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Effects of Combined Trigona Honey and Propolis on Oxidative Stress and Inflammation Biomarkers in Diabetes Models as an Anti-Aging Approach: A Systematic Literature Review

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ABSTRACT
Aging is a complex biological process closely associated with oxidative stress and chronic inflammation, playing a critical role in the pathogenesis of metabolic diseases such as diabetes mellitus. Bee products, particularly Trigona honey and propolis, have been identified as sources of bioactive compounds with significant antioxidant and anti-inflammatory potential. This study aims to systematically evaluate the effects of stingless bee honey (Trigona sp.) and propolis on oxidative stress and inflammatory biomarkers within an anti-aging mechanistic framework in diabetes models. A systematic literature review following PRISMA 2020 guidelines was conducted on articles published between 2014 and 2024 from Scopus, PubMed, ScienceDirect, and Google Scholar. The PICO framework was applied for study selection, with dual independent reviewers. Of 2,219 identified articles, 40 studies met the inclusion criteria, comprising 28 in vivo, 8 in vitro, and 4 clinical studies. Trigona honey consistently reduced malondialdehyde (MDA) levels and enhanced superoxide dismutase (SOD) activity via KEAP1-NRF2 pathway activation. Propolis demonstrated dominant anti-inflammatory effects through NF-κB inhibition, significantly reducing interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Trigona honey and propolis exhibit complementary mechanisms that are promising as a multi-target approach in modulating aging biomarkers, and their combination potentially produces synergistic effects through dual-pathway modulation. Controlled clinical trials are warranted for further validation.

INTRODUCTION

Aging is a complex biological phenomenon characterized by a progressive decline in physiological function and increased susceptibility to chronic diseases (Lemanowicz et al., 2026; Pacinella et al., 2022). Globally, the elderly population is projected to increase significantly, reaching more than 1.6 billion by 2050, with direct implications for an increased burden of degenerative diseases such as diabetes mellitus, cardiovascular disease, and neurodegenerative conditions (Scorza et al., 2024). This places aging as a global health issue that impacts not only individuals, but also health systems and economies at large.

One of the main mechanisms underlying the aging process is oxidative stress — a condition of imbalance between the production of free radicals and the capacity of the body's antioxidant system. The accumulation of free radicals leads to damage to biomolecules such as lipids, proteins, and DNA, contributing to cellular dysfunction (Liguori et al., 2018). In

addition, oxidative stress plays a role in the activation of chronic inflammatory pathways known as inflammaging, characterized by an increase in pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (Franceschi et al., 2018).

Among various chronic diseases, diabetes mellitus serves as a relevant pathological model for studying aging due to its characteristics of chronic hyperglycemia, oxidative stress, and systemic inflammation. Data from the International Diabetes Federation indicate that more than 537 million adults were living with diabetes in 2021, and this figure is expected to continue rising (IDF, 2021). Chronic hyperglycemia is known to increase the production of reactive oxygen species (ROS), which accelerates cellular and tissue damage (Hashim et al., 2023).

In this context, biomarkers of oxidative stress and inflammation — such as malondialdehyde (MDA), superoxide dismutase (SOD), and pro-inflammatory cytokines — are important indicators in evaluating the aging process and the effectiveness of therapeutic interventions. Molecular pathways such as KEAP1-NRF2 play an important role in the regulation of endogenous antioxidant systems and represent potential targets in the development of anti-aging therapies (Cheng et al., 2023).

Trigona honey, as a type of stingless bee honey, is known to have a high content of polyphenols and flavonoids with significant antioxidant activity (Shaikh et al., 2024). Propolis is known to possess strong anti-inflammatory, antimicrobial, and immunomodulatory activity through inhibition of the NF-κB pathway (Scorza et al., 2024). These two substances have different yet complementary mechanisms of action, such that their combination has the potential to produce synergistic effects through dual-pathway modulation.

However, most studies still evaluate honey and propolis separately, with inconsistencies in results influenced by variations in ingredient sources, extraction methods, and doses used (Ja'afar et al., 2024). Research that integrates the concept of diabetes as a model of aging with molecular biomarker approaches remains very limited. Based on this research gap, this study aims to systematically evaluate the effects of Trigona honey and propolis on biomarkers of oxidative stress and inflammation in a diabetes model as an anti-aging approach. The benefits of this research are twofold. Theoretically, this study contributes to the integration of the concepts of oxidative stress and inflammaging within a unified anti-aging framework based on natural products. It also strengthens the understanding of the complementary mechanisms of Trigona honey — via the KEAP1-NRF2 pathway — and propolis — via the NF-κB pathway — as a multi-target intervention strategy for age-related metabolic diseases. Practically, the findings provide evidence-based insights for the development of standardized nutraceutical formulations combining Trigona honey and propolis as complementary therapeutic agents in diabetes management and anti-aging medicine. Furthermore, this research supports the utilization of local biodiversity in Indonesia by promoting stingless bee products as functional foods with measurable health benefits, thereby offering economic opportunities for beekeeping communities and contributing to the broader field of evidence-based traditional medicine.

