Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

*Review*
**Volume 13, Issue 4, 2023, 326**
https://doi.org/10.33263/BRIAC134.326

# Bioactivity of *Heterotrigona itama* Propolis as Anti-Inflammatory: A Review

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Scopus Author ID 56516976300
**Received: 17.05.2022; Accepted: 21.06.2022; Published: 11.09.2022**

**Abstract:** Chronic inflammation is common in infectious diseases, rheumatoid arthritis, gout, and autoimmune diseases. Several pharmaceutical therapies are readily available. However, using non-steroidal anti-inflammatory drugs (NSAIDs) is accompanied by dangerous side effects. Therefore, searching for safer alternative therapies with no side effects is very important. Currently, natural sources of kelulut bee (*Heterotrigona itama*) propolis have not been fully utilized for treatment, especially for inflammation. This study aims to study the bioactivity of kelulut bee propolis *H. itama* as an anti-inflammatory. The literature review was used as a method by searching related journals using Google Scholar, PubMed, Scopus, and Garuda. Based on the study's results, it was found that *H. itama* propolis has the potential to suppress inflammation through the inhibition of free radicals and decrease COX-2. The compounds that have the potential to have this activity are influenced by the resin source collected by the kelulut bees. This information can be used as a reference for developing natural ingredients from propolis for anti-inflammatory properties.

**Keywords:** anti-inflammatory; *Heterotrigona itama*; propolis; stingless bee.



## 1. Introduction

Inflammation is a protective response or effort made by the body to stop invading organisms; it also regulates tissue repair [1]. Inflammatory markers have consistently been altered in mood and psychotic disorders [2]. Signs of inflammation can include redness, heat, pain, and swelling. Chronic inflammation is common in infectious diseases, rheumatoid arthritis, gout, and autoimmune diseases. Inflammation can be overcome by substances that function as anti-inflammatory. [3]. Inflammation medications can relieve symptoms and slow or reduce tissue damage. Several pharmaceutical therapies are available that can be used to treat inflammation; the treatment of inflammation uses anti-inflammatory drugs that can suppress inflammation symptoms, namely non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. However, the use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids is accompanied by dangerous side effects, therefore, the search for safer alternatives by reducing side effects is very important[4].

Recently, the kelulut bee, or stingless bee product, has been significantly demanding during the pandemic [5]. *Heterotrigona itama* was popular kelulut bee species in the beekeeping business [6]. The beekeeper only focuses on their honey. Natural medicine from

this bee product, especially propolis still in limited use. Although, there have been many studies related to the pharmacological properties of their propolis, such as antioxidant, antibacterial, antifungal, and anti-inflammation. Propolis source is the combination of salivary secretions of bees, the resinous substance of plants, beeswax, and use as hive protection [7–9]. It is mainly composed of resins, waxes, essential oils, and pollen [10]. Moreover, propolis's phenolic acid ester and flavonoid aglycones have antibacterial, antifungal, and antiviral activities [11].

The information about the potency *H. itama* propolis as an anti-inflammatory has not been fully utilized for treatment. This study aims to present a comprehensive review of the potential bioactivity of *H. itama* propolis as an anti-inflammatory agent.

## 2. Materials and Methods

Specific information from the journal database (DOAJ, Elsevier, Google Scholar, Science Direct, Scopus, and PubMed) was collected to do this comprehensive review. The range of source articles was from 2010 to 2022, with some important additional information before 2010 also collected. Stingless bee, *Heterotrigona itama*, propolis, phytochemical, compound, anti-inflammatory, and bioactivity was used as finding keywords.

## 3. Results and Discussion

### *3.1. Heterotrigona itama propolis characterization.*

*Heterotrigona itama* is a stingless bee species that can be easily found in forests and is used in apiary [12]. The body size of this bee is small, then possible to collect the unique type of food resource from the plant. *H. itama* was stingless bee species from the Meliponini family [13]. Stingless bees live together in nests as eusocial insects. In Indonesia, several local names were used for this species, such as teuwel (Sundanese), galo-galo (Minang), tannese (Central Sulawesi), and klanceng (Java) [14]. The composition of the stingless bee hive is different from other bee species. *H. itama* has the characteristics of grouping places based on their uses (Figure 1).

