Jurnal Ilmiah Ibnu Sina, 11(1), Maret 2026, 135-152
p-ISSN: 2502-647X; e-ISSN: 2503-1902

IMMUNOSTIMULANT EFFECTS OF PROPOLIS: A study of cytokine production

Mutiara Sani Demira Putri [1], Hannie Fitriani [2*], Yandi Syukri[1], Arba Pramundita Ramadani[1]
[1]Master of Pharmacy Program, Islamic University of Indonesia, Yogyakarta, Indonesia
[2]Department of Pharmacy, Islamic University of Indonesia, Yogyakarta, Indonesia

*Email: hanniefitriani.uii.ac.id

Artikel diterima: 2026-01-13; Disetujui: 2026-03-26
DOI: https://doi.org/10.36387/jiis.2926

ABSTRAK
Propolis adalah produk alami yang berasal dari resin lebah dan telah lama digunakan dalam pengobatan tradisional karena kandungan bioaktifnya terutama flavonoid. Penelitian ini bertujuan untuk menganalisis efek imunostimulan propolis terhadap ekspresi sitokin berdasarkan berbagai studi ilmiah. Metode yang digunakan adalah *narrative review* dengan mengumpulkan literatur dari *database* PubMed, *ScienceDirect*, dan Google Scholar. Sebanyak 48 artikel teridentifikasi pada tahap awal, kemudian diseleksi menjadi 15 artikel yang memenuhi kriteria inklusi untuk dikaji lebih lanjut. Hasil kajian menunjukkan bahwa propolis memiliki aktivitas imunomodulator melalui berbagai mekanisme, antara lain penghambatan jalur NF-κB, penurunan ekspresi COX-2, serta penghambatan produksi *nitric oxide* (NO). Propolis juga terkonfirmasi meningkatkan aktivasi makrofag, stimulasi fagositosis, serta meningkatkan ekspresi sitokin proinflamasi seperti IL-1β, IL-6, IL-2, dan IFN-γ. Namun, pada kondisi inflamasi berlebih, propolis dapat menurunkan ekspresi sitokin proinflamasi yang menunjukkan sifat imunoregulator yang adaptif. Kesimpulan, propolis berpotensi sebagai imunostimulan alami yang bekerja secara relevan sesuai status imunologis *host* dan berpotensi dikembangkan sebagai terapi herbal di masa depan.

Kata kunci: Imunomodulator, Imunostimulan, Inflamasi, Propolis, Sistem Imun, Sitokin

ABSTRACT
Propolis is a natural substance derived from bee resin and has long been used in traditional medicine because of its diverse bioactive compounds, especially flavonoids. This study aims to assess the immunostimulant effects of propolis on cytokine expression based on existing scientific research. A narrative review was conducted by collecting literature from PubMed, ScienceDirect, and Google Scholar. Initially, 48 articles were identified, and 15 articles that met the inclusion criteria were further analyzed. The results show that propolis has immunomodulatory activity through multiple mechanisms, including inhibiting the NF-κB pathway, reducing COX-2 expression, and suppressing nitric oxide (NO) production. Propolis also boosts macrophage activation, promotes phagocytosis, and increases the expression

of pro-inflammatory cytokines such as IL-1β, IL-6, IL-2, and IFN-γ. However, under excessive inflammatory conditions, propolis decreases pro-inflammatory cytokine expression, indicating an adaptive immunoregulatory response. In conclusion, propolis has strong potential as a natural immunostimulant that works contextually according to the host's immunological status and may be developed as a future herbal therapeutic agent.

Keywords: *Cytokines, Immune System, Immunomodulatory, Immunostimulant, Inflammation, Propolis*

INTRODUCTION

Beekeeping is flourishing in various regions of Indonesia, from Sabang to Merauke. The products of this development are widely utilized, including for human health. Bees contain various substances, including honey, pollen, royal jelly, propolis, beeswax, and so on (Rosyidi et al., 2018). Propolis contains various compounds, including flavonoids, phenolic acids and their esters, terpenoids, steroids, amino acids, and its main component, Caffeic Acid Phenethyl Ester (CAPE), which can be used as an immunostimulant and help regulate the body's immune system (Listiani & Susilawati, 2019; Fitria et al., 2021).

Immunomodulators, in regulating the body's immune system, act as immunostimulants and immunosuppressants, protecting the body from pathogen attack by enhancing the immune system or reducing an overactive immune system through stimulation of innate (natural) and adaptive defenses (Megawati & Wijayakesuma, 2022). Immunostimulants are biologically active substances derived from synthetic or natural sources with varying mechanisms of action to enhance the body's immune system, particularly in fighting infectious agents (Wijaya, T., & Yunita, 2023). In general, their mechanism involves increasing cell proliferation and targeting target cells such as macrophages, granulocytes, T lymphocytes, and B lymphocytes. Cytokines, which have various types, play an important role in the body's immune response: pro-inflammatory and anti-inflammatory cytokines. Pro-inflammatory cytokines include Tumor Necrosis Factor-α (TNF-α), interleukin 1 (IL-1), IL-6, IL-11, and IL-8, while anti-inflammatory cytokines include IL-4, IL-10, and IL-13 (Cavalli et al., 2021). Immunostimulants are widely used for diseases that can weaken the immune system, such as viral infections (influenza, HIV/AIDS, hepatitis B and C, COVID-19, and herpes simplex) and bacterial infections (diarrhea, tuberculosis, upper respiratory tract infections, urinary tract infections) (Nazir, 2020). These immunostimulant drugs are taken as supportive therapy, recommended in conjunction with antibiotics or antivirals, to restore the immune system or the body's defenses (Gaziano et al., 2021).

Propolis's immunostimulant mechanism includes antioxidant and anti-inflammatory properties because it can inhibit the activity of pro-inflammatory cells (macrophages and T cells) and suppress COX (cyclooxygenase) activity. CAPE can prevent the production and release of cytokines by inhibiting Nuclear Factor-Kappa B (NF- κB), reducing COX-2 expression, and inhibiting nitric oxide (NO). Propolis acts as an antioxidant by altering the transcription of Signal Transducer and Activator of Transcription 1 (STAT-1), thereby neutralizing free radicals. Propolis scavenges ROS, including hydrogen peroxide, superoxide, hydroxyl ions, and others. Propolis inhibits and downregulates cytokines (IL-1, IL-6, IFN, and TNF) and reduces the migration of immune cells such as macrophages and neutrophils (Depari & Malisie, 2025; Oka et al., 2023; Ulandari et al., 2021).