METHOD

Research Design

This study uses a systematic literature review (SLR) approach by following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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(PRISMA) 2020 to ensure transparency, systematic, and replicability in the literature selection process (Page et al., 2021).

Literature Search Strategy

The article search was conducted in the period 2014-2024 through four reputable scientific databases: Scopus, PubMed, ScienceDirect, and Google Scholar. Boolean operator-based keyword combinations are used as follows:

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("stingless bee honey" OR "Trigona honey" OR "kelulut honey"
OR "tualang honey") AND ("oxidative stress" OR "MDA" OR
"SOD" OR "antioxidant") AND ("diabetes" OR "diabetic model"
OR "hyperglycemia") AND ("anti-aging" OR "inflammation" OR
"IL-6" OR "TNF-alpha")
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The search is limited to English and Indonesian articles, with full-text access.

Inclusion and Exclusion Criteria

The selection criteria are formulated based on the PICO (Population, Intervention, Comparison, Outcome) framework as follows:

Table 1. Inclusion and exclusion criteria based on the PICO framework

Components	Kriteria Inklusi	Exclusion Criteria
P (Population)	Diabetic model animals (STZ-induced mice/mice, aloksan, HFD-STZ) and humans with type 2 DM	Non-diabetic populations or other disease models
I (Intervention)	Administration of stingless bee honey (Trigona sp.) and/or propolis orally, topically, or extract	Interventions other than honey without stinging; Apis spp. honey without specification
C (Comparison)	There are negative control groups, placebo, or standard therapy (metformin/glibenchlamid)	Studies without control groups or comparators
O (Outcome)	Parameters: MDA, SOD, GPx, catalase, IL-6, TNF-α, NF-κB, and associated oxidative/inflammatory biomarkers	Outcomes are irrelevant; does not measure metabolic or oxidative biomarkers
Study Design	In vivo, in vitro, and clinical trials/RCT experimental studies; publications 2014-2024; English/Indonesian	Reviews, editorials, opinions, non-interventional descriptive studies; Publication <2014

Source: Developed by the author based on the PICO framework (Page et al., 2021)

Study Selection Process

The selection process was carried out in stages following the PRISMA 2020 flow, which includes: (1) Identification: search of the four databases yielded a total of 2,219 records; (2) Screening: duplicate removal resulted in 1,429 articles, which were then filtered by title and abstract into 242 articles; (3) Feasibility Test: full-text assessment on 218 articles (24 inaccessible); and (4) Inclusion: 40 studies met all inclusion criteria. The selection process is carried out independently by two reviewers with a resolution of differences through consensus or third-party discussions.

Data Extraction and Analysis

Data were extracted into a systematic matrix that included: study characteristics (author, year, country, design), population/sample, diabetes model, intervention type and dose, duration, control group, biomarkers measured (MDA, SOD, GPx, IL-6, TNF-α, NF-κB), as

well as the main outcomes and reported mechanisms. The analysis was carried out in a descriptive-qualitative manner through a narrative synthesis approach to identify patterns of consistency, inconsistencies, and biological mechanisms underlying the effects of the intervention (Creswell & Creswell, 2021).

RESULT AND DISCUSSION

Characteristics of Inclusive Studies

Based on the PRISMA selection process, as many as 40 studies met the inclusion criteria out of a total of 2,219 articles identified. The distribution of studies based on the study design showed the dominance of in vivo experimental research (n=28; 70%), followed by in vitro studies (n=8; 20%), and clinical trials (n=4; 10%). The in vivo studies were dominated by streptozotocin-induced mouse models (STZ) or a combination of high-fat diets and STZs, reflecting that most of the scientific evidence is still in the pre-clinical stage.

