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Medicinal activities of Tualang honey: a systematic review

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Abstract

Natural products derived from various sources, including plants, have garnered significant interest as alternative therapeutic options. Among these, Tualang honey, extracted from the nectar of Tualang trees (*Koompassia excelsa* (Becc.) Taub.), has a long history of traditional use due to its therapeutic properties. This review aims to examine the pharmacological activities of Tualang honey, encompassing both in vitro and in vivo studies. A systematic search was conducted in multiple databases, including PubMed, Springer, Scopus, Wiley, and Science Direct, up until December 2022 to identify relevant studies on the pharmacological activities of Tualang honey. Two independent reviewers were involved in article selection, followed by data extraction and assessment of methodological quality using Syrcle's risk of bias tool. 123 articles were included, collectively describing the pharmacological activities of Tualang honey, including antimicrobial, anticancer, anti-inflammatory, antioxidant, antinociceptive, neuroprotective effects, and others. Tualang honey has significant promise as an alternative treatment option for treating a wide range of pathological diseases due to its wide range of pharmacological properties. Tualang honey's diverse array of pharmacological actions indicates its potential for multiple medicinal uses.

Keywords Natural products, Tualang honey, Systematic review, Pharmacological activities, Therapeutic properties

Background

In recent years, there has been a surge of interest in the medicinal properties of natural products, particularly those derived from plants. Honey has emerged as a subject of scientific investigation due to the growing demand for safe alternatives in healthcare and the potential to treat various ailments and improve overall health [1]. The traditional use of honey has been passed down verbally from generation to generation, prompting researchers to investigate its therapeutic potential. Thus, various scientific studies have been done to validate community beliefs regarding the therapeutic properties of honey.

Tualang honey (TH), an indigenous multifloral jungle honey from Malaysia, has lately garnered a lot of research attention in scientific circles [2]. TH is produced by the rock bee *Apis dorsata*, which builds its colonies high up in the branches of the tall Tualang tree (*Koompassia excelsa* (Becc.) Taub.) [3]. These tall trees, which may reach heights of up to 250 feet, are mostly found in Malaysia's tropical rainforests, especially in the northeastern area, such as the state of Kedah [2].

In recent years, scientific interest in TH has surged, with numerous studies exploring its pharmacological effects and potential therapeutic applications. The exploration of TH has revealed a remarkable diversity of bioactive compounds, including flavonoids, phenolics, vitamins, and minerals [3–5]. These natural constituents

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are believed to contribute to its wide range of pharmacological properties.

Despite the growing number of research on TH, a comprehensive and systematic evaluation of its pharmacological effects is still absent. Therefore, the purpose of this study is to bridge this essential information gap by conducting an in-depth examination of the existing literature on the pharmacological effects of TH, which will provide significant insights into its possible therapeutic applications. We seek to increase scientific knowledge and stimulate further research in this potential field through analysis of the current data. The relevance of this study lies in supporting the implementation of evidence-based medical practices and encouraging the development of natural therapies. By synthesizing and critically assessing existing research, this review seeks to provide a thorough understanding of Tualang honey's pharmacological effects and potential therapeutic applications. This is particularly significant given the increasing global interest in natural and alternative medicines and the demand for safe, effective treatments for various health conditions. Additionally, the insights gained from this review may guide future research and clinical applications, contributing to the advancement of healthcare by incorporating natural products like TH into contemporary therapeutic strategies. This review might lead to the development of natural products with therapeutic potential based on Tualang honey's immense potential in improving human health.

Methodology

Search strategy

A systematic review was conducted to examine the pharmacological effects of Tualang honey. A comprehensive search was conducted in major selected databases, including PubMed, ScienceDirect, SpringerLink, Scopus, and Wiley. The search spanned a 12-year period from 2010 to 2022. The search terms utilized Boolean operators with keywords "Tualang honey" OR "madu tualang" without any imposed restrictions or limitations. The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria, which provide guidelines for conducting and reporting systematic reviews. Following the PRISMA 2020 Statement, a flow diagram was created using an online tool to visually represent the selection process of included studies and ensure transparency in the review methodology [6].

Study selection

Two independent reviewers performed the study selection process in two stages: title/abstract screening and full-text assessment. During the title/abstract screening, the reviewers assessed the eligibility of each article based on the predetermined inclusion and exclusion criteria. In case of uncertainty or disagreement, the article proceeded to the full-text assessment stage. The full texts of potentially eligible articles were obtained and assessed against the inclusion and exclusion criteria. Any disagreements between the reviewers were resolved through discussion or consultation with a third reviewer.

Inclusion criteria

The inclusion criteria for this systematic review were established based on the PICO framework, representing Population, Intervention, Comparison, and Outcome. We included studies that investigated the pharmacological activities (outcome) of Tualang honey (intervention), across various settings including in vitro, in vivo, and clinical trials (population). Comparisons were not required for inclusion, but studies must have evaluated the therapeutic potential of Tualang honey. Only English-language studies published between January 2010 and December 2022 were considered.

Exclusion criteria

Studies that deviated from the primary focus on Tualang honey were excluded. Additionally, studies that did not assess pharmacological activities were not considered for inclusion, ensuring that the selected studies aligned with the research objective. Studies published in languages other than English were excluded to maintain consistency and facilitate analysis. Moreover, conference abstracts, editorials, commentaries, and letters were not included to maintain the integrity of the review.

Data extraction

Data extraction was performed using a standardized form designed to capture essential information from the selected studies. Data extracted from the studies included: study characteristics (authors, year of publication, study design), experimental details (dosage and duration of Tualang honey treatment, comparators, and methodology), the pharmacological activities assessed, and the outcomes reported.

Data synthesis

The synthesis of data followed the guidelines set forth in the Cochrane Handbook for systematic reviews and the SWIM (Synthesis Without Meta-Analysis) guidelines. Given the heterogeneity among the included studies, a narrative synthesis approach was utilized to aggregate and summarize findings, rather than conducting a meta-analysis. Studies were categorized by the pharmacological effects—antioxidant, anti-inflammatory, anticancer, neuroprotective, and wound healing effects—and analyzed

qualitatively. Emphasis was placed on the consistency of findings across in vitro, in vivo, and clinical studies, with studies featuring robust designs or consistent outcomes receiving more weight. This approach allowed for a comprehensive understanding of the pharmacological activities of Tualang honey while acknowledging the study variability.

Risk of bias

The risk of bias assessment was conducted by two independent reviewers, with any discrepancies resolved through consensus with a third reviewer. The Cochrane Risk of Bias (RoB) tool was employed to evaluate the risk of bias in randomized clinical trials [7]. The risk of bias assessment for animal studies followed the SYstematic Review Centre for Laboratory Animal Experimentation (SYRCLES) tool, which evaluates multiple domains, including selection bias, detection bias, attrition bias, reporting bias, and other potential sources of bias [8]. In vitro studies were assessed using a modified version of the SYRCLES tool with an exclusion of an item related to random housing of animals [9]. Each study underwent a comprehensive assessment for risk of bias, with "yes" indicating low risk, "no" indicating high risk, and "unclear" representing an unclear risk [8].

