

Tuan Ismail  
TNN<sup>1\*</sup>,  
Shahidan  
WNS<sup>1</sup>, Kannan  
TP<sup>1,2</sup>

<sup>1</sup>School of Dental  
Sciences,  
Universiti Sains  
Malaysia, 16150  
Kubang Kerian,  
Kelantan,  
Malaysia

<sup>2</sup>Human Genome  
Centre, School of  
Medical Sciences,  
Universiti Sains  
Malaysia, 16150  
Kubang Kerian,  
Kelantan,  
Malaysia

\*Corresponding  
author  
Tuan Nadrah  
Naim Tuan Ismail  
tnadrah@usm.my

Received 23 March  
2025

Revised 24 Sept  
2025

Accepted 30 Sept  
2025

Published Online 28  
Oct 2025

## The Anti-Acne Potential of Stingless Bee Propolis: A Review

**Abstract** – Acne vulgaris is a prevalent dermatological condition, primarily affecting adolescents, which poses significant physical and psychological burdens. Recent research has highlighted the therapeutic potential of natural substances, such as propolis derived from stingless bees, in addressing acne-related concerns. Propolis has garnered attention due to its broad spectrum of pharmacological activities, including its antibacterial, anti-inflammatory, and antioxidant properties. These attributes suggest its potential efficacy as a treatment option for acne. This narrative review was conducted through a comprehensive search of relevant scientific databases to evaluate the potential of stingless bee propolis as a natural therapeutic agent for acne vulgaris. In particular, it focuses on the bioactive compounds responsible for its pharmacological effects, while also considering potential adverse reactions, such as allergic responses. Stingless bee propolis exhibits significant antibacterial activity, particularly against *Cutibacterium acnes*, the primary bacterium implicated in acne pathogenesis. Its anti-inflammatory properties further mitigate the inflammatory processes that contribute to acne lesion development, while its antioxidant activity helps counteract oxidative stress, which is a known exacerbating factor in acne. The bioactive compounds that underpin these effects include terpenoids, phenolic compounds, and flavonoids, all of which have been well-documented for their therapeutic properties in dermatological applications. Despite these promising attributes, it is important to acknowledge that stingless bee propolis may trigger allergic reactions in sensitive individuals. Therefore, while it holds promise as a natural alternative for acne treatment, rigorous clinical trials are necessary to fully establish its efficacy, safety, and tolerability in broader populations. In summary, stingless bee propolis presents a compelling natural therapeutic option for acne vulgaris due to its antibacterial, anti-inflammatory, and antioxidant effects. However, its potential to induce allergic reactions warrants caution. Further clinical research is essential to confirm its utility and safety for widespread use in dermatological applications, particularly in the treatment of acne.

**Keywords** – *Acne vulgaris*, *antibacterial*, *anti-inflammatory*, *propolis*, *stingless bee*

## 1 INTRODUCTION

Acne vulgaris is a prevalent dermatological condition, especially among adolescents. Moreover, a global disease burden analysis revealed that adolescents aged 15–19 years exhibit the highest age-specific prevalence of acne (1). Although not life-threatening, acne has significant psychosocial implications, often leading to diminished self-esteem, social withdrawal, anxiety, depression, and even suicidal ideation (2). Furthermore, individuals with persistent acne may experience reduced employment prospects and social stigmatization (3), highlighting the need for effective and accessible treatment options.

Conventional acne treatments, including benzoyl peroxide, retinoids, and antibiotics, have demonstrated efficacy but are often associated

with adverse effects. Benzoyl peroxide and topical retinoids frequently cause skin dryness (4), while prolonged antibiotic use contributes to antimicrobial resistance (5). Additionally, oral isotretinoin has reportedly been associated with suicide and a range of psychiatric disorders, including depression and anxiety (6). These limitations have prompted a growing interest in natural and sustainable alternatives that offer comparable therapeutic benefits with fewer side effects.

Propolis, a resinous substance produced by bees, has gained attention in dermatology for its antimicrobial, anti-inflammatory, and antioxidant properties. Acne is a multifactorial disorder characterized by inflammation, excessive sebum production, abnormal keratinization, and bacterial colonization, primarily by *Cutibacterium acnes* (7).

The bioactive compounds in propolis address these underlying mechanisms by inhibiting bacterial proliferation, reducing inflammation, and protecting skin cells from oxidative damage. These properties suggest that propolis could serve as a natural and effective alternative for acne treatment.

Among the different types of propolis, stingless bee propolis, is particularly notable for its unique chemical profile and ecological advantages. Stingless bees are tropical and subtropical social insects that differ from the more familiar honeybees (*Apis* species) in several key aspects, including their smaller size, inability to sting, and remarkable adaptability to a wide range of environmental conditions (8). Notably, stingless bees exhibit greater resilience to environmental stressors and produce propolis with superior antibacterial activity compared to that of *Apis* species (9). Traditionally used in various cultures for medicinal purposes, stingless bee propolis is especially rich in phenolic and flavonoid compounds, contributing to its pronounced antimicrobial and anti-inflammatory effects (10). Growing interest in its bioactive profile has led to increasing recognition of its potential dermatological applications, particularly in the context of acne care.

Recognizing the economic and ecological potential of stingless beekeeping, Malaysian government has implemented strategic policies to foster and regulate its development (11). The National Beekeeping Industry Development Plan 2020-2030, introduced by the Ministry of Agriculture and Food Security, aims to position Malaysia's beekeeping industry on the global stage (12). This initiative focuses on promoting stingless beekeeping as a sustainable agricultural practice, improving production quality, and supporting research on the bioactive compounds of stingless bee-derived products, including propolis. Government policies emphasize the conservation of stingless bee populations, the establishment of quality assurance frameworks, and the development of market access for stingless bee products. These measures not only contribute to economic growth but also encourage the sustainable use of stingless bee-derived ingredients in industries such as skincare and pharmaceuticals.

This narrative review provides a comprehensive analysis of the anti-acne potential of stingless bee propolis, focusing on its antimicrobial, anti-inflammatory, and antioxidant properties. Additionally, it identifies gaps in existing research

to guide future studies on its therapeutic potential, safety, and clinical validation for acne treatment. With increasing interest in sustainable and naturally derived skincare, this review also explores the role of stingless bee propolis in advancing dermatological practices. By synthesizing current evidence, this review aims to support the development of safer, more effective, and eco-friendly acne treatments while highlighting the importance of government policies in promoting stingless beekeeping as a sustainable industry.