In several studies, propolis has been shown to modulate the activation of the immune system through increased macrophage activation, stimulation of phagocytosis, and regulation of cytokine expression such as IL-2, IFN-γ, and TNF-α. Conversely, in pathological inflammatory conditions, propolis also exhibits immunoprotective effects by suppressing pro-inflammatory cytokines such as IL-1β and IL-6 (Herawati et al., 2015; Trinaya et al., 2019). These findings indicate that propolis has dual roles as both an immunostimulant and an immunomodulator depending on the host’s immune condition.

However, most of these studies primarily focus on general immunomodulatory effects (Megawati & Wijayakesuma, 2022; Depari & Malisie, 2025) and do not specifically analyze cytokine expression as a central indicator of immunostimulant activity. In addition, variations in findings across different experimental models have not been comprehensively synthesized (Mulki & Pratama, 2022).

Therefore, this review aims to evaluate and synthesize existing scientific evidence regarding the immunostimulant effects of propolis on cytokine expression in various experimental models.

RESEARCH METHODS

This study employed a *narrative review* approach to evaluate and synthesize research findings related to the immunostimulant effects of propolis on cytokine expression. This approach was selected because it allows the integration of various study designs, including *in vitro*, *in vivo*, and *in silico* studies, thereby providing a comprehensive understanding of the topic. The literature was collected from several scientific databases, namely PubMed, ScienceDirect, and Google Scholar. The search strategy used a combination of keywords such as "propolis", "immunomodulator", "immunostimulant", "cytokines", "inflammation", and "NF-κB", combined with Boolean operators (AND, OR) to obtain relevant results.

The included articles were limited to publications from the last 10 years (2015–2025) to ensure the relevance and novelty of the data. The selected literature consisted of articles published in both English and Indonesian. The inclusion criteria were original research articles that evaluated the effects of propolis on cytokine expression, used *in vitro*, *in vivo*, or *in silico* models, and were available in full-text form. The exclusion criteria included review articles, systematic reviews, or meta-analyses, studies not focused on cytokine expression, and articles with incomplete or inaccessible data.

The literature selection process began with the identification of 48 articles. Duplicate records were then removed manually based on similarities in title, authors, and publication year. Screening based on titles and abstracts resulted in 21 relevant articles. Following full-text evaluation, 15 articles met all inclusion criteria and were included in the final analysis. Data from the selected studies were systematically extracted, including the type of propolis preparation, experimental model, cytokines analyzed, methods used, and key findings. The data were then presented in tabular form and analyzed descriptively to identify patterns in the relationship between propolis use and cytokine expression.

RESULT AND DISCUSSION

Characteristics, Content, and Activity of Propolis

Table 1. Immunostimulant Activity of Various Propolis Preparations Based on produced Cytokines

NO	Propolis Preparation	Subjects & Test Models	Cytokines Produced	Method	Key Results	References
1	Propolis extract (2,5–5 mg/kg)	BALB/c mice	IFN-γ, H_2O_2, NO	in vitro	Increased IFN-γ expression and NO and H_2O_2 production	(Aden & Rifa, 2014)

2	Propolis + $CdCl_2$	Wistar rats	IL-1β, IL-6	ELISA	Significant decrease in IL-1β and IL-6 due to Cd toxicity	(Ayhan et al., 2025)
3	Ethanol extract of propolis (EEP)	Rabbits (BHV-1 model)	IL-2, IFN-γ, TNF-α, IgG	ELISA	Significant increase in pro-inflammatory cytokines and IgG	(Gamil Zeedan et al., 2019)
4	Liquid propolis Trigona spp.	Sprague-Dawley rats (bacterial infection model)	IL-2, NO, IgG	in vivo	The 0.48% dose was most effective in increasing IL-2, NO, and IgG	(Kalsum, 2017)
5	Ethanol extract of propolis (EEP)	Mice	IFN-γ, IL-12, IL-10	in vivo	Increased IFN-γ and IL-12 and Decreased IL-10	(Novryantoro et al., 2024)
6	Ethanol extract of propolis (EEP)	Mice	IL-2, IL-17, IL-10	in vivo	EEP increased the number of $CD4^+$, $CD8^+$, and $CD11b^+$ cells, but not statistically significant ($p > 0.05$), EEP doses of 2 mg and 4 mg decreased the expression of IL-2 and IL-17 in $CD4^+$ cells	(Saad, 2025)
7	Ethanol extract of propolis (EEP)	Mice	IL-3, IL-4, IL-6, IL-13	in vitro and in vivo	Propolis reduces the production of IL-4, IL-6, and IL-13 in basophils activated by IgE/antigen	(Kashiwakura et al., 2021)
8	Ethanol extract of propolis (EEP) from *Yucamiel*, Yucatán, Meksiko	Mice	IL-1β, IL-10, IL-4, TNF-α	in vitro and in vivo	Significant decrease in pro-inflammatory cytokines: IL-1β, IL-6, TNF-α, Increase in anti-inflammatory cytokines: IL-10, IL-4	(Xool-Tamayo et al., 2020)

9	Ethanol extract of propolis (EEP)	Dendritic cell (DCs), and T lymphocytes	TNF-α, IL-6, IL-10, IL-1β, IFN-γ, TGF-β	in vitro	Propolis exhibits immunomodulatory effects by inhibiting pro-inflammatory cytokines and promoting regulatory profiles, particularly T lymphocyte differentiation towards Tregs.	(Santiago et al., 2023)
10	Ethanol extract of propolis flavonoids	Landrace–Yorkshire hybrid sows and PK-15 cells	IL-2, IFN-γ, IL-4, IgM, IgG	in vitro and in vivo	Significant increase in serum levels of IL-2, IL-4, and IFN-γ, indicating an increase in humoral and cellular immune responses	(Ma et al., 2022)
11	Indonesian propolis extract	Rats	TNF-α, IL-6, IFN-γ	in vivo	Decreased TNF-α and IL-6, and increased IFN-γ	(Dewi et al., 2022)
12	Sumatra propolis extract	Rats	IL-6	in vivo	Decreased IL-6	(Megantara et al., 2024)
13	Ethanol extract of Indonesian propolis	Molecular Docking model	IL-6, TNF-α, IL-1β	in silico and in vitro	Propolis in this study has the potential to reduce the expression of IL-6, IL-1β, and TNF-α	(Pratami et al., 2021)
14	3 types of Brazilian green propolis extract formulations (different solvents: ethanol, ethyl acetate, and water)	Murine peritoneal macrophages	IL-1β, IL-6, TNF-α, IL-10	in vitro	All three formulations increased TNF-α, IL-1β, and IL-6 to varying degrees; the ethanol formulation was the most active, and also increased IL-10 as a counterbalance	(Zamarrenho et al., 2023)