Results

Search results and study characteristics

A comprehensive electronic search of PubMed ($n=82$), SpringerLink ($n=123$), Wiley ($n=46$), ScienceDirect ($n=157$), and Scopus ($n=160$) databases yielded a total of 568 studies. Subsequently, 16 duplicate articles were excluded from the analysis. Following careful evaluation of titles, abstracts, and full texts, 123 studies met the pre-established eligibility criteria. The selection process is depicted in Fig. 1. Among the included studies, a total of 64 were in vivo studies, providing insights from animal models. Additionally, 38 studies were in vitro, focusing on cellular and molecular mechanisms observed in controlled laboratory settings. Furthermore, 21 studies were randomized controlled trials (RCTs), offering high-quality evidence through systematic evaluation of interventions. Notably, a significant proportion of these studies were conducted in Malaysia, highlighting the country's leading role in Tualang honey research, while only one study was conducted in Pakistan. The included articles were separated according to their pharmacological activities observed, including antioxidant (26.8%), antimicrobial (11.8%), neuroprotective effects (11.8%), anti-cancer (10.5%), anti-inflammatory (6.3%), reproductive health (6.3%), anti-nociceptive (5.6%), cardioprotective (3.5%), bone function (3.5%), wound healing (2.8%), anxiolytic and antidepressant (2.1%), effects on respiratory system (1.4%), and other pharmacological activities (8.5%).

Risk of bias

The risk of bias assessment for the included animal studies is summarized in Fig. 2. In the systematic review, the majority of the included studies reported employing random allocation of animals to different groups or interventions. However, it is important to note that none of these studies provided adequate information regarding the specific method used for randomization. The baseline characteristics of the animals, such as age, gender, and weight, were reported in all of the studies. On the other hand, the random housing was more comprehensive in the included studies, which was associated with a low risk of bias, indicating that efforts were made to ensure comparability and unbiased assignment of animals to their respective groups. In terms of blinding of investigators and detection bias, which includes random outcome assessment and blinding of outcome assessment, the majority of the studies included in this review were rated as having an unclear risk of bias. This suggests insufficient reporting on these critical aspects in the reviewed studies, and no studies explicitly mentioned implementing blinding for investigators or conducting random outcome assessments. Selective outcome reporting and incomplete outcome data were generally found to have a low risk of bias in the included studies. This means the studies reported all the expected outcomes and analyzed the available data without significant missing information. The comprehensive reporting and analysis enhance the confidence in the reliability and validity of the reported results. Other types of bias are unclear as they are not reported in the included studies.

Pharmacological activities of Tualang honey

Antioxidant

Tualang honey (TH) has consistently demonstrated potent antioxidant effects across 16 in vitro, 19 in vivo, and 3 randomized controlled trials (RCTs) (Table 1). Its high phenolic (42.23–589.2 mg/kg) and flavonoid content (25.31–165.34 mg/kg) significantly surpass other honeys, enhancing its ability to neutralize free radicals and mitigate oxidative stress. Biochemical assays, such as 2,2-Diphenyl-1-picrylhydrazyl (DPPH) and ferric reducing antioxidant power (FRAP), reveal that TH exhibits superior antioxidant capacity compared to other honeys, including Gelam and Borneo, with DPPH IC50 values between 5.24 mg/mL and 7.54 mg/mL and FRAP values up to 892.15 μM Fe[II]/kg [4, 10–18]. In vitro studies have demonstrated TH's protective effects against oxidative stress. For instance, TH scavenges hydrogen peroxide (H2O2) in human corneal epithelial progenitor

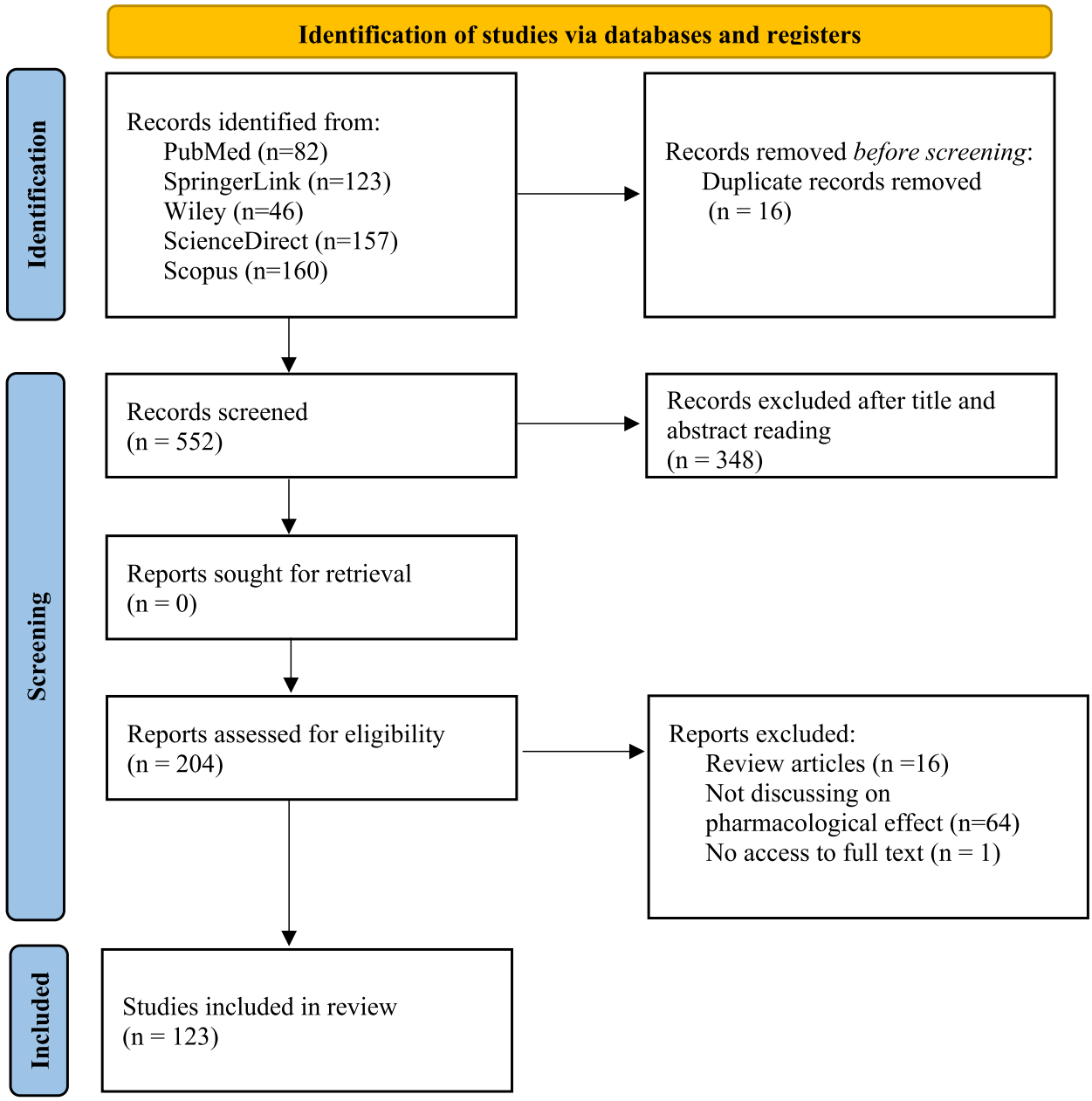

Fig. 1 Flow chart illustrating the search strategy and study selection process in accordance with the PRISMA guidelines

(HCEP) cells, improving cell viability [19]. Furthermore, gamma irradiation of TH has been shown to enhance its antioxidant properties, with higher phenolic and flavonoid content and increased FRAP values [20, 21]. More recent studies indicate that fractions of TH, such as methanolic and ethyl acetate, exhibit even stronger antioxidant activity than gamma-irradiated honey [22]. Additionally, silver nanoparticles derived from TH were shown to possess superior antioxidant activity compared to raw honey, showcasing its versatility in novel applications like nanoparticle formulations [23]. A recent study by Sulaiman et al. in 2022 discovered that the total phenolic and flavonoid content, as well as the DPPH values of Tualang honey significantly increased with higher temperatures [24].