**Figure 1.** The hive of *Heterotrigona itama* bee.

Stingless bee hives have unique characteristics, such as their honey pot, egg placement, and hive entrance. The abundance of *H. itama* propolis was potential for product development for their bioactivities, especially as an anti-inflammatory agent.

### *3.2.Prospect bioactivity of stingless bee propolis.*

Generally, several types of stingless bees have potential bioactivity. Most of the potential contained in propolis is as an antioxidant and antibacterial (Table 1). This showed

that the main function of propolis in bee hives is to avoid entering bacteria and other animals. Its main function as an antioxidant and antibacterial also correlates with the anti-inflammatory pathway. Inflammation can be prevented or inhibited by reducing the oxidative stress that occurs due to inflammation. Bacteria can exacerbate inflammatory conditions in open wounds. Therefore, antibacterial activity also plays a role in healing inflammation.

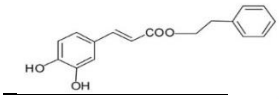
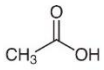
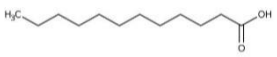
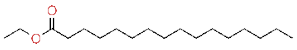
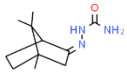
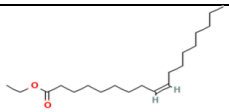
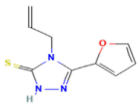
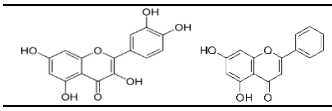
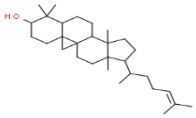
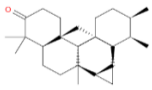
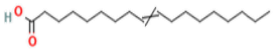
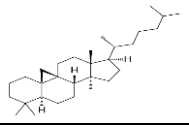
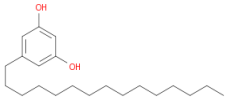
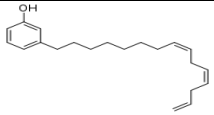
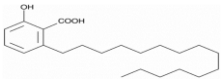
**Table 1.** Several bioactivities from stingless bee propolis extraction.

| Origin | Stingless bee species | Extract | Activity | References |
|---|---|---|---|---|
| Maranhao, Brasil | *Scaptotrigona bipunctat* | Ethanol | Antioxidant with DPPH method has decreased 50% absorbances | [15] |
| Maranhao, Brasil | *Scaptotrigona depilis* | Ethanol | Antioxidant with DPPH method has decreased 50% absorbances | [15] |
| East Kalimantan, Indonesia | *Homotrigona apicalis* | Ethanol | Antioxidant with DPPH method $IC_{50}$= 0.72 ± 0.01 mg/ml | [16] |
| East Kalimantan, Indonesia | *Wallacetrigona incisa* | Ethanol | Antioxidant with DPPH method $IC_{50}$= 42,4 ± 0.00 mg/ml | [16] |
| West Kalimantan | *Heterotrigona itama* | Ethanol | The 4 days were injected with CuSo as an emetogenic substance and showed antiemetic in 111±3.37 concentration. | [17] |
| Kelantan, malaysia | *Trigona thoracia* | Ethanol | Antileptosprial against *Leptospira inokulum* with FIC 0,38 | [18] |
| | *Scaptotrigona bipunctata* | Ethanol | Antibacterial and antifungal activity against *Staphylococcus aureus*, *Escheria coli, Aeromonas hydrophila* (>1000 MIC *); Bacilus subtilis* (62.5 MIC), *P.aeruginosa*(500 MIC) | [19] |
| | *Nannotrigona testaceicornis* | Ethanol | Antibacterial against *Staphylococcus aureus* | [20] |
| | *Trigona spinipes* | Ethanol | Antibacterial against *Staphylococcus aureus* (MIC90) | [20] |
| | *Scaptotrigona sp.* | Ethanol | Antibacterial against *Staphylococcus aureus* (MIC90) | [20] |
| | *Heterotrigona itama* | Ethanol | Antioxidant with $IC_{50}$ 30 µg/mL and the highest percentage of inhibition at 85.69% | [21] |
| | *Geniotrigona thoracica* | Ethanol | Antioxidant with $IC_{50}$ 40 µg/mL and the highest percentage of inhibition at 82.22% | [21] |
| | *Trigona apicalis* | Ethanol | Antioxidant with $IC_{50}$ 128µg/mL and the highest percentage of inhibition at 80,47% | [21] |
| | *Trigona sp* | Ethanol | Antibacterial against *Staphylococcus* mutans | [22] |
| Malaysia | *Heterotrigona itama* | Ethanol | Antioxidant with $IC_{50}$ 5 µg/mL | [23] |
| Indonesia | *Heterotrigona itama* | Ethanol | Antioxidant with $IC_{50}$ 452.52±4.88 µg/mL | [24] |
| Malaysia | *Heterotrigona itama* | Methanol | Antibacterial against *Escherichia coli and Salmonella typhi (In* 6-14 mm) | [25] |
| Malaysia | *Heterotrigona itama* | 80 % Ethanol | Antibacterial against *Esterichia Coli (In 15 mm), Salmonella enterika (In 11 mm), Bacillus subtilis (13 mm), Staphylococcus aureus (In 25 mm)* | [26] |
| Indonesia | *Trigona sp* | 70 % Ethanol | Antioxidant with $IC_{50}$ 987,24 + 4,03 µg/mL | [27] |