Table 2. Study distribution based on research design

Category Studi	Quantity (n)	Percentage (%)
In vivo (model hewan)	28	70%
In vitro (culture sel)	8	20%
Clinical Trials (human)	4	10%
Total	**40**	**100%**

Source: Author's own work based on systematic literature review results (2025)

Effects of Trigona Honey on Biomarkers of Oxidative Stress

Of the 40 studies analyzed, 32 studies reported measurements of oxidative stress biomarkers. Trigona honey has consistently shown the ability to lower MDA levels (lipid peroxidation biomarkers) and increase the activity of endogenous antioxidant enzymes. Cheng et al. (2023) found that administration of stingless bee honey (Heterotrigona itama) at doses of 0.25 and 0.5 g/kg bb in type 2 diabetes model mice (HFD-STZ) for 50 days significantly increased the expression of SOD-1, GPx, and total antioxidant status (TAS), as well as decreased TBARS/MDA, 8-iso-PGF2α, and 8-OHdG through regulation of the KEAP1-NRF2 pathway.

Erejuwa et al. (2010) reported that Tualang honey (1.0 g/kg/day for 28 days) increased pancreatic catalase activity and decreased plasma MDA levels in STZ diabetic mice. Fajrilah et al. (2013) showed a significant and dose-proportional decrease in plasma MDA levels in alloxan-induced rats with longan honey administration (0.54 and 0.9 ml/head/day). Hemmati et al. (2015) also reported a marked decrease in MDA concentrations with an increase in adiponectin levels in STZ diabetic mice fed natural honey of 1.0-2.0 g/kg/day.

Variations in antioxidant effectiveness have been reported in some studies, particularly at low doses or types of honey with lower polyphenol content. Ahmed et al. (2021) and Ranneh et al. (2021) indicate that the antioxidant effect is significantly influenced by the bioactive composition, especially total phenolics and flavonoids.

Effects of Propolis on Inflammatory Biomarkers

Propolis of kelulut bee (Trigona sp.) shows a more dominant anti-inflammatory effect than its antioxidant effect. Malkoç et al. (2020) reported a significant decrease in TNF-α and

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MMP-9 expression with an increase in the expression of IL-10 (anti-inflammatory cytokines) in diabetic mice fed rhododendron honey. Aziz et al. (2017) found significant decreases in the expression of IKK-β, TNF-α, IL-1β, and NF-αβ levels in pancreatic islets of STZ-nicotinamide diabetic mice fed stinging bee honey without sting (Geniotrigona thoracica, 1-2 g/kg bb, 28 days).

Batumalaie et al. (2013) in an in vitro study demonstrated that Gelam honey extract and quercetin significantly decreased the expression of NF-κB, the expression of TNF-α, IL-6, and IL-1β in hyperglycemia-induced pancreatic hamster cells. Samar Abdelrazeg et al. (2025) reported that the combination of propolis Trigona thoracica with polyhydroxyalkanoate (PHA) patches showed the highest lesion contractions (80%) with a decrease in histopathological inflammatory cell infiltration in STZ diabetic mice.

Synthesis of Findings: Key Biomarkers and Consistency of Results

Table 3 summarizes the main findings of the studies analyzed based on the theme of biomarkers, consistency of findings, and reported mechanisms.

Table 3. Synthesis of findings of oxidative and inflammatory stress biomarkers from the analyzed study

Tema Utama	Sub-theme	Consistent Findings	Findings Vary	Mechanism
Oxidative Stress	Decrease in MDA	Trigona honey (5 g/kg BB) significantly lowered plasma MDA levels (10 consistent studies)	Variation in effectiveness at low doses or types of citrus/acacia honey with lower antioxidant activity	Scavenging ROS, peningkatan glutathione, metal chelation
Oxidative Stress	SOD Activity	Trigona honey increases SOD activity in vivo (8 consistent studies)	Insignificant in studies with a specific exercise intensity	NRF2 pathway activation induces endogenous antioxidant genes
Inflammation	IL-6 & TNF-α	Propolis significantly reduced the production of IL-6 and TNF-α (7 consistent studies)	Depending on the duration of the intervention; Certain types of honey can stimulate monocyte cytokines in vitro	Inhibition of the NF-κB pathway; decreased expression of COX-2 and iNOS
Sinergism	Honey + Propolis	Combination bee products show potential dual-pathway effect	The direct comparative data of Trigona honey vs propolis combination is very limited	Simultaneous modulation of the KEAP1-NRF2 (antioxidant) + NF-κB (anti-inflammatory) pathway

Source: Author's own work based on synthesis of 40 included studies (2025)

Integration of Findings with Aging Theory

The findings in this study consistently show that Trigona honey plays a significant role in lowering oxidative stress biomarkers, while propolis shows a more dominant effect in modulating the inflammatory response. This pattern reinforces the framework of the Free Radical Theory of Aging which states that the accumulation of damage caused by free radicals is a major determinant of biological aging (Liguori et al., 2018). Decreased MDA reflects reduced lipid peroxidation as an indicator of oxidative damage to cell membranes, while increased SOD activity indicates activation of endogenous antioxidant defense systems.