Several in vivo studies further validated the antioxidant effects of Tualang honey. For instance, in a series of studies conducted on Sprague–Dawley streptozotocin (STZ)-diabetic rats, TH was found to significantly improve the activity of essential antioxidant enzymes,

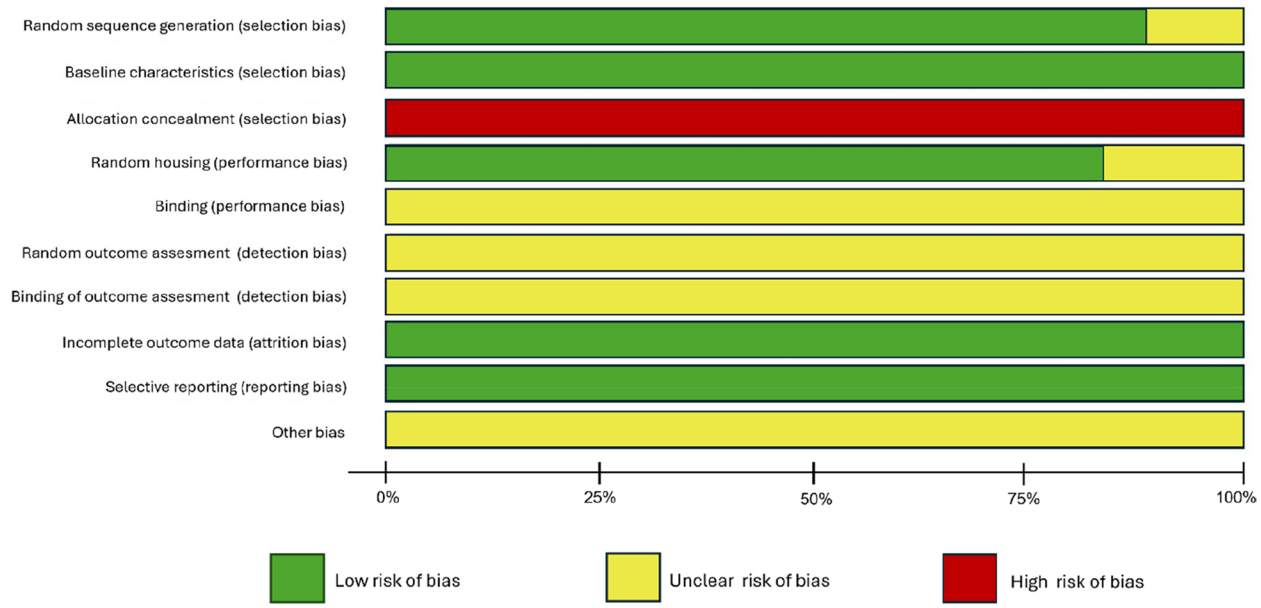

Fig. 2 The overall risk of bias (RoB) for each item assessed using the SYRCLE tool was calculated as a percentage based on all the included studies

such as superoxide dismutase (SOD) and catalase (CAT), while reducing lipid peroxidation levels as measured by malondialdehyde (MDA) [25]. Combination therapies with TH and conventional antidiabetic drugs demonstrated enhanced antioxidant activity and reduced oxidative stress markers [26, 27]. Variability in antioxidant marker effects was observed depending on the animal model used [28, 29]. Additionally, in stress-induced models, TH supplementation consistently boosted antioxidant defenses by increasing the activities of antioxidant enzymes like SOD and glutathione peroxidase (GPx) while lowering oxidative damage markers such as MDA and protein carbonyls (PCO) [30–41]. In a study conducted by Al-Rahbi in 2014, the effects of tualang treatment on Wistar albino rats with isoproterenol-induced myocardial infarction were investigated. The findings revealed that honey treatment significantly reduced lipid peroxidation levels, suggesting a decrease in oxidative damage [42]. In a study involving New Zealand white rabbits with alkali-induced injury caused by sodium hydroxide, the administration of TH did not show significant differences in antioxidant status compared to conventional treatments [43].Human studies have also supported the antioxidant potential of Tualang honey. Ahmad et al. (2017) found that both high (1.5 g/kg) and low (0.75 g/kg) doses of TH significantly increased antioxidant activity and reduced oxidative stress markers, such as MDA and ROS, in female athletes [44]. Similarly, in male collegiate athletes, a higher dose of TH incorporated into energy drinks provided greater antioxidant benefits, with stronger FRAP values and reduced ROS levels compared to a lower dose group [45]. Additionally, in a study involving smokers, daily supplementation with 20 g of TH over 12 weeks resulted in a significant reduction in oxidative stress, as indicated by decreased plasma F2-isoprostanes and increased GPx and CAT activities [46]. Overall, Tualang honey consistently outperforms other honeys in antioxidant efficacy, despite variability in assay types and control conditions. This robust body of evidence underscores its value as a natural agent for mitigating oxidative stress and related disorders.

Antimicrobial

The antimicrobial properties of Tualang honey have been validated in several studies. Research has demonstrated its effectiveness against a wide range of microorganisms, including bacteria, fungi, and viruses. Table 2 summarizes the antimicrobial activities of Tualang honey. The antibacterial effects of Tualang honey have been consistently demonstrated against a wide range of pathogens. Across multiple studies, Tualang honey exhibited strong antibacterial activity, particularly against Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Escherichia coli* [47–49]. The combination of Tualang honey with conventional antibiotics, such as gentamicin, often led to enhanced effects, indicating potential synergistic properties [48]. These findings suggest that Tualang honey could serve as an adjunct treatment in infections where antibiotic resistance is a concern..The effectiveness of Tualang honey against Gram-positive bacteria, however, appears to be less consistent. Some studies reported lower efficacy compared to silver-based dressings or

Table 1 Antioxidant properties of Tualang honey included in the systematic review