15	Brazilian Green Propolis	BALB/c mice	IFN-γ, TNF-α, IL-10, IL-12, IL-4	in vitro	Increased production of pro-inflammatory cytokines that aid parasite elimination, such as IFN-γ and IL-12. Decreased production of anti-inflammatory cytokines such as IL-10, which tend to inhibit an effective immune response	(Rebouças-Silva et al., 2023)

Propolis is a resinous substance collected by bees from tree sap to build and maintain their hives (Fitria & Marwayana, 2015). The resin in propolis acts as a bee glue, derived from plant secretions, mixed with enzymes and saliva collected by the bees (Anjum et al., 2019). Propolis has a distinctive herbal aroma and comes in a variety of colors, including yellow, green, brown, and red. Propolis is lipophilic; when stored in cold temperatures, it becomes hard, brittle, and easily broken, but when stored in warm temperatures, it becomes soft, flexible, and very sticky. Therefore, propolis can be stored at 4°C to prevent spoilage and preserve its primary constituents or secondary metabolites (Ananta et al., 2024; Marcucci, 1995).

Propolis has antimicrobial, antiviral, antifungal, anticancer, anti-inflammatory, immunomodulatory, and wound healing activities, all of which contribute to human health (Lutpiatina, 2015). Propolis consists of 50% resin, 30% wax, 10% essential oils, 5% pollen, and 5% various organic compounds. The chemical compounds contained in propolis are flavonoids, phenolic acid derivatives, cinnamic acid derivatives, terpenes/terpenoids, tannins, and alkaloids. The main components of propolis that play a role in pharmacological activity are pinocembrin, pinobanksin, Caffeic Acid Phenetyl Ester (CAPE), artepillin C, cinnamic acid, p-coumaric acid, caffeic acid, ferulic acid, isoferulic acid, chrysin, galangin, kaempferol, and quercetin (Anjum et al., 2019; Di Pierro et al., 2016; Fitriani et al., 2021; Iqbal et al., 2019). Propolis has polar properties, so the choice of solvent for the extraction process must be adjusted so that the compounds contained in propolis provide maximum results. From the results of the research that has been done, the solvents used are water and 70% ethanol which are polar, then it was shown that 70% ethanol has an extraction activity level ranging from 10.6% to 55%. Meanwhile, solvents that use water are easy to obtain and can extract polar compounds. However, this solvent has the disadvantage of acting as a growth medium for microbes (Ananta et al., 2024).

Flavonoids and CAPE are compounds indicated as immunomodulatory agents. Studies have shown that liquid propolis extract has immunomodulatory effects, enhancing the immune response by increasing the phagocytosis index, NO production, and IgG antibody production in peritoneal macrophages of Sprague Dawley rats (kalsum et al., 2017). Furthermore, another study developed a propolis extract into a nano-formulated preparation, the Self Nano-Emulsifying Drug Delivery System (SNEDDS), as an immunostimulant, affecting the proliferation of lymphocytes, leukocytes, and neutrophils, as evidenced by a significant difference in total cell counts during the study (Fitria et al., 2021). The immunomodulatory mechanism of propolis can be achieved through various mechanisms: inhibiting the activity of pro-inflammatory cells such as macrophages and T cells, suppressing COX enzyme activity, reducing COX-2 expression, and inhibiting nitric oxide (NO) production. CAPE compounds are able to increase anti-inflammatory signals through activation of the PI3K/Akt pathway and suppress the pro-inflammatory JNK/NF-κB pathway in a type 2 diabetes model, demonstrating a broad immunoregulatory spectrum (Nie et al., 2017). In addition, propolis also acts as an antioxidant by altering the transcription of STAT-1 and scavenging free radicals such as hydrogen peroxide, superperoxide, and hydroxyl ions. These effects contribute to the reduction of cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and Tumor Necrosis Factor (TNF) and reduce the migration of immune cells such as macrophages and neutrophils (Aden & Rifa, 2014; Mulki & Pratama, 2022; Toriqoh, 2019).

The Mechanism of the Immune System and the Role of Immunostimulants

All living things, including humans and animals, possess an immune system that protects the body from foreign objects, pathogens, or infections (Marshall et al., 2018). The immune system is divided into two systems: the innate (natural) and the adaptive (Buonacera et al., 2022). The innate immune system is the first line of defense when a pathogen enters the body to attack. This immune system does not rely on specific antigens used by the host to act quickly, but it lacks immunological memory, so it cannot recognize or "remember" the same pathogen if the body is infected with the same pathogen. On the other hand, adaptive immunity differs from innate immunity in that it relies on specific antigens, which can provide a lag time between antigen exposure and maximum response. This immune system possesses immunological memory, allowing the body to respond quickly when infected with the same pathogen (Marshall et al., 2018). The innate and adaptive immune systems work together effectively in the body to maintain balance through their respective roles (Smith, 2014). The innate immune system operates in the initial hours, usually 0-12 hours after infection. Meanwhile, the adaptive immune system works after the first hour of the innate immune phase has finished its work and this adaptive immune system needs 1-2 weeks for host defense during the late phase of infection and during secondary infections because it has to "remember" and fight more effectively against re-stimulation or re-infection involving T and B lymphocytes (Farber et al., 2016).