## 2 MATERIAL AND METHODS

A literature search was conducted using databases such as PubMed, Scopus, Web of Science, and Google Scholar. The search included studies published up to 2025, using keywords such as "stingless bee propolis," "acne vulgaris," "*Cutibacterium acnes*," "antimicrobial," "anti-inflammatory," "antioxidant," and "dermatology." Only peer-reviewed studies on propolis with relevance to acne treatment were included, regardless of the bee species. Eligible studies comprised in vitro, in vivo, and clinical investigations that assessed the biological activities of propolis. Studies were excluded if they were non-English or lacked experimental data. The selected studies were analysed for their bioactive compounds and their reported effects on *Cutibacterium acnes*, inflammation, and oxidative stress. The extracted data were synthesized to provide a comprehensive evaluation of propolis as a potential natural intervention for acne. Additionally, safety concerns, including allergic reactions and cytotoxicity, were reviewed to assess its suitability for dermatological applications.

## 3 DISCUSSIONS

### 3.1 Comparison with Conventional Treatment

While conventional acne treatments such as antibiotics, retinoids, and benzoyl peroxide remain standard in clinical practice, they are often associated with drawbacks including skin irritation, increased photosensitivity, and the mounting threat of antimicrobial resistance (13). These concerns have accelerated interest in plant and bee-derived alternatives with fewer adverse effects and multifunctional therapeutic properties. Stingless bee propolis offers a compelling natural alternative, not only for its antibacterial action against *Cutibacterium acnes*, but also for its anti-inflammatory and antioxidant activities that address multiple aspects of acne pathogenesis.

Unlike single-target conventional therapies, propolis exerts broad-spectrum bioactivity due to its rich composition of flavonoids, phenolic acids, and terpenoids (14).

A comparative overview of stingless bee propolis, as presented in Table 1, reveals marked differences in bioactivity depending on species, geographic origin, and extraction methods. For example, *Tetragonula biroi* propolis from Indonesia contains unique flavonols such as nymphaeol A with notable antibacterial and antioxidant effects (15). *Heterotrigona itama*, studied across regions including Thailand and Malaysia, consistently demonstrates high anti-acne efficacy, attributed to its phenolic and terpenoid content (16, 17). Additionally, species like *Melipona fasciculata* and *Tetragonula pagdeni* have demonstrated selective COX-2 inhibition and downregulation of key inflammatory markers, indicating a pharmacological profile comparable to that of non-steroidal anti-inflammatory drugs (18). These multifunctional effects are further complemented by antioxidant capacities that rival or exceed those of green propolis from *Apis mellifera*, along with low cytotoxicity in human keratinocyte studies and good tolerability in preliminary clinical assessments.

In this context, stingless bee propolis holds potential not merely as a substitute but as an integrative or adjunctive approach to conventional acne therapy. Its multifaceted pharmacological profile allows for a more holistic treatment strategy one that simultaneously addresses bacterial proliferation, inflammation, oxidative stress, and potentially enhances skin recovery with a reduced side effect profile. However, further standardization and clinical validation are necessary to fully realize its therapeutic promise.

### 3.2 Antibacterial Potential of Stingless Bee Propolis in Acne Therapy

Targeted therapy against *Cutibacterium acnes* (*C. acnes*), formerly known as *Propionibacterium acnes* has long been a cornerstone in the management of acne vulgaris (19). Conventional treatments, such as topical and oral antibiotics, are effective but increasingly limited by concerns about antibiotic resistance and adverse effects. This has led to growing interest in natural alternatives like propolis, whose antibacterial activity presents a compelling therapeutic prospect. Propolis, with its well-documented antibacterial properties, offers an alternative approach to acne treatment by inhibiting the growth of this bacterium.

By reducing the bacterial load, propolis helps mitigate acne breakouts, making it a promising candidate for integration into therapeutic regimens for acne management.

The antibacterial properties of propolis are attributed to its diverse chemical composition, primarily consisting of flavonoids, phenolic acids, and aromatic esters. These bioactive compounds exert their antibacterial effects through several mechanisms. One of the key actions is the disruption of bacterial cell walls and membranes, leading to increased permeability and subsequent cell lysis (20). Flavonoids, one of propolis main compounds inhibit bacterial enzymes critical for essential processes like DNA replication and protein synthesis, thereby limiting bacterial growth and survival (21).

Several studies have conducted a comprehensive investigation into the antibacterial potential of propolis. An in vitro study on stingless bee *Tetragonula biroi* propolis from Balikpapan, Indonesia, revealed that the methanol extract of propolis contains several bioactive compounds, including 3'-O-methyldiplacone, 5,7,3',4'-tetrahydroxy-6-geranyl flavonol, and nymphaeol A. Among these, two compounds: nymphaeol A and 5,7,3',4'-tetrahydroxy-6-geranyl flavonol exhibited significant antibacterial activity against *C. acnes*. At a concentration of 1 µg/well, these compounds demonstrated inhibition zones of 14.11 mm and 13.78 mm, respectively (15). Notably, all three isolated compounds also exhibited antioxidant and anti-inflammatory properties, further supporting their potential as therapeutic agents in acne treatment.

However, antibacterial efficacy is not consistent across all stingless bee species or even within the same species collected from different regions. An in vitro study on *Heterotrigona itama* propolis from two Indonesian locations Mangkurawang and Fahutan demonstrated significant differences in antibacterial activity, despite using the same extraction methods (17). The ethanolic extract of the Mangkurawang propolis demonstrated the strongest antibacterial activity against *C. acnes*, with an inhibition rate of 89.33% at a concentration of 500 µg/ml. Additionally, the oil extract from the same region exhibited antibacterial activity, showing 65.58% inhibition at the same concentration. In contrast, neither the ethanolic nor the oil extracts of the propolis from Fahutan demonstrated antibacterial activity against *C. acnes*, indicating potential regional variations in the chemical composition and bioactivity of stingless bee propolis. Such variability suggests

that sourcing and standardization will be pivotal considerations for future product development.