No	Experimental model	Dose/ concentration AND duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
1	In vitro	-	Phenolic and flavonoids content, FRAP assay, DPPH assay	Comparator: Gelam honey, Borneo tropical honey, Honey "B" (supermarket Malaysian honey) Positive control: N/A Adjuvant: N/A	• TH exhibited the highest levels of phenolic and flavonoid compounds, measuring 42.23 ± 0.64 mg/kg and 25.31 ± 0.37 mg/kg, respectively • TH demonstrated the lowest IC50 value of 5.24 ± 0.40 mg/mL, indicating its strong DPPH radicalscavenging activity • TH contained the highest concentration of total antioxidants, with a range of 892.15 ± 4.97 µM Fe[II]/kg	[4]
2	In vitro	-	Phenolic content, DPPH assay, FRAP assay	Comparator: N/A Positive control: N/A Adjuvant: N/A	• Total phenolic content of 251.7 ± 7.9 mg gallic acid/kg honey • Total antioxidant activity of 322.1 ± 9.7 µM Fe(II) • Antiradical activity of 41.30 ± 0.78% inhibition	[10]
3	In vitro	-	Phenolic content, FRAP assay, DPPH assay	Comparator: Gelam honey, pineapple and Indian forest honey Positive control: N/A Adjuvant: N/A	• Significant peroxynitrite and superoxide anion scavenging abilities, with IC50 values of 9.10 ± 0.45 mg/mL and 7.54 mg/mL, respectively • The phenolic content of Tualang honey was significantly elevated at 83.96 ± 4.53 mg gallic acid equivalents per 100 g • TH displayed a greater antioxidant capacity, as measured by FRAP and DPPH assay with a value of 53.06 ± 0.41 mg ascorbic acid equivalents per gram	[11]

Table 1 (continued)

No	Experimental model	Dose/ concentration AND duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
4	In vitro	-	Phenolic and flavonoids content, FRAP assay, DPPH assay	Comparator: Borneo tropical honey Positive control: N/A Adjuvant: N/A	• The polyphenol and flavonoid contents of the analyzed Tualang honey samples varied between 305.47 and 419.86 mg/kg, and 135.29 and 165.34 mg/kg, respectively • The DPPH radical-scavenging activity ranged from 28.48% to 36.94% • The total antioxidant activity measured ranged from 273.46 to 292.34 µM Fe(II)/kg	[12]
5	In vitro	1.0 g/kg	Phenolic and flavonoids content, FRAP assay, DPPH assay, AEAC assay	**Comparator:** Acacia honey, pineapple honey, borneo honey **Positive control:** N/A **Adjuvant:** N/A	TH exhibited the highest concentration of phenolic compounds (352.73 ± 0.81 mg galic acid/kg), flavonoids (65.65 ± 0.74 mg catechin/kg), DPPH radical scavenging activity (59.89%), FRAP values (576.91 ± 0.64 µM Fe (II)/100 g) and displayed the lowest AEAC values (244.10 ± 5.24 mg/kg)	[13]
6	In vitro	-	Phenolic and flavonoids content, DPPH assay	**Comparator:** European honey and Siddar honey **Positive control:** N/A **Adjuvant:** N/A	TH exhibited the highest concentration of phenolic compounds (460.260 ± 4.552 mg galic acid/kg), flavonoids (46.519 ± 3.80 catechin/kg)	[14]
7	In vitro	-	Phenolic content	**Comparator:** Gelam honey, pineapple and Borneo, Kelulut honey **Positive control:** N/A **Adjuvant:** N/A	The total phenolic contents of the Tualang honey was 589.2 mg GAE/kg	[15]
8	In vitro	-	Phenolic content, DPPH, ABTS, and ORAC assay	**Comparator:** Kelulut honey **Positive control:** N/A **Adjuvant:** N/A	• The mean phenolic content of TH ranged from 130 to 180 mg GAE/kg • TH have exhibited scavenging activity with a value of 70% and at concentration of 40 mg/ml • The ABTS value ranged from 45.89 ± 4.37 to 219.36 ± 24.3 • The ORAC value ranged from 22.28 ± 0.4 to 75.47 ± 2.5 (µmoles TE/g)	[16]

Table 1 (continued)

No	Experimental model	Dose/ concentration AND duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
9	In vitro	–	Phenolic content, DPPH assay	**Comparator:** Kelulut and Akasia honey **Positive control:** N/A **Adjuvant:** N/A	TH recorded significantly higher value of DPPH radical scavenging activity (69.3%), and total phenolic content (1284.5 mgGAE/kg)	[17]
10	In vitro	-	Flavonoid content and DPPH assay	**Comparator:** tualang, gelam, acacia, and pineapple and kelulut honey **Positive control:** N/A **Adjuvant:** N/A	Total flavonoid content value of TH is 0.07 ± 0.74 µg catechin equivalent/mg. TH showed DPPH value of IC50 = 182.56 mg/mL	[18]
11	In vitro (HCEP cells)	0.004—4% (48 h)	Oxidative stress assay	**Comparator:** N/A **Positive control:** Ascorbic acid **Adjuvant:** N/A	TH possesses the ability to scavenge hydrogen peroxide (H_2O_2) with improved HCEP viability when subjected to H2O2	[19]
12	In vitro	-	Phenolic and flavonoids content, DPPH assay	**Comparator:** TH samples exposed to different storage condition (gamma irradiation, evaporation, container and temperature) **Positive control:** gallic acid **Adjuvant:** N/A	• The mean concentrations of polyphenols, flavonoids and DPPH radical-scavenging activities in the gamma-irradiated honey samples were higher compared to the non-gammairradiated samples • All honey samples exposed to gamma irradiation showed increased antioxidant potential, while evaporation and temperature changes had little impact on their antioxidant properties	[20]

Table 1 (continued)

No	Experimental model	Dose/ concentration AND duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
13	In vitro	-	FRAP assay, color intensity and AEAC assay	**Comparator:** Different honey processing parameters (temperature, light, gamma irradiation, evaporation and sachet packaging) **Positive control:** gallic acid **Adjuvant:** N/A	• Irradiated TH showed darker colour with higher absorbance values (303.9 ± 5.1 mAU) than nonirradiated honey samples (233.0 ± 10.3 mAU) • Evaporated TH samples showed higher absorbance values (277.6 ± 5.6) than nonevaporated honey samples (228.7 ± 14.3) • Nonevaporated and nonirradiated TH samples showed higher AEAC levels (mean AEAC 35.6 ± 1.3 mg/100 g) than the evaporated and irradiated honey samples (mean AEAC 31.4 ± 1.2 mg/100 g) • Honey samples that were subjected to evaporation and irradiation had the highest mean FRAP values (303.9 ± 5.1 µmol Fe[II]/100 g)	[21]
14	In vitro	-	Phenolic and flavonoids content, DPPH, ABTS and FRAP assay	**Comparator:** THI, MTH, EATH **Positive control:** Gallic acid, trolox **Adjuvant:** N/A	• MTH and EATH exhibited higher levels of total phenolic and flavonoid contents • Among the samples, MTH demonstrated the lowest DPPH scavenging activity, with an IC50 value of 1.42 ± 0.27, followed by EATH (3.25 ± 0.42), THI (31.13 ± 1.20), and TH (71.27 ± 2.42) • In the ABTS assay, MTH and EATH showed higher to TH, while no significant differences were observed between TH and THI samples • MTH and EATH exhibited significantly higher FRAP values compared to TH	[22]

Table 1 (continued)