The innate immune system has a primary function in stimulating the body's immune cells to the site of infection or inflammation very quickly through the production of cytokines and chemokines. Cytokine production occurs when the innate immune system activates defense mechanisms throughout the body, while also activating local cellular responses to infection or injury simultaneously. For example, cytokines can stimulate changes in body temperature regulation that cause fever. Tumor Necrosis Factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) are types of inflammatory cytokines released at the beginning of the bacterial infection response in the body (Nicholson, 2016). The innate immune system has three first lines of defense called barriers consisting of anatomical barriers, humoral barriers, and cellular barriers. Anatomical barriers consist of the skin and mucous membranes, such as the surface of the skin epithelium, normal skin flora, and antimicrobial proteins in tears. The humoral barrier plays a crucial role in the inflammatory process, consisting of complement, coagulation, phagocytes, and antigen-presenting cells (APCs) such as neutrophils and macrophages, natural killer (NK) cells, and lymphokine-activated killer (LAK) cells, which can nonspecifically kill infected and tumor cells. Eosinophils can also kill parasites and stimulate the development of memory B lymphocytes (Buonacera et al., 2022). The adaptive immune system operates when the innate immune system is no longer effective against pathogens and takes over the role of the innate immune system. This immune system works specifically, targeting previously identified pathogens that cause infection, making it slower than the innate immune system (Iwasaki & Medzhitov, 2015; Chi et al., 2024). This immune response is the basis for effective immunization against infectious diseases. T cells involved in the adaptive immune system are activated to proliferate through the action of APCs, while B cells differentiate into plasma cells and produce antibodies (Marshall et al., 2018).

Immunomodulators are compounds that can help improve the body's immune system. Immunomodulators are needed by the body when the immune system is disturbed due to the development of diseases caused by bacterial, viral or fungal infections. Immunomodulators consist of two types, namely immunostimulants that can increase the activity of the immune system and immunosuppressants that can reduce excessive immune system activity (Suhirman et al., 1985; Block & Mead, 2003). Immunomodulators work in various ways, one of which is like several small molecules found in synthetic drugs, namely tofacitinib, baricitinib through the JAK inhibitor pathway, working by inhibiting the Janus kinase enzyme in the JAK-STAT pathway, thereby disrupting the signal transduction of pro-inflammatory cytokines such as IL 6 and IFN γ, an effect that has been shown to be indicated in rheumatoid arthritis through phase III clinical trials on tofacitinib (Kiełbowski et al., 2024). In addition, IMiDs group drugs (thalidomide, lenalidomide, pomalidomide) bind to the cereblon receptor on the E3 ubiquitin ligase which causes the degradation of certain proteins, thus producing immunostimulatory, anti-angiogenic, and anti-proliferative effects, this mechanism has been described in detail in various pre-clinical studies and clinical reviews of multiple myeloma (Chang et al., 2014; Gao et al., 2020; Quach et al., 2010; Li et al., 2010; Yamshon & Ruan, 2019). In propolis content, the compound CAPE has been shown to inhibit the NF-κB and MAPK pathways in LPS-stimulated RAW 264.7 macrophages, thereby reducing the production of pro-inflammatory cytokines such as IL 1β, IL 6, and TNF α (Búfalo et al., 2013).

Immunostimulants contain cytokines that play an important role in the immune response, including pro-inflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α), interleukin 1 (IL-1), IL-6, IL-11, IL-8, and anti-inflammatory cytokines such as IL-4, IL-10, and IL-13. The release of pro-inflammatory cytokines is regulated by nuclear factor-kappa B (NF-κB) and the Mitogen-Activated Protein Kinase (MAPK) pathway (Beyaert et al., 2013). NF-κB plays a role in inducing the expression of the iNOS gene, which is activated after macrophages are activated, allowing iNOS to release nitric oxide (NO) (Aipire et al., 2020). Propolis acts as an immunostimulant through several mechanisms. One of these is the bioactive content of propolis, CAPE, which is known to increase macrophage activation, stimulate phagocytosis, and increase the expression of pro-inflammatory cytokines such as IL-2, IFN-γ, and TNF-α. Under normal immune conditions, increasing cytokine levels is important in strengthening the adaptive immune response, particularly in fighting viral and bacterial infections. Furthermore, propolis can increase the number and activity of CD4+ and CD8+ cells, which also play a role in mediating cellular immune responses (Saad, 2025).