In line with this, a recent in vitro comparative study involving four stingless bee species from Thailand (*Heterotrigona itama*, *Geniotrigona thoracica*, *Tetragonula pagdeni*, and *Lepidotrigona terminata*) demonstrated that while all extracts exhibited antibacterial activity, *H. itama* propolis produced the largest inhibition zones and contained the highest levels of total phenolics and flavonoids (16). The study reported a consistent correlation between high phenolic/flavonoid content and antibacterial potency suggests a potential biomarker-driven approach to predicting propolis efficacy, which could facilitate quality control and standardization in therapeutic development. Interestingly, the researchers also observed that the MIC and MBC values for these propolis extracts (125 µg/mL and 250 µg/mL, respectively) suggest that effective antimicrobial activity can be achieved without reaching cytotoxic levels, as indicated in previous cell viability studies. This favourable therapeutic index supports the feasibility of formulating propolis-based products for topical acne management. However, translation into clinical applications will require further exploration of pharmacokinetics, formulation stability, and skin penetration.

Taken together, these findings underscore that while stingless bee propolis is a promising antibacterial agent against *C. acnes*, its efficacy is not universal and must be evaluated in the context of species origin, extraction method, and chemical composition. A deeper understanding of the bioactive constituents responsible for antimicrobial effects and how these vary between propolis types could inform the rational design of standardized, propolis-based acne therapies. Moreover, the synergy between antibacterial, anti-inflammatory, and antioxidant properties in some extracts highlights the multifunctional advantage of stingless bee propolis, supporting its integration into holistic acne management strategies.

### 3.3 Anti-Inflammatory Potential of Stingless Bee Propolis in Acne Therapy

Inflammation associated with acne can significantly worsen the condition, contributing to increased redness, swelling, and discomfort (22). The incorporation of anti-inflammatory agents in acne treatment can alleviate the inflammatory response within acne lesions, thereby soothing irritated skin. By reducing inflammation, such agents help to diminish the visible severity of acne, minimize the appearance of lesions, and facilitate

more rapid healing. This therapeutic approach not only improves the cosmetic outcomes of acne management but also supports the overall recovery process of the skin. The anti-inflammatory effects of propolis are largely attributed to its complex chemical composition, which includes flavonoids (23), phenolic acids (24, 25), and terpenoids (26).

Several investigations have highlighted the anti-inflammatory potential of propolis. Notably, an in vitro study on stingless bee propolis from Thailand demonstrated significant anti-inflammatory effects (27). The research focused on propolis derived from *Tetragonula pagdeni* Schwarz, which was obtained from an apiary situated within a mangosteen orchard. The study found that the propolis extract exhibited notable anti-inflammatory effects in RAW 264.7 macrophage cells. Phytochemical analysis revealed the  $\alpha$ - and  $\gamma$ -mangostin content in the tested propolis extract to be  $35.80 \pm 0.79$  mg/g and  $33.58 \pm 0.78$  mg/g, respectively. Furthermore, the total phenolic content was quantified at  $14.23 \pm 0.62$  mg GAE/g extract, while the total flavonoid content was measured at  $1.42 \pm 0.05$  mg QE/g extract. According to the authors, the anti-inflammatory effects of the propolis extracts were attributed to their ability to downregulate genes associated with inflammation. Specifically, the results indicated that the propolis extract suppressed the expression of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase, and pro-inflammatory cytokines, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), and interleukin-10 (IL-10). These findings underscore the potential of *Tetragonula pagdeni* propolis as a therapeutic agent for managing inflammation related to various dermatological conditions.

A comparable outcome was observed in an in vitro study investigating the anti-inflammatory properties of propolis derived from the native Brazilian stingless bee species, *Melipona fasciculata* Smith. The ethanolic extract of this propolis exhibited significant anti-inflammatory activity, primarily through the inhibition of the cyclooxygenase (COX) enzyme, with a preferential inhibition of COX-2 (18). The selective inhibition of COX-2 is particularly relevant, as it is a key enzyme involved in the inflammatory response, and its targeted inhibition is associated with reduced inflammatory processes without the gastrointestinal side effects commonly seen with non-selective COX inhibitors. The study identified several bioactive compounds responsible for this anti-inflammatory activity, including corilagin,



typhaneoside, taraxerone, and marsformosanone. These compounds likely act synergistically to modulate the inflammatory cascade, contributing to the overall efficacy of the propolis extract in reducing inflammation. Such findings highlight the therapeutic potential of *Melipona fasciculata* propolis as a natural anti-inflammatory agent, with promising implications for its use in treating inflammatory skin conditions such as acne vulgaris.

Similarly, an in vitro study on propolis sourced from *Heterotrigona itama* in Sarawak, Malaysia found that its ethanolic extract, rich in terpenoids, demonstrated strong anti-inflammatory properties (26). The extract was found to inhibit key inflammatory mediators, including inducible nitric oxide synthase, interleukin-1 $\beta$  (IL-1 $\beta$ ), and IL-10, which play crucial roles in the regulation of inflammatory responses. The suppression of these mediators suggests that *Heterotrigona itama* propolis may effectively reduce inflammation through multiple molecular pathways, particularly by targeting both pro-inflammatory and anti-inflammatory cytokines. The study further reported that the terpenoid content of the extract reached 46.44% following a 72-hour extraction process using a solvent mixture of 95% ethanol and 5% water. Terpenoids, known for their antimicrobial and anti-inflammatory properties, likely contribute significantly to the extract's bioactivity. This high concentration of terpenoids underscores the therapeutic potential of *Heterotrigona itama* propolis as a natural anti-inflammatory agent, particularly in conditions involving chronic inflammation, such as acne vulgaris. The findings emphasize the value of this species' propolis for potential applications in dermatological treatments.

Likewise, an in vitro study on the ethanolic extract of stingless bee propolis from the *Tetragonisca fiebrigi* species, collected in the Midwest region of Brazil, also exhibited anti-inflammatory activity. The study identified phenolic compounds as the predominant constituents, with benzoic acid and kaurenoic acid accounting for 9.2% and 11.8%, respectively (28). The anti-inflammatory mechanism of this propolis extract was attributed to the inhibition of the hyaluronidase enzyme, a key enzyme involved in the breakdown of hyaluronic acid, which plays a crucial role in tissue integrity and inflammatory processes. The study demonstrated that at the highest concentration tested (75 mg/mL), the ethanolic extract inhibited  $43.06 \pm 3.06\%$  of hyaluronidase

enzymatic activity, highlighting its significant anti-inflammatory potential.