No	Experimental model	Dose/ concentration AND duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
15	In vitro	0.05 – 2.0 g/ml	DPPH and FRAP assay	**Comparator:** silver nanoparticles derived from TH **Positive control:** ascorbic acid **Adjuvant:** N/A	The silver nanoparticles derived from TH exhibited remarkable antioxidant activity with DPPH and reducing antioxidant power values of 95.54 ± 0.96 (%) and 1032.30 ± 102.76 µM Fe(II), respectively which is higher than raw honey	[23]
16	In vitro	-	Phenolic and flavonoids content, DPPH assay	**Comparator:** Kelulut and Acacia honey **Positive control:** Gallic acid, quercetin **Adjuvant:** N/A	The total phenolic and flavonoids content and DPPH values increased significantly as the honey temperature increased	[24]
17	In vivo (Sprague–Dawley rats, STZ-induced diabetic)	1.0 g/kg (4 weeks)	MDA, SOD, GPx,CAT, GR and GST assay	**Comparator:** normal rats and diabetic control rats **Positive control:** N/A **Adjuvant:** N/A	• The pancreatic SOD and MDA activity was significantly reduced compared to diabetic control rats • The pancreatic CAT activity significantly increased pancreatic CAT activity compared to diabetic control rats • Treatment with TH did not affect pancreatic GPx, GST and GR activity	[25]
18	In vivo (Sprague–Dawley rats; STZ-induced diabetic)	1.0 g/kg (4 weeks)	MDA, SOD, GPx, CAT, GR and GST assay	**Comparator:** normal rats and diabetic control rats **Positive control:** Glibenclamide and metformin **Adjuvant:** Glibenclamide and metformin (combined or individually)	• Combination of glibenclamide, metformin, and honey significantly up-regulated CAT activity, down-regulated GPx activity, and reduced levels of MDA in the pancrease • Combination of glibenclamide, metformin, and honey had no effect on SOD activity in diabetic rats	[26]

Table 1 (continued)

No	Experimental model	Dose/ concentration AND duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
19	In vivo (Sprague–Dawley rats; STZ-induced diabetic)	1.0 g/kg (4 weeks)	MDA, SOD, GPx, CAT, GR and GST and TAS Assay	**Comparator:** normal rats and diabetic control rats **Positive control:** Groups receiving glibenclamide, metformin, or both **Adjuvant:** glibenclamide and metformin	• Treatment with metformin, glibenclamide, or their combination with TH resulted in significant increases in CAT, GR activities, TAS and GSH concentration in kidney of diabetic rats, when compared to diabetic control rats • It also significantly reduced SOD activity and restored the levels of MDA • Although not statistically significant, all the treatments and their combinations improved the ratio of reduced glutathione (GSH) to oxidized glutathione (GSSG)	[27]
20	In vivo (Wistar-Kyoto rats; STZ-induced diabetic and SHR rats)	1.0 g/kg (3 weeks)	MDA, SOD, GPx, CAT, GR and GST, TAS and GSH:GSSG assay	**Comparator:** Normal rats and diabetic control rats (WKY and SHR rats) **Positive control:** N/A **Adjuvant:** N/A	• Treatment with TH in diabetic WKY reduced the GR activity • Treatment with TH in diabetic SHR rats increased GR, TAS and GSH activity • Treatment with TH did not restore CAT activity, significantly restored GPx activity, reduced MDA activity and significantly increased the GSH-toGSSG ratio in both groups. The SOD and GST activities remained unchanged	[28]
21	In vivo (Wistar-Kyoto rats; SHR rats)	1.0 g/kg (12 weeks)	MDA, SOD, GPx, CAT, GR and GST and TAS Assay	**Comparator:** Normal WKY rats and SHR rats (without TH treatment) **Positive control:** N/A **Adjuvant:** N/A	• In SHR, MDA levels, TAS, CAT and GST activities was reduced with honey treatment • The levels of SOD, GPx, and GR, GSH, GSSG, and GSH/GSSG ratio were similar in the control and TH-treated WKY and SHR groups • In WKY, honey treatment resulted in significantly lower CAT activity compared to WKY control	[29]

Table 1 (continued)

No	Experimental model	Dose/ concentration AND duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
22	In vivo (Sprague–Dawley rats; stressed OVX)	0.2 g/kg (18 days)	MDA, SOD, GPx, CAT, GR and GST, TAS and PCO Assay	**Comparator:** Control rats (normal, stressed), OVX rats (normal, stressed) **Positive control:** 17βEstradiol **Adjuvant:** N/A	• TH supplementation resulted in increased activity or levels of GR, GST, and TAC, while decreasing activity or levels of CAT, PCO, and MDA, comparable to the control rats • The treated stressed OVX rats showed significantly higher levels of SOD and GPx, although still lower than those observed in the sham-operated control rats	[30]
23	In vivo (Sprague–Dawley rats; KA-induced excitotoxicity)	1.0 g/kg (2.5 days; five doses every 12 h)	MDA and TAS assay	**Comparator:** Control group (saline and KA-treated group) **Positive control:** Topiramate, aspirin **Adjuvant:** N/A	• TH pre-treatment significantly attenuated an increase of MDA level induced by KA • TH pretreatment significantly attenuated a decrease of in TAS level induced by KA	[31]
24	In vivo (Sprague–Dawley rats; prenatally stressed rats	1.2 g/kg (Day 1 of pregnancy until delivery)	MDA, GSH, CAT and SOD assay	**Comparator:** pregnant rats (with and without stress) **Positive control:** N/A **Adjuvant:** N/A	• Offspring from the TH group showed improvement in MDA, GSH and CAT activity in the spinal cord which shown by higher levels of GSH, CAT and SOD, and a lower level of MDA when compared to the stressed group	[32]
25	In vivo (Sprague–Dawley rats; formalin induced pain)	1.2 g/kg (10 days)	SOD, MDA and CAT levels	**Comparator:** Control group (normal rat) **Positive control:** Vitamin C **Adjuvant:** N/A	• The levels of SOD and CAT were significantly higher in the Tualang honey (TH) group compared to the control group, but no such increase was observed in the Vitamin C group • No significant difference in serum MDA	[33]
26	In vivo (Sprague–Dawley rats; cadmium-induced)	200 mg/kg (6 weeks)	MDA and CAT levels	**Comparator:** Normal rat **Positive control:** cadmium group **Adjuvant:** N/A	TH normalized the ovarian malondialdehyde and catalase levels in comparison with cadmium group	[34]
27	In vivo (Sprague–Dawley rats; exposed to normobaric hypoxia)	0.2 g/kg (2 weeks)	MDA, TAS, SOD,CAT and GPx assay	**Comparator:** Sucrose-treated (nonhypoxia and hypoxia) **Positive control:** N/A **Adjuvant:** N/A	A significant increase in TAS, CAT, SOD and GPx, and a decrease in MDA levels were observed especially in honey with hypoxia group compared to sucrose with hypoxia group	[35]

Table 1 (continued)