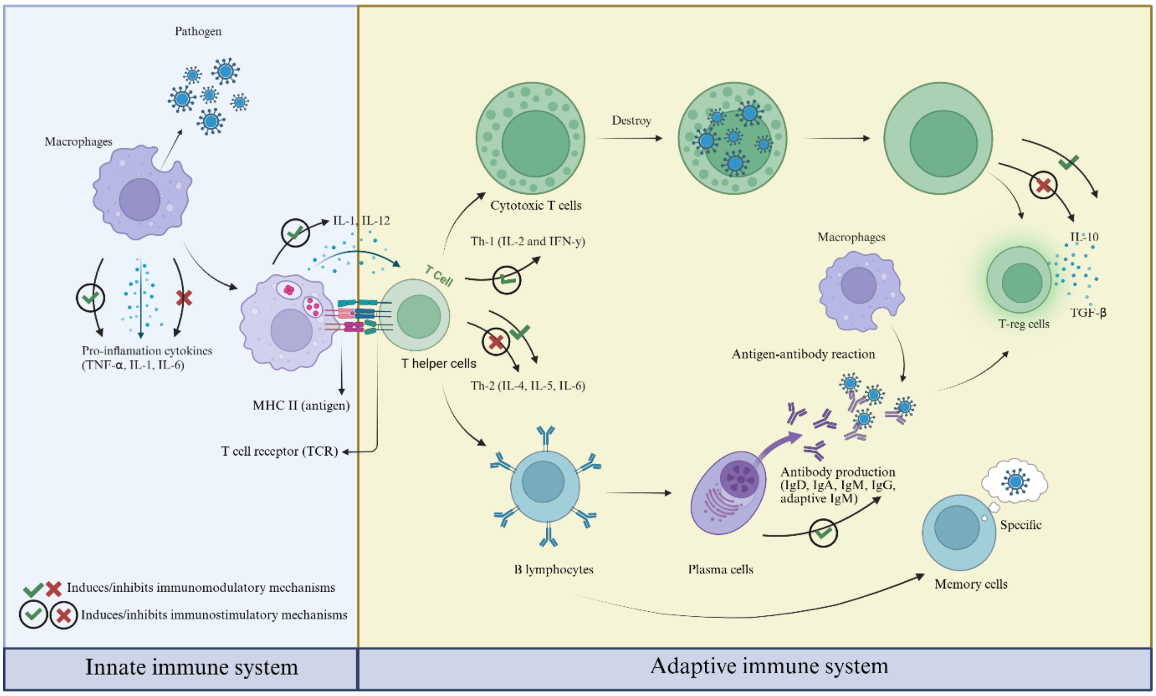

Figure 1. Mechanisms of Innate and Adaptive Immune Response

Propolis Activity on Cytokine Expression

The research reviewed in **Figure 1 and Table 1** shows that propolis can modulate the immune system by increasing macrophage activation, stimulating phagocytosis, and increasing the expression of pro-inflammatory cytokines such as IL-2, IFN-γ, and TNF-α in normal immune conditions. This activation is part of the enhancement of adaptive immune function, which plays a crucial role in fighting both viral and bacterial infections. For example, several studies have shown that administering propolis extract at certain doses can increase the number of CD4 and CD8 cells however, the changes were not statistically significant, and a decrease in IL-2 expression was observed at certain doses (Saad, 2025) whereas in toxic conditions, such as Cd exposure, propolis actually reduces IL-1β and IL-6 (Ayhan et al., 2025). However, in pathological inflammatory conditions, such as severe infections, propolis actually exhibits immunoprotective effects by suppressing the expression of pro-inflammatory cytokines such as IL-1β, IL-17, and IL-6. This was seen in mouse models exposed to cadmium or experiencing bacterial infections. This study reinforces the concept that propolis acts not only as a resident immunostimulant but also as an immunoregulator that works on the basis of host immunology (Gamil Zeedan et al., 2019; Kalsum, 2017).

In vivo studies in mice exposed to $CdCl_2$, for example, showed that propolis significantly reduced the expression of IL-1β and IL-6, which are generally increased under conditions of severe oxidative stress due to heavy metal toxicity. Meanwhile, in *Staphylococcus aureus* or BHV-1 infection models, propolis significantly increased pro-inflammatory cytokines and antibodies, indicating activation of systemic and humoral immune responses. This dual effect is consistent with previous review studies, which report that propolis exhibits context-dependent immunomodulatory activity, enhancing immune responses under infectious conditions while suppressing excessive inflammation under pathological stress (Magnavacca et al., 2022; Mulki & Pratama, 2022; Anjum et al., 2019; Megawati & Wijayakesuma, 2022). Ethanol-based propolis from various countries, such as Mexico, Egypt, and Turkey, showed similar effects. Key bioactive compounds, such as CAPE, quercetin, pinocembrin, and artepilin C, are thought to play a role in immune modulation, such as NF-κB, STAT-1, and MAPK, which are directly related to the expression of cytokine genes. This mechanism also explains propolis's ability to reduce COX-2 expression and NO production while accelerating immune transmission, particularly by increasing the expression of IL-10 and TGF-β as balancers (T-regs) in several test models (Magnavacca et al., 2022; Hasan et al., 2011; Xool-Tamayo et al., 2020). Studies using ethanol extracts of propolis flavonoids in hybrid pigs showed significant increases in serum IL-2, IL-4, and IFN-γ, indicating an enhanced humoral and cellular immune response across species (Ma et al., 2022).

Studies using Sumatran propolis showed a decrease in IL-6 gene expression. This finding suggests differences in bioactive composition based on geographic source (Megantara et al., 2024). Another study compared three formulations of Brazilian green propolis with different solvents (ethanol, ethyl acetate, and water) in peritoneal macrophages. The ethanol formulation demonstrated the highest activity in increasing TNF-α, IL-1β, and IL-6, as well as increasing IL-10 as a T-reg (Zamarrenho et al., 2023). Overall, this study reinforces the concept that propolis works adaptively, adapting to the host's immune state and suppressing overactivity when it is hyperactive. This would therefore be an advantage for propolis compared to other conventional immunostimulant agents.

CONCLUSION

Propolis has been shown to have immunomodulatory effects, particularly immunostimulant effects, which work contextually on cytokine expression and adapt to the host's immunological state. Its potential for development as a herbal-based therapy is promising, although further research is needed to standardize and ensure its safety.

THANK-YOU NOTE

The author gratefully acknowledges all previous researchers and authors whose scholarly works were utilized as references in the preparation of this literature review. Their contributions of ideas, data, and scientific findings greatly enriched the discussion and reinforced the theoretical framework of this study.

REFERENCES

Aden, A. Z., & Rifa, M. (2014). Bioactivity of Ethanolic Extract of Propolis (EEP) in Balb / C Mice ' s. *J.Exp. Life Sci.*, *4*(2), 2–7. https://doi.org/10.21776/ub.jels.2014.004.02.03

Aipire, A., Mahabati, M., Cai, S., Wei, X., & Yuan, P. (2020). The immunostimulatory activity of polysaccharides from Glycyrrhiza uralensis. 1–18. https://doi.org/10.7717/peerj.8294

Ananta, M. N. F., Nuralyza, I., Solehah, K., Pratama, I. S., & Aini, S. R. (2024). Skrining fitokimia ekstrak air dan ekstrak etanol 70% Propolis Trigona sp. asal Lombok Utara. *Sasambo Journal of Pharmacy*, *5*(1), 38–45. https://doi.org/10.29303/sjp.v5i1.305

Anjum, S. I., Ullah, A., Khan, K. A., Attaullah, M., Khan, H., Ali, H., Bashir, M. A., Tahir, M., Ansari, M. J., Ghramh, H. A., Adgaba, N., & Dash, C. K. (2019). Composition and functional properties of propolis (bee glue): A review. *Saudi Journal of Biological Sciences*, *26*(7), 1695–1703. https://doi.org/10.1016/j.sjbs.2018.08.013

Ayhan, H., Adiguzel, C., Bayram, K. K., Akin, A. T., Apaydin, F. G., & Kalender, Y. (2025). Effect of propolis supplementation on cadmium toxicity associated with renal and hepatic dysfunction in rats. *Journal of Trace Elements in Medicine and Biology*, *87*(October 2024), 127587. https://doi.org/10.1016/j.jtemb.2024.127587

Beyaert, R., Beaugerie, L., Van Assche, G., Brochez, L., Renauld, J. C., Viguier, M., Cocquyt, V., Jerusalem, G., Machiels, J. P., Prenen, H., Masson, P., Louis, E., & De Keyser, F. (2013). Cancer risk in immune-mediated inflammatory diseases (IMID). *Molecular Cancer*, *12*(1), 1–12. https://doi.org/10.1186/1476-4598-12-98