Another in vitro study on stingless bee propolis collected from Brazil, but derived from a different species, *Melipona orbignyi*, identified flavonoids, glycosylated phenolic acid derivatives, and terpenoids as the predominant compounds (29). This study also reported that the anti-inflammatory action was mediated by inhibiting the hyaluronidase enzyme. However, at the same concentration (75 mg/mL), the inhibition of enzymatic activity was lower, at 35.6%. These findings suggest that while both species exhibit anti-inflammatory effects via the same enzymatic inhibition mechanism, differences in chemical composition, particularly phenolic and terpenoid content, may influence the potency of their bioactive properties.

Aligning with previous findings, an in vivo study on *Tetragonula biroi* Friese propolis, collected from the Philippines, demonstrated notable anti-inflammatory activity using a lambda-carrageenan-induced hind paw oedema model in mice (30). The administration of propolis led to statistically significant reductions in inflammation within 24 hours, with the most pronounced ameliorative effects observed at 6 hours post-injection. This reduction in dermal oedema was comparable to the results seen in the group treated with diclofenac sodium, a standard nonsteroidal anti-inflammatory drug. Furthermore, both the propolis-treated and diclofenac sodium-treated groups exhibited significantly lower levels of protein expression for the pro-inflammatory cytokine tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) compared to the control group that received distilled water. The study highlights the efficacy of stingless bee propolis in reducing inflammatory responses through the modulation of key cytokines, positioning it as a potential natural alternative to conventional anti-inflammatory treatments. This finding reinforces the therapeutic promise of stingless bee propolis in managing inflammation-driven skin conditions such as acne vulgaris, where inflammation plays a central role in disease progression.

Despite promising results, a critical gap remains in standardizing propolis formulations for dermatological use. The wide variation in chemical composition between bee species, geographical regions, and extraction methods complicates efforts to develop uniform therapeutic agents. Moreover, most studies to date have focused on short-term in vitro or animal models; clinical validation in human acne populations is still

limited. Addressing these gaps will be essential for translating preclinical insights into effective, evidence-based skincare products.

In conclusion, the anti-inflammatory potential of stingless bee propolis is both multifactorial and species-dependent, offering a compelling alternative or adjunct to conventional acne treatments. Its ability to modulate both pro- and anti-inflammatory pathways, combined with antioxidant and antimicrobial effects, supports its inclusion in an integrated approach to acne management. However, the future utility of stingless bee propolis in clinical dermatology will depend on deeper chemical characterization, standardized extraction techniques, and well-designed clinical trials.

### 3.4 Antioxidant Potential of Stingless Bee Propolis in Acne Therapy

Various dermatological conditions, including acne, are frequently associated with oxidative stress, which results from an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them (31). Natural antioxidants play a crucial role in protecting the skin by scavenging free radicals that contribute to oxidative damage (32). The antioxidant properties of propolis have been shown to mitigate free radical-induced damage (33). This mechanism safeguards the skin against oxidative damage and its associated effects. By reducing oxidative damage, propolis may significantly decrease the severity of acne, highlighting its potential therapeutic application in the management of this condition. The antioxidant potential of propolis is primarily attributed to its rich content of phenolic acids and flavonoids (34, 35).

An in vitro study investigating the antioxidant properties of ethanolic extracts of Korean propolis demonstrated significant effects on oxidative stress in epidermal HaCaT keratinocytes (36). In this study, the ethanolic extract was fractionated into hydrophilic and lipophilic components. The authors reported that the hydrophilic fraction exhibited notable antioxidant properties and was non-toxic to the cells. This antioxidant effect was attributed to the inhibition of ROS production, lipid peroxidation, and glutathione oxidation. Conversely, while the lipophilic fraction and the total ethanolic extract also demonstrated antioxidant effects, they were found to possess a degree of cytotoxicity towards the keratinocytes. The hydrophilic fraction was identified to contain bioactive compounds such as caffeic acid, p-coumaric acid, and ferulic acid, with ferulic acid

being the most effective in inhibiting ROS production, lipid peroxidation, and glutathione oxidation. In contrast, the lipophilic fraction contained caffeic acid phenethyl ester (CAPE), which, despite exhibiting antioxidant properties, also demonstrated cytotoxic effects on keratinocytes. These findings highlight the complex interplay between the antioxidant efficacy and cytotoxicity of different fractions of propolis, suggesting that further investigation is warranted to optimize its therapeutic potential in dermatological applications.

Numerous studies have indicated a positive correlation between the antioxidant activities of stingless bee propolis and their total phenolic and flavonoid content. For instance, a previous investigation of water extracts from three distinct Indo-Malayan stingless bee species in Selangor, Malaysia revealed that higher concentrations of flavonoids and phenolic compounds corresponded with enhanced antioxidant activity (37). This study specifically examined the flavonoid and phenolic content, as well as the antiradical activity, of extracts from *Tetrigona apicalis*, *Tetrigona binghami*, and *Homotrigona fimbriata*. Among the species assessed, *Homotrigona fimbriata* exhibited the highest levels of total phenolic and flavonoid content, alongside superior antiradical activity. These findings underscore the significance of phenolic and flavonoid compounds in determining the antioxidant efficacy of propolis derived from various stingless bee species, suggesting their potential for therapeutic applications in combating oxidative stress. In addition to their rich content of phenolic compounds and flavonoids, the propolis from these four Malaysian stingless bee species has been found to contain a diverse array of 35 chemical compounds, classified into several categories. These include sugars (31.4%), carboxylic acids (17.1%), terpenoids (14.3%), sugar alcohols (11.4%), hydrocarbons (5.7%), aldehydes (5.7%), amino acids (2.9%), and a group of other miscellaneous compounds (11.4%). This complex chemical composition highlights its potential as a multifunctional bioactive agent.

Similarly, investigations conducted in Brunei on ethanolic extract of propolis from *Geniotrigona thoracica*, *Heterotrigona itama*, and *Tetrigona binghami* revealed that their antioxidant capacity, as measured through radical scavenging assays, aligned with their total phenolic content (38). In addition to phenolic compounds, the propolis from these three stingless bee species predominantly comprises lipids, accounting for 45.60–47.86% of

its composition. In contrast, it contains minimal amounts of carbohydrates (0.17–0.48%) and proteins (0.18–1.18%).

Furthermore, a study of methanolic extract of *Tetragonula biroi* propolis sourced from Indonesia reported significant antioxidant activity, with a DPPH radical scavenging capacity of 82.31% at a concentration of 6.25 µg/mL (15).