*3.3. Secondary metabolite of H. itama propolis.*

Several research about compounds from *H. itama* propolis has been found. Their secondary metabolite is also found and distributed in plant sources. Propolis was collected from plant resin and is specific. Table 2 shows the potential compounds found in *H.itama* propolis and plants.

**Table 2**. Compounds from *H. itama* propolis and their potential activity.

| Compounds found in *H.itama* propolis | Compound Name | Activity | Plants sources | References |
|---|---|---|---|---|
|  | Caffeic acid phenethyl ester (CAPE) | Anticancer, Antiinflmation, Antioxidant | *polyphenolic compound from plants derivation* | [28] |
|  | Acetic acid | Antioxidant, antibacterial | *Hibiscus sabdariffa* | [29] |
|  | Styrene | Antioxidant, antibacterial | *Cinnamomum* sp. | [30] |
|  | Dodecanoic acid or Lauric acid | Antioxidant, antibacterial | *Dypsis lutescens*, *Myristica fragrans*, *Durio zibethinus* | [31] |
|  | Hexadecanoic acid, ethyl ester, or ethyl palmitate | Antioxidant, antibacterial | *Vitis* sp., *Psidium guajava*, *Cucumis melo*, *Ananas comosus* | [31, 32] |
|  | Ethyl Oleate | Antioxidant, antibacterial | *Annona muricata*, *Solanum torvum* | [33, 34] |
|  | octadec-9-enoic acid or Oleic acid | Antioxidant, antibacterial | *Jatropha curcas* | [35] |
|  | 4-Allyl-5-furan-2-yl-2,4-dihydro-[1,2,4]triazole-3-thione | Antioxidant, antibacterial | *Jatropha curcas* | [35, 36] |
|  | Quercetin and Chrysin | Antioxidant, anticancer | *Uncaria gambir* | [37, 38] |
|  | 4H-Pyran-4-one, 2,3-dihydro-3,5-di-hydroxy-6-methyl- | Antioxidant, anticancer | *Kleinhovia hospita*, *Punica granatum* | [39–41] |
|  | 9,19-Cyclolanost-24-en-3-ol or cycloartenol | Antioxidant, antibacterial | *Artocarpus* sp., *Garcinia* sp. | [42–44] |
|  | 13,27- Cycloursan-3-one | Antioxidant, antibacterial | *Artocarpus heterophyllus* | [45] |
|  | 9-Octadecenoic acid | Hepatoprotective, antihistaminic, antioxidant, anti-cancer | *Jatropha curcas*, *Swietenia* sp. | [46] |
|  | cycloartane | Antidiabetic, antioxidant, hepatoprotective | *Kleinhovia hospita* | [47] |
|  | Cardol | Anticancer, antibacterial | *Mangifera indica*, *Anacardium occidentale* | [48] |
|  | Cardanol | Anticancer, antibacterial | *Mangifera indica*, *Anacardium occidentale* | [48] |
|  | Anacardic acid | Antioxidant, anticancer, antibacterial | *Mangifera indica*, *Anacardium occidentale* | [48] |