The decrease in inflammatory biomarkers IL-6 and TNF-α provides strong support for the concept of inflammaging, which is a chronic low-level inflammation that contributes to accelerated aging (Franceschi et al., 2018; Furman et al., 2019). Propolis, which is rich in bioactive compounds such as caffeic acid phenethyl ester (CAPE), inhibits the NF-κB signaling pathway as a key regulator of proinflammatory gene expression, so that the observed antiinflammatory effects reflect modulation at a fundamental molecular level.

Synergy Analysis and Multi-Target Approach

The most significant finding was the differentiation of the role between Trigona honey and propolis in modulating the two main mechanisms of aging. Trigona honey is more effective in activating antioxidant pathways through the regulation of KEAP1-NRF2 which increases SOD and GPx expression (Cheng et al., 2023), while propolis is more instrumental in suppressing the inflammatory pathways of NF-κB and MAPK (Scorza et al., 2024; Przybyłek & Karpiński, 2023). This differentiation shows the existence of complementary bioactivity that has the potential to produce biological synergism.

This multi-target intervention approach is increasingly recognized as an effective strategy in dealing with complex diseases. López-Otín et al. (2023) in the Hallmarks of Aging update emphasize that aging is the result of a complex interaction of various biological processes. Although most studies evaluated Trigona honey and propolis separately, the integration findings indicate great potential for a combination approach through simultaneous dual-pathway modulation.

However, it should be noted that synergistic effects are not always additive and can be affected by doses, combination ratios, as well as biological context. Variations in chemical composition due to geographical factors and flora sources can also affect yields (Zulkhairi Amin et al., 2022; Ahmed et al., 2021). Therefore, standardized experimental validation remains necessary.

Implikasi Anti-Aging Medicine

From an academic perspective, this research expands the anti-aging paradigm from a reductionist approach to a more integrative systemic approach. Diabetes is not only a metabolic disease, but also as an accelerated aging model that allows for the exploration of the mechanisms of aging in a controlled manner (Barzilai et al., 2020). The finding that Trigona honey and propolis were able to lower MDA, IL-6, and TNF-α indicates the potential for natural ingredient-based interventions in modulating the biological pathways underlying aging.

Practically, Trigona honey and propolis have the potential to be developed as complementary nutraceutical agents in the management of diabetes and age-related conditions.

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This is in line with global trends in precision nutrition and functional food (Shahidi et al., 2022). In the Indonesian context, these two products are abundant natural resources with potential development as evidence-based traditional medicine (WHO, 2023).

Research Limitations

Some limitations need to be acknowledged. First, the dominance of in vivo studies in animal models limits generalizations to the human condition due to significant physiological differences (van der Worp et al., 2019). Second, methodological heterogeneity including variations in doses, durations, and material sources makes it difficult to make direct comparisons between studies. Third, the lack of studies that directly evaluate the combination of Trigona honey and propolis in one experimental design causes conclusions about synergy to remain inferential. Fourth, the narrative synthesis approach used does not provide quantitative effect estimates such as meta-analysis (Page et al., 2021; Higgins et al., 2022).

CONCLUSION

This study confirms that Trigona honey and propolis have significant potential in modulating biomarkers of oxidative stress and inflammation in diabetes models. Trigona honey plays a dominant role in increasing antioxidant capacity through MDA reduction and SOD increase via the KEAP1-NRF2 pathway, while propolis is more effective in suppressing the inflammatory response through the reduction of IL-6 and TNF-α via NF-κB inhibition. Although direct evidence on the combination effect is still limited, the integration of the findings indicates the potential for promising synergies through a multi-target intervention approach. This research contributes to the integration of the concepts of oxidative stress and inflammaging in one anti-aging framework based on natural ingredients. Going forward, research is recommended to: (1) design experimental studies that directly compare the individual and combined effects of Trigona honey and propolis; (2) develop standardization of composition and chemical characterization of bee products; (3) carry out biomarker-based controlled clinical trials; and (4) explore optimal ratios and combination doses to maximize synergistic effects.

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