Additionally, studies of stingless bee propolis from several regions in Brazil also showed potent antioxidant activity (39). Notably, propolis from different stingless bee species, including *Melipona quadrifasciata* anthidioides and *Tetragona clavipes* collected from the southeast region, as well as *Scaptotrigona* spp. from the northeast, exhibited considerable antioxidant properties. Among these, the ethanolic extract of propolis from *Melipona quadrifasciata* anthidioides displayed the highest antioxidant activity. Interestingly, the activity was even more potent than the antioxidant activity of green propolis from *Apis mellifera* (39).

Yet, despite promising findings, critical gaps remain. The majority of antioxidant studies rely on chemical assays (e.g., DPPH, ABTS), which do not fully capture the biological context of oxidative stress in human skin. Future research should emphasize biologically relevant models, such as co-cultures of sebocytes and immune cells, and consider synergistic effects between antioxidants, anti-inflammatory compounds, and antimicrobial agents within propolis.

In conclusion, the antioxidant properties of stingless bee propolis are strongly supported by emerging research and are largely driven by its phenolic and flavonoid content. However, the variability in composition across species and regions, as well as the potential for cytotoxic effects depending on extraction polarity, underscores the need for careful formulation and standardization. When properly harnessed, the antioxidant activity of stingless bee propolis represents a powerful adjunct in acne treatment, not only reducing oxidative damage but also supporting tissue regeneration and barrier repair.

### 3.5 Cytotoxicity Considerations in the Use of Stingless Bee Propolis for Dermatological Applications

The existing literature regarding the cytotoxic effects of stingless bee propolis on epidermal cells remains limited. One notable study conducted on stingless bee propolis namely *Melipona scutellaris* (*M. scutellaris*) sourced from Brazil assessed its cytotoxicity by evaluating the viability of HaCaT

cells following exposure to varying concentrations of the extract (40). The findings indicated that cell viability was maintained at 67.40% at a concentration of 220 µg/ml after 24 hours of exposure. Although not indicative of acute toxicity, the reduction in viability suggests a degree of cellular stress that warrants attention, particularly when considering higher concentrations or repeated application to compromised skin. Moreover, the use of a single immortalized keratinocyte line limits the extrapolation of these findings to in vivo conditions, where skin homeostasis involves intricate interactions among keratinocytes, fibroblasts, sebocytes, immune cells, and a functional skin barrier. It is plausible that certain cell types especially under inflammatory conditions or in barrier-impaired skin may exhibit heightened sensitivity to propolis. Therefore, comprehensive cytocompatibility profiling across multiple skin-relevant cell types and exposure durations is essential before definitive safety claims can be made.

Importantly, the effective concentrations of *M. scutellaris* propolis extract exhibiting antimicrobial, anti-inflammatory, and antioxidant properties, along with its capacity to reduce sebum production, are typically reported to be less than 1000 µg/ml (40). The emergence of cytotoxicity only at higher concentrations supports a favourable therapeutic window for topical application. This reinforces the potential of stingless bee propolis as a safe and effective ingredient in dermatological formulations, particularly those targeting conditions such as acne vulgaris. However, translating this potential into clinical or commercial use necessitates further investigation into its concentration-dependent effects, long-term safety, and compatibility within complex formulation matrices.

An additional critical consideration is the marked variability in propolis composition, influenced by bee species, floral sources, and extraction techniques. The cytotoxicity profile observed in *M. scutellaris* propolis cannot be assumed to represent other stingless bee species. For instance, propolis enriched in compounds such as caffeic acid phenethyl ester (CAPE) or specific terpenoids may exhibit dual effects conferring therapeutic benefits at low concentrations while exerting cytotoxicity at higher doses or in specific vehicles (36). This pharmacological duality underscores the importance of standardized extraction protocols and rigorous dose-response evaluations to ensure that therapeutic efficacy is achieved without compromising cellular integrity. A

nuanced understanding of these species-specific chemical profiles and their biological effects is therefore essential to fully harness the dermatological potential of stingless bee propolis in a safe and effective manner.

### 3.6 Allergy Reaction

There is a paucity of information regarding allergic reactions associated with stingless bee propolis. A clinical study conducted with 20 volunteers investigated the safety of a facial serum formulated with honey and propolis sourced from stingless bees in East Kalimantan (41). The participants applied the serum twice daily to the upper arm for a duration of seven days, and the assessment of allergic reactions was conducted using the International Contact Dermatitis Research Group System, while the Primary Irritation Index was employed to evaluate any irritating reactions. On the first day of application, four volunteers reported moderate irritation, while the remaining 16 participants exhibited typical skin responses. Notably, the skin of all 20 participants remained normal from the second to the seventh day following treatment. Although the facial serum containing honey and stingless bee propolis induced mild irritation during its initial application, it was deemed safe for continued use thereafter. These findings suggest that while initial irritation may occur, the formulation is generally well-tolerated in a clinical context, highlighting the need for further research to comprehensively evaluate the safety profile of stingless bee propolis in dermatological applications.

Despite the limited information available on allergic reactions specifically associated with stingless bee propolis, several cases have been documented regarding allergies linked to propolis derived from honeybee species. A clinical study involving 722 patients with dermatitis in Sweden revealed that the frequency of positive patch-test reactions to propolis sourced from four different regions: China, Lithuania, North America, and Sweden, ranged from 2.4% to 3.6% (42). This observation aligns with subsequent research examining patch-test reactions in dermatitis patients from various European countries, utilizing propolis sourced from the same origins (43). In this follow-up study, 1,470 consecutive patients with dermatitis residing in Denmark, Sweden, Lithuania, and North America exhibited patch-test reaction rates ranging from 1.3% to 5.8% in response to propolis sourced from these regions.

Similarly, a study conducted among 216 dermatitis patients in Singapore reported a 5.1% incidence of positive reactions to the propolis patch test (44). These findings highlight the potential for allergic reactions to propolis derived from honeybee species, underscoring the need for further investigation into the allergenic properties of propolis from stingless bees. This research gap is particularly relevant given the increasing use of propolis in various cosmetic and therapeutic applications.

One challenge in studying propolis allergies is the lack of standardization in its composition, as its chemical makeup can vary significantly depending on geographic origin, the plant sources bees use to collect resin, and the methods used to process propolis. This variability complicates the understanding of which specific compounds in propolis are responsible for triggering allergic reactions.