No	Experimental model	Dose/ concentration AND duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
28	In vivo (Sprague–Dawley rats; LPS-induced)	200 mg/kg (2 weeks)	MDA, SOD, GR, GPx and CAT	**Comparator:** Normal and LPS-induced rats **Positive control:** Memantine **Adjuvant:** N/A	• CAT and GPx levels were significantly higher in all treatment groups compared to the LPS group • GR and SOD levels were notably higher in the Tualang Honey (TH) and memantine groups, with GR levels specifically elevated in the TH group • MDA levels were significantly reduced in both the TH and MTH groups, but not in the memantine group, compared to the LPS group	[36]
29	In vivo (Sprague–Dawley rats; chronic stressinduced)	1 g/kg (4 weeks)	MDA and GSH:GSSG ratio assay	**Comparator:** Control and stress group (no treatment) **Positive control:** DHA-rich fish oil **Adjuvant:** TH + DHA-rich fish oil	• DHA-rich fish oil and Tualang honey both reduced stress-related increases in serum corticosterone and lipid peroxidation and boosted overall antioxidant capacity • Tualang honey specifically reduced oxidized glutathione levels and normalized the GSH/GSSG ratio • Combining DHA-rich fish oil and Tualang honey did not offer additional benefits compared to using them individually	[37]
30	In vivo (Sprague–Dawley rats; REM sleep-deprived)	1.2 g/kg (3 days)	MDA, GSH,GR, SOD and CAT assay	**Comparator:** Control and tank control groups **Positive control:** N/A **Adjuvant:** N/A	Administration of TH was associated with a significantly higher level of GSH, GR, SOD and CAT, and a significantly lower level of MDA compared to the REMsd untreated group	[38]
31	In vivo (Sprague–Dawley aged rats; exposed to loud noise stress	200 mg/kg (5 weeks)	MDA, PCO GPx, GR, CAT, and TAS assay	**Comparator:** Placebo group (stress and non-stressed) **Positive control:** N/A **Adjuvant:** N/A	Stressed rats treated with TH exhibited significantly lower levels of MDA and PCO, and significantly higher SOD activity compared to stressed control rats	[39]

Table 1 (continued)

No	Experimental model	Dose/ concentration AND duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
32	In vivo (Sprague–Dawley young and aged rats; exposed to loud noise stress	200 mg/kg (4 weeks)	MDA, PCO GPx, GR, CAT, and TAS assay	**Comparator:** Placebo group (stress and non-stressed) **Positive control:** N/A **Adjuvant:** N/A	• The stressed rats treated with TH exhibited lower levels of oxidative stress markers such as MDA and PCO • In young stressed rats, honey treatment increased the activities of antioxidant enzymes (SOD, GPx, and GR) and total antioxidant status, whereas in aged stressed rats, only SOD activity was significantly affected	[40]
33	In vivo (Sprague–Dawley rats; prenatally stressed)	1.2 g/kg (day 1 of pregnancy until delivery)	MDA, SOD and CAT assay	**Comparator:** pregnant rats (with and without stress) **Positive control:** N/A **Adjuvant:** N/A	Increase levels of CAT and SOD, and a lower level of MDA in the thalamus when compared to the stressed group	[41]
34	In vivo (Wistar albino rats; ISO-induced MI)	3 g/kg (45 days)	MDA, SOD, GPx, CAT, GR and GST, assay	**Comparator:** Normal rats **Positive control:** N/A **Adjuvant:** N/A	• TH treatment significantly reduced MDA levels • Rats pretreated with TH prior to ISO administration significantly increased the activities of GPx, GRx, and GST enzymes	[42]
35	In vivo (New Zealand white rabbits; alkali injury with NaOH)	1.0 gm/kg (1 week)	MDA and TAS assay	**Comparator:** Conventional treated groups **Positive control:** Prednisolone acetate + Ciprofloxacin + ascorbic acid **Adjuvant:** N/A	No significant difference in the levels of total antioxidant status or lipid peroxidation products in the aqueous humor, vitreous humor,, and serum between the TH-treated and conventional groups	[43]
36	Randomized control trial (Female athletes)	0.75—1.5 g/kg (Postprandial measurement over 3 hours)	Phenolic content, FRAP, MDA and ROS assay	**Comparator:** two different doses TH **Positive control:** N/A **Adjuvant:** N/A	• Consumption of high (1.5 g/kg BW) and low (0.75 g/kg BW) doses of TH enhances phenolic content antioxidant capacity and reduces oxidative stress (MDA and ROS)	[44]
37	Randomized control trial (male collegiate athletes)	0.5—1.0 g/kg (Postprandial measurement over 3 hours)	Phenolic content, FRAP, ROS and MDA assay	**Comparator:** two different doses of the energy drink **Positive control:** N/A **Adjuvant:** N/A	• FRAP value was higher while ROS and phenolic content was lower in the high dose compared to low dose watermelon and Tualang honey based energy drinks groups • MDA showed no significant difference between both trials	[45]

Table 1 (continued)

No	Experimental model	Dose/ concentration AND duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
38	Randomized control trial (smokers)	20 g/day (12 weeks)	Plasma F2isoprostanes, SOD, CAT, and GPx and TAS assay	**Comparator:** Smokers without TH supplementation **Positive control:** N/A **Adjuvant:** N/A	• Smokers who received honey supplementation showed a significant decrease in F2-isoprostanes and a significant increase in total antioxidant status, glutathione peroxidase, and catalase levels	[46]

Abbreviation list: *STZ* Streptozotocin, *MDA* Malondialdehyde, *SOD* Superoxide dismutase, *GPx* Glutathione peroxidase, *CAT* Catalase, *GR* Glutathione reductase, *GST* Glutathione-S-transferase, *TH* Tualang honey, *DPPH* 2,2-diphenyl-1-picrylhydrazyl, *FRAP* Ferric reducing antioxidant power, *TAS* Total antioxidant status, *GSH* Reduced glutathione, *GSSG* Oxidized glutathione, *SHR* Spontaneously hypertensive rats, *NaOH* Sodium hydroxide, *OVX* Ovariectomized, *PCO* Carbonyl proteins, *HCEP* Human corneal epithelial cells, H_2O_2 Hydrogen peroxide, *ISO* Isoproterenol, *AEAC* Ascorbic acid equivalent antioxidant capacity, *ROS* Reactive oxygen species, *KA* Kainic acid, *ABTS* 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), *ORAC* Oxygen radical absorbance capacity, *MTH* Methanolic fraction of Tualang honey, *EATH* Ethyl acetate fraction of Tualang honey, *THI* gamma-irradiated Tualang honey

Table 2 Antimicrobial properties of Tualang honey included in the systematic review

No	Experimental model	Dose/ concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	FINDINGS	REFERENCES
1	In vivo (Sprague–Dawley rats; full-thickness burn wounds)	0.1 ml/cm^2; (topical, 3 weeks)	Colony count	**Comparator:** Hydrofibre and hydrofibre silver dressings **Positive control:** N/A **Adjuvant:** N/A	Tualang honey treatment significantly reduced bacterial growth in wounds infected with *Pseudomonas aeruginosa*. However, in wounds infected with *Acinetobacter baumannii*, the hydrofibre and hydrofibre silver treatments were more effective than the honey treatment	[47]
2	In vivo (New Zealand white adult rabbits, Pseudomonas-induced keratitis in eye)	30% (topical, 8 days)	Colony count	**Comparator:** N/A **Positive control:** gentamicin **Adjuvant:** gentamicin +TH	Topical gentamicin, topical TH, and their combination demonstrated comparable clinical and antimicrobial effectiveness in treating *Pseudomonas*-induced keratitis in rabbits	[48]
3	In vivo (Patients with partial thickness burn)	200 µl (24 h)	Bactericidal activity (zone of inhibition)	**Comparator:** Aquacel® Ag dressing **Positive control:** Aquacel® Ag dressing **Adjuvant:** N/A	• Aquacel-Tualang honey dressings showed to have bactericidal and bacteriostatic effects against the tested Gram-negative bacteria namely *Enterobacter cloacae, Klebsiella pneumoniae, Pseudomonas* spp. and *Acinetobacter* spp. • Aquacel-Tualang honey dressings less effective against Gram-positive bacteria compared to silverbased or medical-grade honey dressings	[49]

Table 2 (continued)