Chemical studies inside *H. itama* propolis are still limited. Recent studies are still exploring the pharmacological activity, phytochemical and total phenolics at the crude extract level. Fatty acid was a dominant chemical category content in *H. itama* propolis. Other fatty

acids such as Dodecanoic acid, lauric acid, and benzyl caffeate are also found in *Trigona* sp. propolis. This compound was dispersed in a vegetable plant.

### *3.4. Anti-inflamation activities from Heterotrigona itama propolis.*

*H. itama* propolis has various bioactive compounds such as quercetin, terpenoid, fatty acid, and phenolic compound. Its correlation with anti-inflammatory is their free radical scavenging activity. Inflammation occurs, causing free radicals and damage to cells. There are several anti-inflammatory mechanisms that inhibit the cause of infection and cell disruption.

Radical Oxidative stress is chemical substance that have unpaired electrons generated by molecular oxygen. Dysregulation of ROS metabolism will lead to inflammation. The role of antioxidant compounds is very important in preventing inflammation [49]. *H. itama* propolis is rich in antioxidant compounds that can potentially prevent inflammation through ROS inhibition. This compound reacted with free radicals and captured their electron to get stable. Molecule loss was attacked with its electron and converted to a free radical, then the initiation of chain reaction disrupted living cells.

Quercetin has an inhibitory effect as eicosanoids and prostaglandins catalyzed by inflammatory enzymes response, COX-1 and 12-LOX. These mechanisms reduce nitric oxide production, interleukin-6, and nuclear factor NF-kB [50].

One of the causes of inflammation is lipopolysaccharide (LPS), an endotoxin in gram-negative bacteria. As an endotoxin related to pathogens and infections, LPS could trigger NF-B and cause inflammation. Although the *H. itama* propolis terpenoid-rich extract showed a relatively low antioxidant effect, it can inhibit inflammatory response by decreasing the inflammatory mediators iNOS, IL-1β, and IL-10, and increasing the antioxidant mediators HO-1 [51]. CAPE has potential as an anti-inflammation by arrangement in molecular targets transcription factors. Several pathways were correlated with cancer treatment targets, such as NF-κB, TNF-α, IL-6, COX-2, Nrf2, iNOS, NFAT cells, HIF-1α, and STAT pathway [52].

