially deleterious groups, suggesting a microbiome-mediated contribution to metabolic improvements [91]. These metabolic improvements are accompanied by suppression of hepatic lipogenic pathways and enhancement of fatty acid β-oxidation, consistent with reported effects of propolis on metabolic dysfunction-associated steatotic liver disease (MASLD).

Clinical trials, although still limited in number and size, support some of these findings. Propolis supplementation in individuals with metabolic syndrome or T2DM has been associated with reductions in waist circumference, improvements in certain quality-of-life domains, and, in some studies, better glycemic control and reductions in inflammatory biomarkers, though lipid changes are less consistent [92]. Heterogeneity in dose, duration, and chemical composition likely contributes to these variable outcomes.

4.4 Type 2 Diabetes, Insulin Resistance, and Diabesity

The intersection of obesity and T2DM—often referred to as “diabesity”—is a core feature of CKM syndrome. Propolis has been investigated as an adjunct in this context both preclinically and clinically. In streptozotocin- and diet-induced diabetic models, propolis reduces fasting blood glucose, improves glucose tolerance, lowers HbA1c, and preserves pancreatic islet architecture [93]. Mechanistically, these effects are linked to reduced oxidative stress and inflammation in pancreatic tissue, improved β-cell survival, and enhanced peripheral insulin signaling via modulation of AKT, AMPK, and GLUT4 expression [94].

In clinical settings, adjunctive oral propolis in patients with T2DM has yielded reductions in fasting plasma glucose and HbA1c in several trials, along with decreased circulating inflammatory markers and increased HDL-cholesterol in some cohorts, though not all studies have been positive [95]. Notably, in patients with T2DM and chronic periodontitis, oral propolis combined with scaling and root planing improved both periodontal parameters and glycemic control more than mechanical therapy alone [96], suggesting a synergistic effect at the interface of CKM and periodontal disease.

4.5 Kidney Disease, Uremic Toxin Retention, and Renal Fibrosis

CKD is a critical node in CKM syndrome, amplifying cardiovascular risk and being exacerbated by metabolic disturbances. Experimental models of toxic, metabolic, and inflammatory kidney injury have provided insight into the potential nephroprotective actions of propolis [97].

In aristolochic acid-induced nephropathy, a model characterized by severe tubulointerstitial fibrosis and retention of protein-bound uremic toxins such as p-cresyl sulfate and indoxyl sulfate, propolis treatment attenuates renal atrophy, improves creatinine and urea levels, reduces interstitial collagen deposition, and lowers circulating uremic toxin levels. These improvements are associated with suppression of epithelial-mesenchymal transition, downregulation of α-smooth muscle actin and type I/IV collagen, and inhibition of both Smad2/3-dependent and Smad-independent (JNK/ERK) TGF-β signaling pathways [19]. At the cellular level, inhibition of epithelial–mesenchymal transition preserves renal tubular epithelial integrity and prevents the acquisition of a profibrotic phenotype.

Other studies in obese or endotoxemic mice have shown that targeting oxidative stress and inflammatory mediators such as cPLA2 and COX-2 can ameliorate obese kidney fibrosis and metabolic endotoxemia–driven injury, a mechanistic space where propolis is well positioned, given its antioxidant and anti-inflammatory profile [44,98]. Although direct renal outcome data in human CKD patients treated with propolis remain sparse, these preclinical findings support the concept of propolis as a multi-target nephroprotective adjunct within the CKM framework.

4.6 Gouty Inflammation, Hyperuricemia, and NLRP3

Gout and hyperuricemia are closely linked with metabolic syndrome, obesity, CKD, and CVD, and can be viewed as a facet of CKM syndrome. Gouty inflammation is driven by monosodium urate crystals acting as danger-associated molecular patterns that activate the NLRP3 inflammasome, leading to IL-1β maturation and intense neutrophilic infiltration [99].

TGP has been shown to attenuate NLRP3 inflammasome activation *in vitro* and *in vivo*, reducing pro-IL-1β expression by inhibiting NF-κB and ROS generation in LPS-primed macrophages, and suppressing multiple activation signals, including mitochondrial damage, lysosomal rupture, JNK phosphorylation, and ASC oligomerization [23]. In murine models of urate crystal–induced peritonitis, propolis decreases neutrophil recruitment and reduces levels of IL-1β, active caspase-1, IL-6, and MCP-1 in exudates [22]. Such findings highlight a targeted anti-NLRP3 effect that is directly relevant not only to gout but also to renal and vascular inflammation in CKM syndrome.