No	Experimental model	Dose/ concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	FINDINGS	REFERENCES
4	In vitro	5 – 100% (v/v)	Agar well diffusion assay (zone of inhibition)	**Comparator:** European honey and Siddar honey **Positive control:** N/A **Adjuvant**: N/A	• All honey samples inhibited bacterial growth, while fungi and yeast required higher concentrations for inhibition • European honey showed higher activity against *E. coli, B. subtilis, S. typhi, P. aeruginosa,* and *A. niger* • Small and Siddar honey showed higher activity against *E. aerogenes, S. aureus, C. albicans*, and C. *utilis* compared to TH. TH showed greater activity against *K pneumonia*. Overall, Gram-negative bacteria were more susceptible to honey than Gram-positive bacteria	[14]
5	In vitro	-	Agar well diffusion (zone of inhibition), MIC assay	**Comparator:** Black seed honey and garanda honey **Positive control:** N/A **Adjuvant**: N/A	• Garanda honey showed the highest antibacterial activity against Vibrio cholerae with a 5.0% MIC, compared to black seed honey (6.0%) and Tualang honey (8.0%) • Garanda honey inhibited all ATCC reference strains at lower concentrations (4.3 to 8.3%) than black seed honey (6.0 to 11.6%) and Tualang honey (7.0 to 12%)	[52]
6	In vitro	5 – 50% (w/v)	MIC, MBC and agar well diffusion assay	**Comparator:** Acacia, gelam, kelulut, pineapple, manuka honey **Positive control:** N/A **Adjuvant**: N/A	• Tualang honey had antibacterial activity comparable to New Zealand Manuka honey with only a slight difference in activity against *Bacillus cereus*, where Tualang honey exhibited slightly higher MIC and MBC values. In general, Tualang honey demonstrated strong antibacterial effects similar to Manuka honey, with the exception of this minor variation in potency against *B. cereus*	[50]

Table 2 (continued)

No	Experimental model	Dose/ concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	FINDINGS	REFERENCES
7	In vitro	5 – 100% (w/v)	Agar well diffusion (zone of inhibition), MIC assay	**Comparator:** Gelam, acacia and manuka honey **Positive control:** N/A **Adjuvant**: N/A	• Tualang honey showed strong antimicrobial effects, with MIC of 50% (w/v) for *Salmonella typhimurium* and 3.1–6.3% (w/v) for *Candida albicans* • It was more effective than Manuka honey, especially against *C. albicans*	[51]
8	In vitro	6.25 – 25% (w/v)	MIC, MBC, growth and time-kill curve	**Comparator:** N/A **Positive control:** N/A **Adjuvant**: N/A	• The MIC of Tualang honey was 18.5% (w/v) for *P. aeruginosa* and 13% (w/v) for *S. pyogenes*, with an MBC of 25% (w/v) for both bacteria. The MIC_{90} values, indicating 90% bacterial inhibition, were 18.5% for *P. aeruginosa* and 15% for *S. pyogenes*. A time-kill test showed that Tualang honey achieved a 4-log reduction in bacteria within 8 h, demonstrating its bactericidal effect	[53]
9	In vitro	0.195—50% (w/v)	Disc and well diffusion, MIC, MBC, and time-kill curve	**Comparator:** Acacia and Yemeni Sumur honey **Positive control:** N/A **Adjuvant**: N/A	• The MIC values ranged between 12.5 to 50% while MBC ranged from 25 to 50% •TH demonstrated complete inhibition of *Staphylococcus aureus* (food isolate) after 6 h at a concentration twice the MIC whereas for *Staphylococcus aureus*, a reduction of 3.84 log CFU/g was observed after 6 h	[54]
10	In vitro	3.125 – 25% (w/v)	Agar well diffusion assay, MIC assay	**Comparator:** Kelulut and acacia honey at different temperature **Positive control:** N/A **Adjuvant:** N/A	The antimicrobial properties of Tualang honey decreased as the heating temperature increased. In the agar well diffusion test, Tualang honey did not maintain inhibition at all temperatures, unlike Kelulut honey	[24]

Table 2 (continued)

No	Experimental model	Dose/ concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	FINDINGS	REFERENCES
11	In vitro	-	Dual agar overlay	**Comparator:** LAB isolates from various honey types (Al-Seder, Al-Hanon, Al-Maray honey) **Positive control:** N/A **Adjuvant**: N/A	*Pediococcus acidilactici HC* was isolated from Tualang honey and demonstrated antifungal activity against various Candida species although its specific inhibition zones or comparative effectiveness were not detailed as prominently as other LAB isolates	[55]
12	In vitro	0.78 – 50.00 mg/mL	MIC and MFC assay	**Comparator:** Stingless bee propolis **Positive control:** N/A **Adjuvant**: N/A	• The MICs of Tualang honey against *C. albicans* and *C. neoformans* were 6.25 mg/mL and 1.56 mg/mL (visual inspection) and 6.25 mg/mL and 3.13 mg/mL (spectrophotometric reading), respectively. The MFCs of Tualang honey against *C. albicans* and *C. neoformans* were 12.50 mg/mL and 6.25 mg/mL, respectively • Both TH and propolis exhibited significant antifungal activities against *C. albicans* and *C. neoformans*	[56]
13	In vitro	5 – 25% (v/v) (48 h)	Colony count	**Comparator:** Acacia, Kelulut honey **Positive control:** N/A **Adjuvant**: N/A	• Tualang honey showed a gradual reduction in the growth of *A. niger* as the concentration increased from 5 to 15% (v/v), with total inhibition of growth at 25% (v/v). For *C. albicans*, Tualang honey also displayed a steady decrease in colony count, achieving total growth inhibition at 25% (v/v) • Kelulut honey demonstrated stronger antifungal activity compared to Tualang honey.	[57]
14	In vitro	1 – 10 mg/mL	Agar well diffusion	**Comparator:** Individual natural products (curcumin, piperine **Positive control:** fluconazole	• The nanoemulsions containing Tualang honey, along with curcumin and piperine, demonstrated significant antifungal activity, with over 80% effectiveness against various Candida species	[58]

Table 2 (continued)

No	Experimental model	Dose/ concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	FINDINGS	REFERENCES
				Adjuvant: Curcumin, piperine	• The antifungal activity of Tualang honey, when combined in the nanoemulsion, was superior to its activity alone, likely due to improved bioavailability • Some Candida strains that were resistant to fluconazole showed susceptibility to the nanoemulsions containing Tualang honey, suggesting its potential use in treating resistant fungal infections	
15	In vitro (Vero cells)	5 – 20 mg/mL (2 h)	Virucidal activity (Anti-adsorption, anti-entry and plaque assay)	**Comparator:** nontreated control **Positive control:** N/A **Adjuvant**: N/A	Tualang honey demonstrated significant virucidal effects against CHIKV, with a maximum inhibition of 99.71%. It also exhibited prophylactic properties by reducing the viral entry by up to 82.21% after 48 h of infection	[59]
16	Randomized control trial (asymptomatic HIV positive subjects)	20 – 60 g/day (6 months)	Viral load	**Comparator:** Control (no treatment) **Positive control:** N/A **Adjuvant:** N/A	In the control group, viral load increased by 130%, and in the TH intermediate group, it increased by 31%. In contrast, VL decreased by 25% in the TH low group and by 8% in the TH high concentration group. While these changes were not significant within groups, there were significant differences between the TH low and TH high concentration groups compared to the control group after six months of treatment	[60]