While several studies have suggested that propolis may cause allergic reactions in certain individuals, particularly those with sensitivity to bee products. However, conflicting evidence exists, with other research indicating that propolis may possess antiallergic properties (45). These studies suggest that propolis can inhibit the release of histamine and other inflammatory mediators, potentially reducing allergic responses. The variation in findings could be attributed to differences in study design, participant populations, and the chemical composition of propolis, which can vary depending on its geographical origin and the types of plants involved in its production. Further research is needed to reconcile these discrepancies and to fully understand the potential allergenic versus antiallergic effects of propolis.

## 4 CONCLUSION

In conclusion, the evidence presented in this review underscores the substantial potential of stingless bee propolis as a therapeutic agent for the management of acne vulgaris. Its multifaceted properties, including strong antibacterial, anti-inflammatory, and antioxidant effects, make it a promising alternative to conventional acne treatments, which are often associated with adverse effects and the risk of antibiotic resistance. The presence of bioactive compounds such as flavonoids, phenolic acids, and terpenoids in stingless bee propolis contributes to its efficacy in modulating the pathophysiological mechanisms underlying acne.



**Table 1.** Anti-acne properties of stingless bee propolis

| Property          | Stingless Bee Species        | Origin                  | Extract/Active Compounds                                                     | Effect                                                             | Reference |
|-------------------|------------------------------|-------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------|-----------|
| Antibacterial     | <i>Tetragonula biroi</i>     | Balik Papan, Indonesia  | 3'-O-methyldiplacone, 5,7,3',4'-tetrahydroxy-6-geranyl flavonol, nymphaeol A | Inhibits <i>C. acnes</i> growth                                    | (15)      |
| Antibacterial     | <i>Heterotrigona itama</i>   | Mangkurawang, Indonesia | Ethanollic extract                                                           | Strong inhibition of <i>C. acnes</i> (89.33% at 500 µg/ml)         | (17)      |
| Antibacterial     | <i>Heterotrigona itama</i>   | Thailand                | Ethanollic extract                                                           | Inhibition zone: 14.43 mm                                          | (16)      |
| Anti-inflammatory | <i>Tetragonula pagdeni</i>   | Thailand                | α-mangostin, γ-mangostin                                                     | Downregulates inflammatory cytokines (COX-2, TNF-α, IL-6)          | (27)      |
| Anti-inflammatory | <i>Melipona fasciculata</i>  | Brazil                  | Corilagin, typhaneoside, taraxerone, marsformosanone                         | Selective COX-2 inhibition, reduces inflammation                   | (18)      |
| Anti-inflammatory | <i>Heterotrigona itama</i>   | Sarawak, Malaysia       | Terpenoid-rich ethanollic extract                                            | Inhibits IL-1β, IL-10, and nitric oxide production                 | (26)      |
| Antioxidant       | <i>Tetragonula biroi</i>     | Indonesia               | Methanollic extract                                                          | High DPPH radical scavenging activity (82.31% at 6.25 µg/mL)       | (15)      |
| Antioxidant       | <i>Homotrigona fimbriata</i> | Malaysia                | Water extract                                                                | High phenolic and flavonoid content, strong antioxidant properties | (46)      |
| Cytotoxicity      | <i>Melipona scutellaris</i>  | Brazil                  | Ethanollic extract                                                           | Non-toxic at ≤ 1000 µg/mL, potential for skincare use              | (40)      |
| Allergy Potential | Mixed species                | East Kalimantan         | Facial serum formulation                                                     | Mild irritation initially, but safe for long-term use              | (41)      |

Despite the encouraging findings, there remains a need for further research to comprehensively elucidate the mechanisms of action, optimize formulation strategies, and establish the safety and efficacy of stingless bee propolis in clinical settings.

Notably, the chemical composition and biological activity of propolis can vary significantly across stingless bee species and geographic regions. These variations highlight the importance of species selection and standardization in developing consistent and effective propolis-based formulations.

Additionally, potential allergic reactions, although limited, warrant consideration when incorporating propolis into dermatological

applications. As interest in natural products continues to grow, stingless bee propolis may emerge as a valuable component in the development of innovative and effective acne treatment modalities, contributing to improved patient outcomes and a more sustainable approach to skincare.

#### ACKNOWLEDGEMENT

The authors would like to express sincere gratitude to Universiti Sains Malaysia for supporting this work through the Short-Term Grant (304/PPSG/61312066). This funding has facilitated research on propolis and its potential on acne.

**ETHICAL STATEMENT**

Not applicable.

**CONFLICT OF INTEREST**

The authors declare that they have no conflicts of interest.