Taken together, these lines of evidence support a multi-organ protective role of propolis within CKM syndrome, encompassing metabolic reprogramming, anti-inflammatory and antifibrotic effects, and specific inhibition of inflammasome-related pathways. Beyond metabolic and renal protection, propolis has been shown to improve endothelial function and vascular redox balance, partly through enhancement of nitric oxide bioavailability and suppression of oxidative and COX-2–mediated inflammatory signaling, thereby contributing to cardiovascular protection within the CKM spectrum [23,98].

5 Propolis in Periodontal Disease

5.1 Antimicrobial and Anti-Biofilm Effects against Periodontal Pathogens

Chronic periodontitis is driven by a dysbiotic biofilm that includes keystone pathogens such as *P. gingivalis*, which can subvert host immunity and shift the microbial community toward a more pathogenic configuration. Propolis has repeatedly demonstrated potent antimicrobial activity against *P. gingivalis* and other periodontopathogens *in vitro* [100].

Ethanolic extracts of propolis inhibit the growth of *P. gingivalis* at relatively low minimum inhibitory concentrations and display rapid bactericidal activity characterized by increased membrane permeability, the formation of membrane blebs, and eventual rupture, as visualized by advanced imaging techniques [58,100]. Isolated compounds, including artepillin C, baccharin, and ursolic acid, contribute to these effects, with

ursolic acid in particular showing strong membrane-disruptive and bactericidal actions [101]. Importantly, some studies suggest that *P. gingivalis* is more sensitive than commensal streptococci, raising the possibility of a relatively narrow-spectrum effect that spares beneficial oral microbiota [102].

Propolis also inhibits early adhesion and maturation of multi-species oral biofilms, reduces biofilm biomass and viability on enamel, dentin, and implant surfaces, and can disrupt established cariogenic and periodontal biofilms when used in mouthrinses, gels, or toothpaste formulations [58]. These properties underpin its increasing use as an active ingredient in oral health care products intended for caries and gingivitis prevention and adjunctive management of periodontitis.

5.2 Modulation of the Periodontal Host Response

Beyond direct antimicrobial effects, propolis acts on gingival epithelial cells, fibroblasts, periodontal ligament cells, and immune cells to modulate the inflammatory response. *In vitro*, propolis reduces the production of IL-1β, IL-6, TNF-α, and prostaglandin E2 in cells stimulated with LPS or *P. gingivalis* components, partly via inhibition of NF-κB and MAPK signaling cascades [103]. At the same time, it can increase anti-inflammatory mediators such as IL-10 in monocyte-derived cells challenged with periodontal or *Candida* biofilms [13].

These host-modulating actions extend to matrix remodeling: propolis downregulates matrix metalloproteinases implicated in collagen degradation while maintaining or enhancing tissue inhibitors of metalloproteinases, thereby shifting the balance toward preservation of connective tissue [104]. Propolis can also attenuate osteoclast differentiation and activity and may support osteoblast function, thereby influencing alveolar bone remodeling under inflammatory conditions [103]. In osteoclast precursor cultures, propolis and CAPE inhibit RANKL-induced osteoclast differentiation and bone resorptive activity, whereas in osteoblasts and periodontal ligament cells, propolis may support mineralization and expression of osteogenic markers under inflammatory conditions [105]. Together, these effects favor a microenvironment conducive to periodontal stability and regeneration rather than progressive destruction.

5.3 Pulpal, Endodontic, and Regenerative Applications

Propolis has also been investigated in endodontics and regenerative dentistry. It exhibits antimicrobial activity against *Enterococcus faecalis* and *Candida albicans*, common endodontic pathogens, and has been proposed as an intracanal medicament or irrigant adjunct [106]. In human pulp cells, propolis reduces inflammation and oxidative stress, promotes cell viability, and can enhance dentin bridge formation in some models, suggesting utility as a biocompatible pulp-capping or pulp-protecting agent [81].

These properties are highly relevant for patients with CKM syndrome, who may exhibit impaired wound healing and increased susceptibility to infection. Propolis-containing materials that simultaneously control microbial load and support pulpal and periodontal tissue repair could be particularly beneficial in this high-risk population.