Block, K. I., & Mead, M. N. (2003). Immune system effects of echinacea, ginseng, and astragalus: A review. *Integrative Cancer Therapies*, *2*(3), 247–267. https://doi.org/10.1177/1534735403256419

Búfalo, M. C., Ferreira, I., Costa, G., Francisco, V., Liberal, J., Cruz, M. T., Lopes, M. C., Batista, M. T., & Sforcin, J. M. (2013). Propolis and its constituent caffeic acid suppress LPS-stimulated pro-inflammatory response by blocking NF-κB and MAPK activation in macrophages. *Journal of Ethnopharmacology*, *149*(1), 84–92. https://doi.org/10.1016/j.jep.2013.06.004

Buonacera, A., Stancanelli, B., Colaci, M., & Malatino, L. (2022). Neutrophil to Lymphocyte Ratio: An Emerging Marker of the Relationships between the Immune System and Diseases. *International Journal of Molecular Sciences*, *23*(7). https://doi.org/10.3390/ijms23073636

Cavalli, G., Colafrancesco, S., Emmi, G., Imazio, M., Lopalco, G., Maggio, M. C., Sota, J., & Dinarello, C. A. (2021). Interleukin 1α: a comprehensive review on the role of IL-1α in the pathogenesis and treatment of autoimmune and inflammatory diseases. *Autoimmunity Reviews*, *20*(3), 102763. https://doi.org/10.1016/j.autrev.2021.102763

Chang, X., Zhu, Y., Shi, C., & Stewart, A. K. (2014). Mechanism of immunomodulatory drugs' action in the treatment of multiple myeloma. *Acta Biochimica et Biophysica Sinica*, *46*(3), 240–253. https://doi.org/10.1093/abbs/gmt142

Chi, H., Pepper, M., & Thomas, P. G. (2024). Principles and therapeutic applications of adaptive immunity. *Cell*, *187*(9), 2052–2078. https://doi.org/10.1016/j.cell.2024.03.037

Depari, E., & Malisie, R. F. (2025). Review : Propolis Sebagai Terapi Tambahan Antiinflamasi pada Penyakit Ginjal Kronis A Review : Propolis As An Antiinflammatory Adjunct Therapy in Chronic Kidney Disease. *Jurnal Farmasimed (Jfm)*, *7*(2), 293–301. https://doi.org/10.35451/jfm.v7i2.2613

Dewi, R. T. K., Redhono, D., Susanto, A., Prasetyo, D. H., Nurhayatun, E., Nurwati, I., & Purwanto, B. (2022). Indonesian Propolis Inhibit Proinflammatory Cytokines, Apoptosis and Oxidative Stress in Anthrax Animal Model. *Indonesian Biomedical Journal*, *14*(3), 309–315. https://doi.org/10.18585/inabj.v14i3.1873

Di Pierro, F., Zanvit, A., & Colombo, M. (2016). Role of a proprietary propolis-based product on the wait-and-see approach in acute otitis media and in preventing evolution to tracheitis, bronchitis, or rhinosinusitis from nonstreptococcal pharyngitis. *International Journal of General Medicine*, *9*, 409–414. https://doi.org/10.2147/IJGM.S118967

Farber, D. L., Netea, M. G., Radbruch, A., Rajewsky, K., & Zinkernagel, R. M. (2016). Immunological memory: Lessons from the past and a look to the future. *Nature Reviews Immunology*, *16*(2), 124–128. https://doi.org/10.1038/nri.2016.13

Fitria, A., Hanifah, S., Chabib, L., Uno, A. M., Munawwarah, H., Atsil, N., Pohara, H. A., Weuanggi, D. A., & Syukri, Y. (2021). Design and characterization of propolis extract loaded self-nano emulsifying drug delivery system as immunostimulant. *Saudi Pharmaceutical Journal*, *29*(6), 625–634. https://doi.org/10.1016/j.jsps.2021.04.024

Fitria, L., & Nurrahman Marwayana, O. (2015). Potensi Propolis Sebagai Imunomodulator Pada Tikus (Rattus norvegicus Berkenhout, 1769) Galur Wistar yang diinduksi Penisilin-G. *Biogenesis: Jurnal Ilmiah Biologi*, *3*(2), 124–131. https://doi.org/10.24252/bio.v3i2.937

Fitriani, H., Fitria, A., Miladiyah, I., & Syukri, Y. (2021). Pengembangan Self-Nano Emulsifying System (SNES) Ekstrak Temulawak (Curcuma xanthorrhiza): Formulasi, Karakterisasi, dan Stabilitas. *Jurnal Sains Farmasi & Klinis*, *8*(3), 332. https://doi.org/10.25077/jsfk.8.3.332-339.2021

Gamil Zeedan, G. S., El-Hamid Abd El-Razik, K. A., Abdel-Shafy, S., Farag, T. K., & Mahmoud, A. H. (2019). The effects of green tea and propolis extracts on pro-inflammatory cytokines TNF-α, IFN-γ, IL2, and immunoglobulin production in experimentally infected rabbits with bovine herpesvirus-1. *Journal of World's Poultry Research*, *9*(4), 329–339. https://doi.org/10.36380/SCIL.2019.WVJ42

Gao, S., Wang, S., & Song, Y. (2020). Novel immunomodulatory drugs and neo-substrates. *Biomarker Research*, *8*(1), 1–8. https://doi.org/10.1186/s40364-020-0182-y

Gaziano, R., Pistoia, E. S., Campione, E., Fontana, C., Marino, D., Favaro, M., Pica, F., & Francesco, P. D. I. (2021). Immunomodulatory agents as potential therapeutic or preventive strategies for COVID-19. *European Review for Medical and Pharmacological Sciences*, *25*(11), 4174–4184. https://doi.org/10.26355/eurrev_202106_26061

Hasan, A. E. Z., Artika1, I. M., A.K, P., & Lasmiyanti, M. (2011). Propolis sebagai alternatif bahan antikaries gigi. *Jurnal Ilmu Pertanian Indonesia*, *16*(1), 45–53. https://doi.org/10.35799/cp.4.1.2011.26504