**REFERENCES**

- [1] Zhu Z, Zhong X, Luo Z, Liu M, Zhang H, Zheng H, et al. Global, regional and national burdens of acne vulgaris in adolescents and young adults aged 10–24 years from 1990 to 2021: a trend analysis. *British Journal of Dermatology*. 2025;192(2):228-37 <https://doi.org/10.1093/bjd/ljae352>.
- [2] Stamu-O'Brien C, Jafferany M, Carniciu S, Abdelmaksoud A. Psychodermatology of acne: psychological aspects and effects of acne vulgaris. *Journal of cosmetic dermatology*. 2021;20(4):1080-3 <https://doi.org/10.1111/jocd.13765>.
- [3] Shields A, Nock MR, Ly S, Manjaly P, Mostaghimi A, Barbieri JS. Evaluation of stigma toward individuals with acne. *JAMA dermatology*. 2024;160(1):93-8 <https://doi.org/10.1001/jamadermatol.2023.4487>.
- [4] Kontzias C, Zaino M, Feldman SR. Tretinoin 0.1% and benzoyl peroxide 3% cream for the treatment of facial acne vulgaris. *Annals of Pharmacotherapy*. 2023;57(9):1088-93 <https://doi.org/10.1177/10600280221147338>.
- [5] Karadag A, Aslan Kayiran M, Wu CY, Chen W, Parish L. Antibiotic resistance in acne: changes, consequences and concerns. *Journal of the European Academy of Dermatology and Venerology*. 2021;35(1):73-8 <https://doi.org/10.1111/jdv.16686>.
- [6] Tan NKW, Tang A, MacAlevey NCYL, Tan BKJ, Oon HH. Risk of suicide and psychiatric disorders among isotretinoin users: a meta-analysis. *JAMA dermatology*. 2024;160(1):54-62 doi:10.1001/jamadermatol.2023.4579.
- [7] Cruz S, Vecerek N, Elbuluk N. Targeting inflammation in acne: current treatments and future prospects. *American journal of clinical dermatology*. 2023;24(5):681-94 <https://doi.org/10.1007/s40257-023-00789-1>.
- [8] Hrnčir M, Maia-Silva C, da Silva Teixeira-Souza VH, Imperatriz-Fonseca VL. Stingless bees and their adaptations to extreme environments. *Journal of Comparative Physiology A*. 2019;205(3):415-26 <https://doi.org/10.1007/s00359-019-1327-3>.
- [9] Gomes KO, Messias da Silva LCF, Dos Santos RD, Prado BA, da Silva Montes P, Silva Rodrigues LF, et al. Chemical characterization and antibacterial activities of Brazilian propolis extracts from *Apis mellifera* bees and stingless bees (*Meliponini*). *Plos one*. 2024;19(7):e0307289 <https://doi.org/10.1371/journal.pone>.
- [10] Zulhendri F, Perera CO, Chandrasekaran K, Ghosh A, Tandean S, Abdulah R, et al. Propolis of stingless bees for the development of novel functional food and nutraceutical ingredients: A systematic scoping review of the experimental evidence. *Journal of Functional Foods*. 2022;88:104902 <https://doi.org/10.1016/j.jff.2021>.
- [11] Ismail MM, Ismail WIW, editors. Development of stingless beekeeping projects in Malaysia. E3S web of conferences; 2018: EDP Sciences.
- [12] BERNAMA. MOA launches National Kelulut Honey Industry Development Plan for 2020–2030. BERNAMA. 2019: <https://www.bernama.com/en/news.php?id=1795035>.
- [13] Santer M, Burden-Teh E, Ravenscroft J. Managing acne vulgaris: an update. *Drug and Therapeutics Bulletin*. 2024;62(1):6-10 <https://doi.org/1136/dtb.2023.000051>.
- [14] Rozman AS, Hashim N, Maringgal B, Abdan K. A comprehensive review of stingless bee products: Phytochemical composition and beneficial properties of honey, propolis, and pollen. *Applied Sciences*. 2022;12(13):6370 <https://doi.org/10.3390/app12136370>.
- [15] Arung ET, Kusuma IW, Paramita S, Amen Y, Kim Y-U, Naibaho NM, et al. Antioxidant, anti-inflammatory and anti-acne activities of stingless bee (*Tetragonula biroi*) propolis. *Fitoterapia*. 2023;164:105375 <https://doi.org/10.1016/j.fitote.2022>.
- [16] Wattanuruk D, Matintarangson N. Antioxidant and Anti-acne Activities of Stingless Bee Honey and Propolis Extract. *Journal of Food Health and Bioenvironmental Science*. 2024;17(1).
- [17] Rusman R, Arung E, editors. Phytochemical and Bioactivity of Propolis Extracts Produced by Stingless Bee *Heterotrigona itama* from Two Cultivation Locations. IOP Conference Series: Earth and Environmental Science; 2023: IOP Publishing.
- [18] Barboza JR, Pereira FAN, Fernandes RA, Vasconcelos CC, Cartágenes MdSdS, Oliveira Lopes AJ, et al. Cytotoxicity and Pro-Apoptotic, Antioxidant and Anti-Inflammatory Activities of Geopropolis Produced by the Stingless Bee *Melipona fasciculata* Smith. *Biology*. 2020;9(9):292 <https://doi.org/10.3390/biology9090292>.
- [19] Mohammadi M. Cutibacterium acnes bacteriophage therapy: exploring a new frontier in acne vulgaris treatment. *Archives of Dermatological Research*. 2025;317(1):1-12 <https://doi.org/10.1007/s00403-024-3585-x>.
- [20] Vadillo-Rodríguez V, Cavagnola MA, Pérez-Giraldo C, Fernández-Calderón MC. A physico-chemical study of the interaction of ethanolic extracts of propolis with bacterial cells. *Colloids and Surfaces B: Biointerfaces*. 2021;200:111571 <https://doi.org/10.1016/j.colsurfb.2021>.
- [21] Donadio G, Mensitieri F, Santoro V, Parisi V, Bellone ML, De Tommasi N, et al. Interactions with microbial proteins driving the antibacterial activity of flavonoids. *Pharmaceutics*. 2021;13(5):660 <https://doi.org/10.3390/pharmaceutics13050660>.
- [22] Huang L, Yang S, Yu X, Fang F, Zhu L, Wang L, et al. Association of different cell types and inflammation in early acne vulgaris. *Frontiers in Immunology*. 2024;15:1275269 <https://doi.org/10.3389/fimmu.2024>.
- [23] Xu W, Lu H, Yuan Y, Deng Z, Zheng L, Li H. The antioxidant and anti-inflammatory effects of flavonoids from propolis via Nrf2 and NF-κB pathways. *Foods*. 2022;11(16):2439 <https://doi.org/10.3390/foods11162439>.
- [24] Ferreira JC, Reis MB, Coelho GD, Gastaldello GH, Peti APF, Rodrigues DM, et al. Baccharin and p-coumaric acid from green propolis mitigate inflammation by modulating the production of cytokines and eicosanoids. *Journal of ethnopharmacology*. 2021;278:114255 <https://doi.org/10.1016/j.jep.2021>.
- [25] Almeida-Junior S, de Oliveira KRP, Marques LP, Martins JG, Ubéda H, Santos MFC, et al. In vivo anti-inflammatory activity of Baccharin from Brazilian green propolis. *Fitoterapia*. 2024;175:105975 <https://doi.org/10.1016/j.fitote.2024>.
- [26] Zhang W, Cai Y, Chen X, Ji T, Sun L. Optimized extraction based on the terpenoids of *Heterotrigona itama* propolis and their antioxidative and anti-inflammatory activities. *Journal of Food Biochemistry*. 2020;44(8):e13296 <https://doi.org/10.1111/jfbc>.