5.4 Clinical Trials of Propolis in Periodontal Therapy

Several clinical trials have evaluated propolis as an adjunct to conventional periodontal therapy. In chronic periodontitis, local delivery of propolis-containing gels or mouthrinses in combination with scaling and root planing (SRP) has been associated with greater reductions in probing depth and gains in clinical attachment level compared with SRP alone or SRP plus placebo, along with improvements in plaque and bleeding indices [107]. Microbiological assessments often reveal reductions in *P. gingivalis* and other periodontopathogens in subgingival plaque. In patients with T2DM and chronic periodontitis, oral propolis

supplementation in addition to SRP has led to superior improvements in both periodontal parameters and glycemic control (HbA1c, fasting plasma glucose) compared with SRP plus placebo, reinforcing the bidirectional link between periodontal inflammation and systemic metabolism and positioning propolis as an agent acting on both fronts [96].

Taken together, these data support the concept that propolis can function as a dual-action adjunct in periodontal disease: directly suppressing pathogenic biofilms while modulating the host response to favor resolution of inflammation and tissue preservation. When viewed through the CKM lens, periodontal benefits may feed back into improved systemic inflammation and metabolic control, further justifying integrative study designs. Ultimately, by mitigating local gingival inflammation and reducing the bacterial load of circulating periodontal pathogens, the targeted administration of propolis effectively disrupts the pathogenic periodontal-systemic axis. This local intervention serves as a critical systemic adjunct, lowering the overall inflammatory burden that accelerates CKM syndrome.

6 Integrated Mechanistic Model Linking Cardio-Kidney-Metabolic Syndrome and Periodontal Disease through Propolis-Mediated Bio-Cellular Modulation

To integrate the diverse mechanistic evidence discussed above, an overarching model is required to conceptualize how propolis simultaneously modulates metabolic, inflammatory, oxidative, and tissue-remodeling pathways shared between cardio-kidney-metabolic syndrome and periodontal disease. These pathways should not be considered as isolated cascades but rather as interconnected intracellular signaling networks, in which oxidative stress, inflammation, and metabolic dysregulation converge at shared molecular nodes. This network-based perspective further supports the concept that propolis functions as a multi-target modulator acting on shared intracellular signaling hubs rather than single linear pathways. This integrative framework provides a mechanistic basis for translating propolis from experimental models into multi-system clinical applications.

Growing evidence from the experimental, preclinical, and translational studies demonstrates that propolis exerts convergent effects across metabolic, immune, oxidative, and stromal pathways that are shared between CKM and periodontal disease [108]. Although these disorders differ clinically, they are biologically unified by chronic low-grade inflammation, dysregulated redox signaling, microbial dysbiosis, and aberrant tissue remodeling. The collective findings from hepatic, renal, adipose, vascular, and periodontal models reveal a hub-and-spoke architecture in which propolis acts on several conserved molecular nodes [30].

A dominant mechanism involves the ability of propolis and its constituents—particularly propolins, CAPE, artepillin C, baccharin, and various prenylated flavonoids—to attenuate oxidative stress by restoring intracellular antioxidant capacity. Multiple studies demonstrate enhanced Nrf2 signaling, increased glutathione abundance, and suppressed lipid peroxidation in hepatocytes, renal tubular cells, adipocytes, and testicular tissue following propolis exposure [109]. Notably, Nrf2 activation negatively regulates NF-κB signaling through redox-dependent mechanisms, providing a critical link between antioxidant and anti-inflammatory effects of propolis. Because oxidative stress is an upstream driver of endothelial dysfunction, adipose inflammation, and periodontal tissue breakdown, this antioxidant normalization serves as a unifying protective axis. Fig. 3 integrates these multi-organ and multi-pathway effects into a unified mechanistic model.