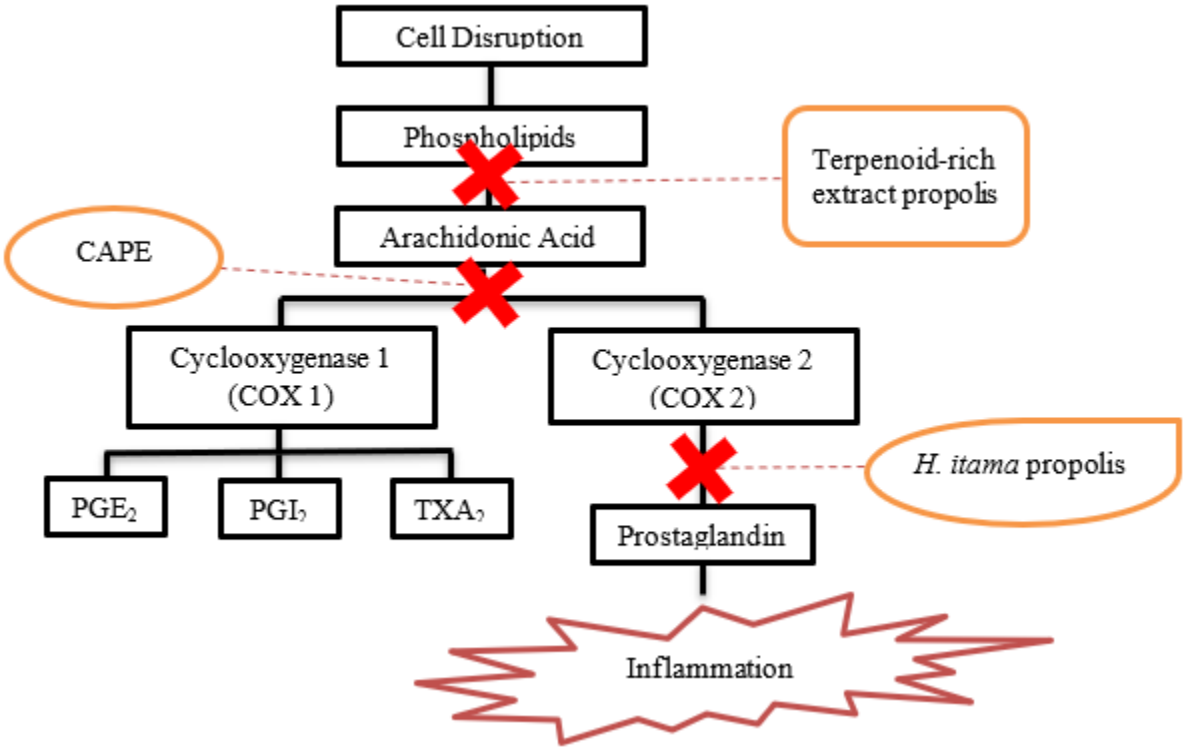



**Figure 2.** The general antiinflammatory mechanism of *Heterotrigona itama* propolis.

Furthermore, its anti-inflammatory activity also affects the healing of other diseases, such as hepatoprotective, anticancer, antivirus, and antibacterial. The 9-Octadecenoic acid was a propolis compound that has functions as hepatoprotective, antihistaminic, hypocholesterolemic, anti-eczemic, antioxidant, and anticancer properties [31].

The propolis extract has contributed to inhibiting lipid peroxidation and activated endogenous antioxidant enzymes. Hexadecanoic acid, a major compound from *H. itama* propolis, origin from Malaysia and reported cell infiltration on a cardioprotective mechanism [53]. Generally, the anti-inflammatory mechanism of *H. itama* propolis focuses on the inhibition signaling pathway by decreasing the inflammatory mediators, inhibiting ROS in the formation of arachidonic acid, and decreasing COX-2 (Figure 2).

### *3.4. Prospective product development from stingless bee propolis.*

Stingless bee propolis has the potential to be developed as several products. This stingless bee propolis product has been reported and showed impressive bioactivity (Table 3). Most of them are used as cosmetic properties. Modification of propolis products is aimed to increase its absorption [54]. These findings can be used as a reference in developing further propolis products.

**Table 3.** Product development from stingless bee propolis.

| Origin | Product | Bioactivity | References |
|---|---|---|---|
| Indonesia | Nanoparticles | 0,02 - 10 % concentration have antibacterial against *E.coli* | [55] |
| Bandung | Paste | The stability of this product for antibacterial activity showed good performance | [56] |
| Indonesia | Edible coating | 5% w/v concentration had stable performance to preserved bananas after post-harvest | [57] |
| South Sulawesi | Gel | This product has antibacterial activity against Porphyromonas gingivalis with diffusion assay (6.17±0.48 mm) | [58] |
| Indonesia | Gel mask | This product has antibacterial activity against *P.acne* bacteria and antioxidant activity | [59] |
| Indonesia | Capsule | DPPH assay showed that this capsule has antioxidant with $IC_{50}$ 691±24.04 ppm | [60] |

## 4. Conclusions

Based on the results of the study, it was found that *Heterotriogona itama* propolis has the potential to suppress inflammation by inhibiting free radicals and decreasing COX-2. Compounds that have the potential to have this activity are influenced by the resin source collected by the kelulut bees. The bioactive compounds from *H. itama* propolis have potential as an anti-inflammatory agent and can be developed as a functional product.

## Funding

This research received no external funding.

## Acknowledgments

The authors would like to thank the Research and Community Development Center, Universitas Muhammadiyah Kalimantan Timur, for their support.

## Conflicts of Interest

The authors declare no conflict of interest

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