Herawati, I., Husin, U. A., & Sudigdoadi, S. (2015). Pengaruh Ekstrak Etanol Propolis Terhadap Aktivitas dan Kapasitas Fagositosis pada Kultur Makrofag yang Diinfeksi Enteropathogenic Escherichia coli (EPEC). *Majalah Kedokteran Bandung*, *47*(2). 10.15395/mkb.v47n2.460

Iqbal, M., Fan, T. ping, Watson, D., Alenezi, S., Saleh, K., & Sahlan, M. (2019). Preliminary studies: the potential anti-angiogenic activities of two Sulawesi Island (Indonesia) propolis and their chemical characterization. *Heliyon*, *5*(7), e01978. https://doi.org/10.1016/j.heliyon.2019.e01978

Iwasaki, A., & Medzhitov, R. (2015). Control of adaptive immunity by the innate immune system. *Nature Immunology*, *16*(4), 343–353. https://doi.org/10.1038/ni.3123

Kalsum, N. (2017). Preliminary Studies of the Immunomodulator Effect of the Propolis Trigona spp. Extract in a Mouse Model. *IOSR Journal of Agriculture and Veterinary Science*, *10*(2), 75–80. https://doi.org/10.9790/2380-1002027580

Kalsum, N., Sulaeman, A., Setiawan, B., & Wibawan, I. W. T. (2017). Efek

Propolis Cair Trigona spp. Terhadap Respons Imun Tikus Sprague Dawley yang Diinfeksi Sthapylococcus aureus. *Jurnal Gizi Dan Pangan*, *12*(1), 23–30. https://doi.org/10.25182/jgp.2017.12.1.23-30

Kashiwakura, J. ichi, Yoshihara, M., Saitoh, K., Kagohashi, K., Sasaki, Y., Kobayashi, F., Inagaki, I., Kitai, Y., Muromoto, R., & Matsuda, T. (2021). Propolis suppresses cytokine production in activated basophils and basophil-mediated skin and intestinal allergic inflammation in mice. *Allergology International*, *70*(3), 360–367. https://doi.org/10.1016/j.alit.2020.11.005

Kiełbowski, K., Plewa, P., Bratborska, A. W., Bakinowska, E., & Pawlik, A. (2024). JAK Inhibitors in Rheumatoid Arthritis: Immunomodulatory Properties and Clinical Efficacy. *International Journal of Molecular Sciences*, *25*(15). https://doi.org/10.3390/ijms25158327

Li, S., Gill, N., Lentzsch, S., & Division. (2010). Recent advances of IMiDs in cancer therapy. *Current Opinion in Oncology*, *22*(5), 579–585. https://doi.org/10.1097/CCO.0b013e32833d752c

Listiani, N., & Susilawati, Y. (2019). Review Artikel: Potensi Tumbuhan Sebagai Immunostimulan. *Farmaka*, *17*(2), 222–231. https://doi.org/10.24198/jf.v17i2.22045

Lutpiatina, L. (2015). Efektivitas Ekstrak Propolis Lebah Kelut (Trigona spp) dalam Menghambat Pertumbuhan Salmonella typhi, Staphylococcus aureus dan Candida albicans. *Jurnal Skala Kesehatan*, *6*(1), 1–8. https://doi.org/10.31964/jsk.v6i1.32

Ma, X., Guo, Z. H., Li, Y., Yang, K., Li, X., Liu, Y., Shen, Z., Zhao, L., & Zhang, Z. (2022). Phytochemical Constituents of Propolis Flavonoid, Immunological Enhancement, and Anti-porcine Parvovirus Activities Isolated From Propolis. *Frontiers in Veterinary Science*, *9*(April), 1–11. https://doi.org/10.3389/fvets.2022.85718

Magnavacca, A., Sangiovanni, E., Racagni, G., & Dell'Agli, M. (2022). The antiviral and immunomodulatory activities of propolis: An update and future perspectives for respiratory diseases. *Medicinal Research Reviews*, *42*(2), 897–945. https://doi.org/10.1002/med.21866

Marcucci, M. C. (1995). Propolis: chemical composition, biological properties and therapeutic activity. *Apidologie*, *26*(2), 83–99. https://doi.org/10.1051/apido:19950202

Marshall, J. S., Warrington, R., Watson, W., & Kim, H. L. (2018). An introduction to immunology and immunopathology. *Allergy, Asthma and Clinical Immunology*, *14*(s2), 1–10. https://doi.org/10.1186/s13223-018-0278-1

Megantara, I., Murad, C., Pahlevi, F., Sylviana, N., Goenawan, H., & Lesmana, R. (2024). The Effect of Propolis Extract from Sumatra, Indonesia on Escherichia coli and IL-6 Gene Expression in Male Wistar Rats Fed with a High-Fat Diet. *Tropical Journal of Natural Product Research*, *8*(6), 7350–7354. https://doi.org/10.26538/tjnpr/v8i6.3

Megawati, G., & Wijayakesuma, A. (2022). Literature Review: Potensi Propolis Sebagai Imunomodulator. *Jurnal Kesehatan*, *13*(3), 636–641. https://doi.org/10.26630/jk.v13i3.2742

Mulki, M. A., & Pratama, R. (2022). Literature Review: Senyawa Bioaktif Dan Efek Farmakologis Secara Molekuler Dari Propolis. *Journal of Pharmacopolium*, *5*(3), 326–335. https://doi.org/10.36465/jop.v5i3.109

4

Nazir, E. (2020). Efek Imunostimulan Ekstrak Etanol Daun Seledri terhadap Mencit Putih Jantan. *Jurnal Penelitian Farmasi Indonesia*, *9*(1), 1–7. https://doi.org/10.51887/jpfi.v9i1.788

Nicholson, L. B. (2016). The immune system. *Essays in Biochemistry*, *60*(3), 275–301. https://doi.org/10.1042/EBC20160017

Nie, J., Chang, Y., Li, Y., Zhou, Y., Qin, J., Sun, Z., & Li, H. (2017). Caffeic Acid Phenethyl Ester (Propolis Extract) Ameliorates Insulin Resistance by Inhibiting JNK and NF-κB Inflammatory Pathways in Diabetic Mice and HepG2 Cell Models. *Journal of Agricultural and Food Chemistry*, *65*(41), 9041–9053. https://doi.org/10.1021/acs.jafc.7b02880