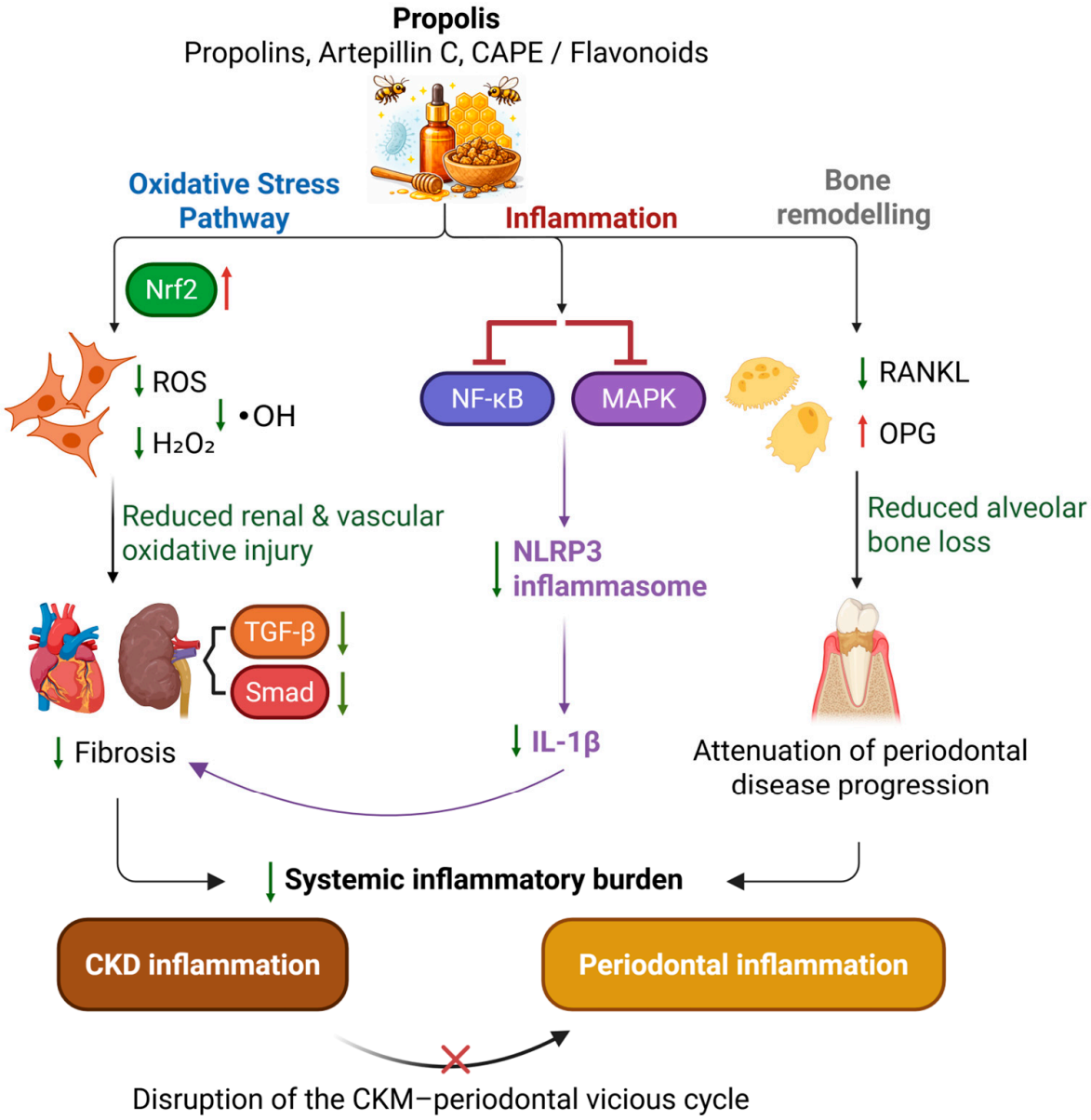

Figure 3: An integrated disease-network model depicting the macroscopic, systemic cross-talk between local periodontal infections and the cardio-kidney-metabolic (CKM) syndrome, and how propolis disrupts this pathogenic axis–vicious cycle. Propolis and its major bioactive constituents (propolins, artepillin C, caffeic acid phenethyl ester, and flavonoids) exert coordinated antioxidant, anti-inflammatory, anti-fibrotic, and bone-protective effects across the CKM–periodontal axis. Propolis activates Nrf2-dependent antioxidant signaling, reducing reactive oxygen species and limiting renal and vascular oxidative injury while suppressing TGF-β/Smad–mediated fibrosis. Concurrently, propolis inhibits NF-κB and MAPK signaling, leading to suppression of the NLRP3 inflammasome and decreased IL-1β production, thereby attenuating cardio–renal inflammation and fibrotic remodeling. In periodontal tissues, propolis modulates bone remodeling by decreasing RANKL and increasing OPG, resulting in reduced alveolar bone loss and slowed periodontal disease progression. Collectively, these actions lower the systemic inflammatory burden and disrupt the bidirectional inflammatory loop between CKM-related inflammation and periodontal inflammation. These effects reflect coordinated modulation of interconnected intracellular signaling pathways, highlighting the role of propolis as a multi-target regulator at the cellular and molecular levels. ↓: decrease; ↑: increase. Created in https://BioRender.com (accessed on 26 December 2025).