- [27] Parichatikanond W, Mangmool S, Chewchinda S, Hirunpanich V, Vongsak B. Anti-inflammatory activity of propolis extract from the stingless bee, *Tetragonula pagdeni*, in mangosteen orchard. The Thai Journal of Pharmaceutical Sciences. 2024;47(3):6 <https://doi.org/10.56808/3027-7922.2832>.
- [28] Campos JF, Santos UPd, Rocha PdSd, Damião MJ, Balestieri JBP, Cardoso CAL, et al. Antimicrobial, antioxidant, anti-inflammatory, and cytotoxic activities of propolis from the stingless bee *Tetragonisca fiebrigi* (Jatai). Evidence-based Complementary and Alternative Medicine. 2015;2015(1):296186 <https://doi.org/10.1155/2015/>.
- [29] Santos HFd, Campos JF, Santos CMd, Balestieri JBP, Silva DB, Carollo CA, et al. Chemical profile and antioxidant, anti-inflammatory, antimutagenic and antimicrobial activities of geopropolis from the stingless bee *Melipona orbignyi*. International journal of molecular sciences. 2017;18(5):953 <https://doi.org/10.3390/ijms18050953>.
- [30] Calimag KPD, Arbis CCH, Collantes TMA, Bariuan JV, Ang MJC, Cervancia CA, et al. Attenuation of carrageenan-induced hind paw edema and plasma TNF- $\alpha$  level by Philippine stingless bee (*Tetragonula biroi* Friese) propolis. Experimental Animals. 2021;70(2):185-93 <https://doi.org/10.1538/expanim.20-0118>.
- [31] Popa GL, Mitran CI, Mitran MI, Tampa M, Matei C, Popa MI, et al. Markers of oxidative stress in patients with acne: A literature review. Life. 2023;13(7):1433 <https://doi.org/10.3390/life13071433>.
- [32] Michalak M. Plant-derived antioxidants: Significance in skin health and the ageing process. International journal of molecular sciences. 2022;23(2):585 <https://doi.org/10.3390/ijms23020585>.
- [33] Tolay MM, Sacchetto J, Massad WA, Airaghi FL, González M, Natera JE. Yungas propolis in the scavenging of vitamin B2-photogenerated ROS. Journal of Photochemistry and Photobiology A: Chemistry. 2024;452:115611 <https://doi.org/10.1016/j.jphotochem.2024>.
- [34] Asem N, Abdul Gapar NA, Abd Hapit NH, Omar EA. Correlation between total phenolic and flavonoid contents with antioxidant activity of Malaysian stingless bee propolis extract. Journal of Apicultural Research. 2020;59(4):437-42 <https://doi.org/10.1080/00218839.2019.1684050>.
- [35] Kasote DM, Pawar MV, Gundu SS, Bhatia R, Nandre VS, Jagtap SD, et al. Chemical profiling, antioxidant, and antimicrobial activities of Indian stingless bees propolis samples. Journal of Apicultural Research. 2019;58(4):617-25 <https://doi.org/10.1080/00218839.2019.1584960>.
- [36] Bae IA, Ha JW, Choi JY, Boo YC. Antioxidant effects of Korean propolis in HaCaT keratinocytes exposed to particulate matter 10. Antioxidants. 2022;11(4):781 <https://doi.org/10.3390/antiox11040781>.
- [37] Syed Salleh SNA, Mohd Hanapiah NA, Ahmad H, Wan Johari WL, Osman NH, Mamat MR. Determination of total phenolics, flavonoids, and antioxidant activity and GC-MS analysis of Malaysian stingless bee propolis water extracts. Scientifica. 2021;2021 <https://doi.org/10.1155/2021/3789351>.
- [38] Abdullah NA, Zulkiflee N, Zaini SNZ, Taha H, Hashim F, Usman A. Phytochemicals, mineral contents, antioxidants, and antimicrobial activities of propolis produced by Brunei stingless bees *Geniotrigona thoracica*, *Heterotrigona itama*, and *Tetrigona binghami*. Saudi Journal of Biological Sciences. 2020;27(11):2902-11 <https://doi.org/10.1016/j.sjbs.2020.09.014>.
- [39] Pazin WM, Monaco LdM, Egea Soares AE, Miguel FG, Berretta AA, Ito AS. Antioxidant activities of three stingless bee propolis and green propolis types. Journal of Apicultural Research. 2017;56(1):40-9 <https://doi.org/10.1080/00218839.2016.1263496>.
- [40] Borges MG, Lima L, Veras AC, Ferreira R, Alves D, Medeiros I, et al. Cytotoxicity and Biological Activities of Geopropolis Extract from the Stingless Bee (*Melipona scutellaris*) in Clinical Isolates of *Staphylococcus aureus*. Chemistry & Biodiversity. 2024:e202301982 <https://doi.org/10.1002/cbdv>.
- [41] Dewi JK, Toruan VML, Paramita S, Arung ET. A Dermatological Safety Test of a Face Serum Formulation Derived from Honey and Propolis of Stingless Bee from East Kalimantan. International Journal of Multidisciplinary: Applied Business and Education Research. 2024;5(3):748-54 <https://doi.org/10.11594/ijmaber.05.03.01>.
- [42] Nyman G, Wagner SO, Prystupa-Chalkidis K, Ryberg K, Hagvall L. Contact allergy in western Sweden to propolis of four different origins. Acta Dermato-Venereologica. 2020;100(16):1-5 <https://doi.org/10.2340/00015555-3615>.
- [43] Nyman GS, Giménez-Arnau AM, Grigaitienė J, Malinauskienė L, Paulsen E, Hagvall L. Patch testing with propolis of different geographical origins in a baseline series. Acta Dermato-Venereologica. 2021;101(11):1-5 <https://doi.org/10.2340/actadv.v101.423>.
- [44] Kwong HL, Lim SPR. Prevalence of propolis allergy in Singapore. JAAD international. 2020;1(1):39-41 <https://doi.org/10.1016/j.jdin.2020.04.001>.
- [45] Liew KY, Kamise NI, Ong HM, Aw Yong PY, Islam F, Tan JW, et al. Anti-allergic properties of propolis: Evidence from preclinical and clinical studies. Frontiers in Pharmacology. 2022;12:785371 <https://doi.org/10.3389/fphar.2021>.
- [46] Salleh SNAS, Hanapiah NAM, Johari WLW, Ahmad H, Osman NH. Analysis of bioactive compounds and chemical composition of Malaysian stingless bee propolis water extracts. Saudi journal of biological sciences. 2021;28(12):6705-10 <https://doi.org/10.1016/j.sjbs.2021.07.049>.