Novryantoro, V., Septiara, A., Tirtasari, K., Suwanti, L. T., Edila, R., Mufasirin, M., Kuncorojakti, S., & Puspitasari, H. (2024). Immunomodulatory effect of propolis Trigona spp. in mice infected with Toxoplasma gondii. *Open Veterinary Journal*, *14*(9), 2280–2286. https://doi.org/10.5455/OVJ.2024.v14.i9.16

Oka, M., Kamayani, A., Lestari, A. A. W., Tirtayasa, K., Nyoman, I., & Astawa, M. (2023). Potensi Propolis Sarang Lebah Hitam (Trigona Spp) untuk penyembuhan luka bakar," *Community of Publishing in Nursing (COPING)*, vol. 11, no. 4, pp. 367–370, Aug. 2023, doi: https://doi.org/10.24843/coping.2023.v11.i04.p15

Pratami, D. K., Desmiaty, Y., Simorangkir, E. M., & Faradhila, D. (2021). Standardisasi dan Uji Aktivitas Antioksidan Ekstrak Bahan Alam Propolis untuk Terapi Infeksi SARS-CoV2. *Jurnal Ilmu Kefarmasian Indonesia*, *19*(2), 272. https://doi.org/10.35814/jifi.v19i2.1062

Quach, H., Ritchie, D., Stewart, A. K., Neeson, P., Harrison, S., Smyth, M. J., & Prince, H. M. (2010). Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma. *Leukemia*, *24*(1), 22–32. https://doi.org/10.1038/leu.2009.236

Rebouças-Silva, J., Amorim, N. A., Jesus-Santos, F. H., de Lima, J. A., Lima, J. B., Berretta, A. A., & Borges, V. M. (2023). Leishmanicidal and immunomodulatory properties of Brazilian green propolis extract (EPP-AF®) and a gel formulation in a pre-clinical model. *Frontiers in Pharmacology*, *14*(February), 1–17. https://doi.org/10.3389/fphar.2023.1013376

Rosyidi, D., Eka Radiati, L., Minarti, S., Mustakim, M., Susilo, A., Jaya, F., & Azis, A. (2018). Perbandingan Sifat Antioksidan Propolis pada Dua Jenis Lebah (Apis mellifera dan Trigona sp.) di Mojokerto dan Batu, Jawa Timur, Indonesia. *Jurnal Ilmu Dan Teknologi Hasil Ternak*, *13*(2), 108–117. https://doi.org/10.21776/ub.jitek.2018.013.02.5

Saad, B. (2025). "Immunomodulatory and Anti-Inflammatory Properties of Honey and Bee Products*", Immuno,* 5(2), p.19, 2025, doi: https://doi.org/10.3390/immuno5020019

Santiago, K. B., Conti, B. J., Cardoso, E. de O., Conte, F. L., Tasca, K. I., Romagnoli, G. G., Golim, M. de A., Cruz, M. T., & Sforcin, J. M. (2023). Propolis anti-inflammatory effects on MAGE-1 and retinoic acid-treated dendritic cells and on Th1 and T regulatory cells. *Journal of Venomous Animals and Toxins Including Tropical Diseases*, *29*(July 2022), 1–12. https://doi.org/10.1590/1678-9199-JVATITD-2022-0044

Smith, G. P. (2014). Chapter 1. Introduction to the Immune Response. *The Variation and Adaptive Expression of*

Antibodies, *2024*, 1–11. https://doi.org/10.4159/harvard.9780674365148.intro

Suhirman, S. and Winarti, C . (2010). *Prospek dan fungsi tanaman obat sebagai imunomodulator* (pp. 121–131). Bogor: Balai Penelitian Tanaman Obat dan Aromatik. https://www.academia.edu/download/37067837/4Obat.pdf

Toriqoh, L. (2019). Peran Propolis Sebagai Antibakteri. *Jurnal Farmasi Malahayati*, *2*(2), 203–209. https://doi.org/10.33024/jfm.v2i2.2295

Trinaya, A. A. A. B. A., Linawati, N. M., Wahyuniari, I. A. I., Ratnayanti, I. D., Arijana, I. N., Sugiritama, I. W., & Wiryawan, I. S. (2019). Pengaruh Teh Kombinasi Bunga Euphorbia Milii dan Propolis Terhadap Jumlah Nodulus Limfatikus dan Diameter Sentrum Germinativum pada Limpa Mencit yang Diinfeksi Mycobacterium Tuberculosis. *E-Jurnal Medika Udayana*, *8*(6), 1–8. https://doi.org/10.3390/immuno5020019

Ulandari, K. S., Yoga, P. C. P., Lestari, M. W., & Agustini, N. N. M. (2021). Efektivitas Ekstrak Propolis Dalam Penyembuhan Luka Bakar Derajat Ii Pada Hewan Uji. *Ganesha Medicine*, *1*(2), 80. https://doi.org/10.23887/gm.v1i2.39185

Wijaya, T., & Yunita, F. (2023). Pola Penggunaan Imunostimulan Bahan Herbal pada. *Jurnal Riset Rumpun Ilmu Kedokteran (JURRIKE)*, *2*(1), 27–32. https://doi.org/10.55606/jurrike.v2i1.864

Xool-Tamayo, J., Chan-Zapata, I., Arana-Argaez, V. E., Villa-de la Torre, F., Torres-Romero, J. C., Araujo-Leon, J. A., Aguilar-Ayala, F. J., Rejón-Peraza, M. E., Castro-Linares, N. C., Vargas-Coronado, R. F., & Cauich-Rodríguez, J. V. (2020). In vitro and in vivo anti-inflammatory properties of Mayan propolis. *European Journal of Inflammation*, *18*. https://doi.org/10.1177/2058739220935280

Yamshon, S., & Ruan, J. (2019). IMiDs New and Old. *Mcl*. https://doi.org/10.1007/s11899-019-00536-6

Zamarrenho, L. G., de Lima, M. H. F., Hori, J. I., Lima, J. A., Ambrósio, S. R., Bastos, J. K., De Jong, D., & Berretta, A. A. (2023). Effects of Three Different Brazilian Green Propolis Extract Formulations on Pro- and Anti-Inflammatory Cytokine Secretion by Macrophages. *Applied Sciences (Switzerland)*, *13*(10). https://doi.org/10.3390/app13106247