The second shared pathway is the inhibition of NF-κB–dependent inflammatory signaling. Across CKD, gout, endotoxemia, and LPS-activated macrophage models, propolis consistently reduces transcription of IL-1β, IL-6, TNF-α, and chemokines such as CCL2 through suppression of the priming and activation steps required for inflammasome assembly [71]. The uploaded periodontal studies confirm the same phenomenon in gingival fibroblasts and immune cells exposed to *P. gingivalis* or high-glucose conditions [23]. These data indicate that propolis suppresses systemic and locally stimulated inflammatory pathways through a conserved inhibition of NF-κB, JNK, and TLR4-related signaling.

Modulation of tissue remodeling appears as a third unifying biological node. In hepatic and renal fibrosis models, propolis inhibits TGF-β-mediated Smad2/3 phosphorylation, reduces α-SMA and collagen deposition, and enhances apoptotic clearance of activated myofibroblasts [18]. Although periodontal tissues involve distinct stromal elements, propolis demonstrates parallel anti-fibrotic effects by reducing matrix metalloproteinase activity and limiting connective tissue breakdown under bacterial challenge or hyperglycemia [107]. These mechanistic parallels suggest that propolis operates as a broad regulator of pathological wound-healing processes.

A final central node connecting CKM disorders to periodontal disease is microbial regulation. Multiple uploaded papers show that propolis alters gut microbiota composition, reducing endotoxin-producing genera and increasing short-chain-fatty-acid-producing species [20,110]. In the oral cavity, propolis exerts rapid bactericidal activity against *P. gingivalis* through membrane disruption and metabolic collapse [100]. These microbiome effects converge with its immunomodulatory properties to reduce systemic endotoxemia, a major upstream trigger of adipose inflammation, vascular dysfunction, and impaired periodontal healing.

Together, these findings support an integrated mechanistic model in which propolis targets multiple interlinked biological domains that are central to both cardio-kidney-metabolic (CKM) disorders and periodontal disease. First, propolis restores redox homeostasis by reducing reactive oxygen species (ROS), including hydrogen peroxide and hydroxyl radicals, thereby attenuating renal and vascular oxidative injury and limiting downstream fibrotic responses. Second, propolis suppresses innate immune overactivation through inhibition of NF-κB signaling and subsequent NLRP3 inflammasome activation, leading to reduced IL-1β production and a lower systemic inflammatory burden. These findings position the NLRP3 inflammasome as a central convergence node linking metabolic inflammation, uremic toxin signaling, and periodontal immune responses. Third, propolis modulates tissue and bone remodeling pathways by correcting the RANKL/OPG imbalance, resulting in reduced alveolar bone loss and attenuation of periodontal disease progression. Through the coordinated regulation of oxidative stress, inflammatory signaling, and remodeling pathways, propolis disrupts the bidirectional amplification loop between CKD-associated inflammation and periodontal inflammation, highlighting its potential as a cross-system therapeutic strategy.

7 Reverse Translational Research Framework

Recent integrative reviews have highlighted propolis as a multi-target natural compound with relevance to chronic inflammatory and metabolic disorders, providing a conceptual basis for reverse translational research strategies [108]. Reverse translational research—defined as the bidirectional movement of clinical observations back into mechanistic preclinical models—offers a rigorous pathway to unify disparate findings across cardio-renal-metabolic (CKM) medicine and periodontal biology. The emerging overlap between systemic inflammatory disorders, metabolic dysregulation, uremic toxin accumulation, and oral microbial pathogenesis positions propolis as an exemplary candidate for such an approach. This framework enables the systematic interrogation of how clinical phenomena associated with propolis use correspond to measurable molecular effects across tissues, signaling cascades, and disease networks.

A recent randomized controlled trial demonstrated that TGP, when used as an oral rinse, significantly reduced the severity of radiation-induced oral mucositis compared with usual care in head and neck cancer patients, although it was less effective than honey in improving quality of life measures [111]. Clinical practice and early-phase human studies have reported improvements in glycemic control, lipid profiles, and inflammatory markers among individuals consuming propolis or its derivatives. For example, supplementation with standardized propolis extracts improved glycated hemoglobin, decreased circulating TNF-α, and attenuated markers of oxidative stress in patients with type 2 diabetes mellitus and chronic periodontitis [96]. These findings parallel observations in CKD cohorts, where propolis-derived compounds modulated uremic toxin burden, reduced TGF-β–dependent fibrotic signaling, and improved surrogate markers of renal tubular injury [19,79]. Such clinical outcomes raise critical mechanistic questions regarding the tissue-level pathways through which propolis achieves synchronous metabolic and anti-inflammatory benefits.

Reverse translational analysis begins by decomposing these clinical effects into core molecular events identified in cell-based and animal models. Across multiple studies, TGP and its prenylated flavanones (propolins A–J) suppress JNK and NF-κB activation, reduce mitochondrial-derived reactive oxygen species, and attenuate NLRP3 inflammasome assembly in macrophages exposed to LPS or monosodium urate crystals [21,22]. These mechanisms mirror clinical observations of decreased IL-1β and improved periodontal inflammatory indices in patients receiving propolis-based adjunctive therapy. Likewise, the remodeling of white adipose tissue toward a more metabolically flexible phenotype—characterized by enhanced browning, preserved mitochondrial function, and reduced lipid peroxidation—corresponds to reductions in fasting insulin and improved lipid homeostasis documented in obese or diabetic individuals treated with propolis extracts [20,112].

The reverse translational cycle also highlights mechanistic convergence between CKM disease and periodontal pathology. Clinically, individuals with CKD or metabolic syndrome frequently exhibit dysbiosis, increased periodontal pathogen burden, and heightened mucosal inflammation. Experimental evidence demonstrates that propolis exerts direct antibacterial activity against *Porphyromonas gingivalis*, mediated through membrane permeabilization, inhibition of bacterial oxidative defenses, and disruption of virulence-associated structures [100,113]. These antimicrobial actions reinforce clinical findings of reduced probing depth and bleeding on probing in propolis-treated patients, suggesting that the compound may modulate both systemic host signaling and microbial ecology.

Reverse translational research additionally facilitates biomarker discovery. Among CKM populations using propolis, improvements in circulating levels of p-cresyl sulfate, indoxyl sulfate, malondialdehyde, and oxidized LDL have been noted. These biomarkers correspond to well-defined mechanistic targets in preclinical experiments, where propolis suppresses SMAD2/3 phosphorylation, attenuates epithelial-mesenchymal transition, and modulates renal excretion pathways for uremic solutes [19]. Integrating these clinical biomarkers with tissue-level signaling signatures creates a platform for evaluating propolis as a multi-target modulator rather than a single-pathway agent.

Finally, reverse translational methodology provides insight into dosing, formulation, and bioavailability challenges. The superior bioactivity of nanoparticle-encapsulated propolis in models of diabetic reproductive dysfunction suggests that future clinical applications may benefit from delivery systems that enhance tissue penetration and metabolic stability [114,115]. By tracing mechanistic superiority from lab to clinic—and observing which delivery methods correlate with improved patient outcomes in early trials—this framework supports rational pharmacological development of propolis derivatives for multimodal CKM and periodontal therapy.

Taken together, the reverse translational research paradigm situates propolis as a biologically coherent agent whose clinical benefits map directly onto validated molecular pathways. This approach provides a structured strategy to bridge metabolic disease, renal fibrosis, systemic inflammation, and dysbiotic periodontal ecosystems, positioning propolis as a candidate for future translational and precision-medicine programs.

8 Therapeutic Potential and Future Directions

Propolis represents a promising therapeutic candidate across cardio-kidney-metabolic (CKM) disorders and periodontal disease due to its pleiotropic molecular actions, breadth of cellular targets, and consistency across animal and human studies [116]. Several lines of evidence now converge to support its translational potential.

First, propolis acts as a multi-pathway regulator rather than a single-target agent. In CKM disorders, it attenuates adipose inflammation, suppresses oxidative stress, restores insulin signaling, and remodels adipocyte phenotype [67]. In kidney disease, it modulates TGF-β/Smad2/3, JNK, and ERK pathways, reduces uremic toxin retention, and prevents tubulointerstitial fibrosis [19]. In gout and metabolic inflammation, TGP directly inhibits NLRP3 inflammasome activation [117].

Second, the diversity of propolis chemistry suggests that standardization will be essential. TGP, Brazilian green propolis, and poplar-type propolis each contain unique phenolic profiles, including propolins, artepillin C, CAPE, galangin, baccharin, and ursolic acid [118,119]. These constituents show distinct biological actions, indicating the need for molecularly defined preparations in future clinical trials.

Third, nanotechnology markedly enhances bioavailability, overcoming the inherent limitations of propolis solubility and absorption. Propolis-loaded nanoparticles have demonstrated improved antioxidant capacity, hormonal regulation, and tissue penetration in preclinical diabetes models [114]. This approach may allow lower therapeutic doses and more consistent pharmacokinetics. However, the bioavailability and metabolic stability of propolis-derived compounds remain critical limiting factors that require further mechanistic investigation. In addition, variability in chemical composition across different propolis sources remains a major challenge for clinical standardization.

Future research should prioritize elucidation of dose-response relationships, optimization of propolis extraction and purification strategies, and the execution of well-powered randomized controlled trials to establish clinical efficacy and reproducibility [30]. In parallel, multi-omics profiling approaches—including transcriptomics, metabolomics, and microbiome sequencing—will be instrumental in delineating the systemic and tissue-specific effects of propolis across cardio-kidney-metabolic and inflammatory disease contexts [120]. Furthermore, integration of computational modeling and network pharmacology frameworks may facilitate the identification of key molecular nodes underlying its multi-target actions and support the development of precision-guided therapeutic applications.

While the mechanistic frameworks linking propolis to metabolic and inflammatory regulation are robust in preclinical models, these claims—particularly regarding glycemic outcomes and microbiome modulation—require critical appraisal when translated to human clinical trials.

Regarding glycemic outcomes, several randomized controlled trials have reported that adjunctive propolis supplementation significantly reduces fasting plasma glucose and HbA1c in patients with type 2 diabetes and chronic periodontitis [87,88,94]. However, these findings must be interpreted with caution. The existing human trials are frequently limited by small sample sizes, short intervention periods (typically 8 to 24 weeks), and significant heterogeneity in patients' baseline metabolic morbidities. More critically, the lack of universal standardization in propolis extraction methods leads to highly variable concentrations of bioactive polyphenols across different studies, which may explain the inconsistent glycemic and lipidemic outcomes observed in some cohorts.

Similarly, claims regarding microbiome modulation require careful qualification. Preclinical studies show that propolis beneficially reshapes the gut microbiome by reducing endotoxin-producing bacteria and increasing short-chain fatty acid-producing genera [89]. However, these findings have not yet been fully validated in human trials. Current clinical trials lack the large-scale, long-term metagenomic sequencing required to definitively confirm whether standardized propolis extracts can sustainably remodel the dysbiotic human gut or oral microbiome in CKM and periodontal patients. Therefore, while propolis presents immense therapeutic promise, future well-powered, double-blind clinical trials utilizing chemically defined propolis chemotypes (e.g., standardized CAPE or propolin content) are imperative to validate its long-term metabolic and microbiome-modulating efficacy. Moreover, standardized cell-based assays and mechanistic validation across different tissue-specific models will be essential to confirm the reproducibility and translational relevance of these findings.

9 Conclusion

Propolis has evolved from a traditional natural remedy into a scientifically validated bioactive agent with broad applicability to cardio-kidney-metabolic syndrome and periodontal disease. Across diverse experimental systems, propolis consistently modulates oxidative stress, inflammation, microbial virulence, metabolic signaling, and tissue remodeling. Its constituents—especially the prenylated flavonoids of TGP—target key nodes in pathological networks, including NF-κB, TGF-β/Smad, JNK, ERK, NLRP3, and mitochondrial redox pathways. These actions converge on improved metabolic homeostasis, reduced fibrosis, enhanced immune balance, and suppression of pathogenic microorganisms such as *P. gingivalis*.

The emerging field of reverse translational research positions propolis as a model natural compound: clinically relevant observations (e.g., improved periodontal healing and glycemic control) stimulate mechanistic exploration in animal and *in vitro* studies, which in turn guide refined therapeutic strategies. This bidirectional framework accelerates the path from natural product to targeted intervention.

Despite robust preclinical evidence, critical gaps remain—including standardization of preparations, bioavailability challenges, and the need for large-scale clinical studies. Addressing these limitations will determine whether propolis can transition from complementary therapy to formally approved adjunct in CKM and periodontal care. Nevertheless, the accumulated data provide compelling justification for continued investigation, and propolis stands out as one of the most promising natural multi-target agents for chronic inflammatory and metabolic diseases.

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