Abbreviation list: *MIC* Minimum inhibitory concentration, *MBC* Minimum bactericidal concentration, *MFC* Minimum fungicidal concentration, *CHIKV* Chikungunya virus

other honey types [14, 50–54]. This variability suggests that Tualang honey's antibacterial properties may be more suited for Gram-negative bacterial infections, although further studies are needed to clarify its efficacy against Gram-positive strains.. Environmental factors, such as temperature, have been shown to affect the antimicrobial properties of Tualang honey. Higher temperatures significantly reduce its efficacy against both Gram-negative and Gram-positive bacteria, as evidenced in a recent study by Sulaiman et al. [24]. This highlights the need for standardized conditions in both experimental and clinical applications to maximize the potential benefits of Tualang honey. Overall, the antibacterial activity of Tualang honey is well-supported by a diverse range of studies, with stronger evidence for its efficacy against Gram-negative bacteria and potential for use in combination with antibiotics to combat resistant strains.

Evidence also supports the antifungal effects of Tualang honey, particularly against *Candida* species and *Aspergillus niger*. Several studies have consistently shown that Tualang honey inhibits the growth of these fungal pathogens at concentrations ranging from 1.58 mg/ml to 25% (v/v) [55–57].. Furthermore, the use of Tualang honey in combination therapies, such as nanoemulsions with curcumin and piperine, has shown enhanced antifungal effects, especially against drug-resistant Candida strains [58]. These findings suggest that Tualang honey could play a significant role in treating fungal infections, particularly in cases where conventional antifungal drugs are ineffective. Its fungicidal properties, demonstrated across multiple studies, provide a strong basis for further investigation in human trials.The antiviral properties of Tualang honey, while less studied, are promising. In a notable in vitro study, Tualang honey demonstrated significant virucidal activity against Chikungunya virus (CHIKV), with nearly complete inhibition of viral replication [59]. In a randomized controlled trial on asymptomatic HIV-positive subjects, Tualang honey supplementation showed promising effects in reducing viral load. Viral load reductions were observed in the low (20g/day) and high dose (60g/day) honey groups [60]. Although more research is needed in this area, the initial findings indicate that Tualang honey could be explored further as a potential antiviral agent.

Neuroprotective

Tualang honey has demonstrated consistent neuroprotective properties across both human and animal studies (Table 3). The strongest evidence supports its cognitive-enhancing effects, particularly in improving immediate memory and mitigating stress-related cognitive decline. Clinical studies have reported that Tualang honey improves immediate memory in postmenopausal women and enhances learning performance in patients with schizophrenia. These results suggest that Tualang honey may have cognitive-enhancing properties comparable to established therapies, potentially benefiting individuals with cognitive impairments [61, 62]. . Animal studies further support Tualang honey's neuroprotective role. It has been shown to reduce stress-induced cognitive decline and promote neuronal regeneration. For instance, in stressed rats, Tualang honey supplementation improved memory and restored neuronal morphology in the hippocampus and prefrontal cortex. Similarly, it mitigated the adverse effects of hypoxia and lipopolysaccharide (LPS) exposure, indicating its protective role against various forms of neurodegeneration [63–70]. In LPS-induced rats, Tualang honey and its methanolic fraction improved spatial and recognition memory comparably to memantine, an Alzheimer's medication [69 Subsequent studies revealed that Tualang honey is effective against oxidative stress, hippocampal neurodegeneration, and amyloid deposition induced by LPS, with slightly stronger protective activity compared to its methanolic fraction [36]. Further research has highlighted the potential age-related differences in Tualang honey's neuroprotective effects. Studies revealed that while Tualang honey improved memory function and neuronal count in young, stressed rats, its benefits in aged, stressed rats were observed only in specific brain regions [39, 40].

Supplementation at 1 g/kg/day protected midbrain dopaminergic neurons in paraquat-exposed rats, as shown by increased tyrosine-hydroxylase positive neurons [71]. It also notably reduced neuronal degeneration in the piriform cortex of rats exposed to kainic acid [31]. Additionally, a dose of 1.2 g/kg improved cognitive performance and increased neuronal counts in the offspring of prenatally stressed Sprague-Dawley rats [72]. This evidence collectively supports Tualang honey's potential as a natural neuroprotective agent.

Anticancer and antiproliferative

The existing literature on Tualang honey underscores its promising anti-cancer properties across various cancer models and mechanisms (Table 4). The most robust evidence highlights its effects in breast cancer, oral squamous cell carcinoma, and leukemia, while also showing potential in other cancer types. In vitro studies reveal that Tualang honey promotes apoptosis in human breast cancer cells, enhancing its potential as an adjunct therapy. It has been shown to increase apoptotic cell percentages and, when combined with tamoxifen, enhances the efficacy of this established breast cancer treatment [73–76]. Animal studies further support these findings, demonstrating significant reductions in tumor growth, size, and grade in Tualang honey-treated groups compared

Table 3 Neuroprotective properties of Tualang honey included in the systematic review

No	Experimental model	Dose/ concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
1	Randomized controlled trial (postmenopausal women)	20 g/day (16 weeks)	MVAVLT	**Comparator:** Untreated control **Positive control:** Estrogen plus Progestin Therapy **Adjuvant**: N/A	Postmenopausal women receiving TH displaying enhanced immediate memory similar to those receiving estrogen plus progestin therapy	[61]
2	Randomized controlled Trial (schizophrenia patient)	20 g/day (8 weeks)	MVAVLT	**Comparator:** Control (no TH treatment) **Positive control:** N/A **Adjuvant**: N/A	Supplementing schizophrenia patients with an 8-week treatment of TH improved total learning performance in the immediate memory domain, but did not show significant improvement in long-term memory among patients with schizophrenia	[62]
3	In vivo (Sprague–Dawley rats; stressed OVX)	0.2 g/kg (18 days)	NOR test, neuronal counts (Cresyl violet-stained)	**Comparator:** Sham-operated and OVX control rats **Positive control:** 17-β estradiol (E2) **Adjuvant:** N/A	Both the E2 and Tualang honey treatments led to improvements in both short-term and long-term memory, as well as increased neuronal proliferation in the CA2, CA3, and dentate gyrus regions of the hippocampus, when compared to untreated stressed OVX rats	[63]
4	In vivo (Sprague–Dawley rats; exposed to loud noise stress)	0.2 g/kg (35 days)	NOR test	**Comparator:** Control nonstressed and stressed group (no treatment) **Positive control:** N/A **Adjuvant**: N/A	The rats supplemented with honey exhibited significantly higher mean discrimination index scores in both short-term and long-term memory tasks compared to the control rats, suggesting superior memory performance in the TH-treated group	[64]
5	In vivo (Sprague–Dawley rats; exposed to loud noise stress)	1 mL/100 g bw (12 weeks)	RAM test and neuronal counts (Cresyl violet-stained)	**Comparator:** Control (no treatment) **Positive control:** N/A **Adjuvant**: N/A	Significant decreases observed in total errors, reference memory errors, and working memory errors indicate that the consumption of TH significantly improved learning and/or memory • TH groups showed numbers of neurons in hippocampal CA1, CA3a and CA3c layers were significantly higher than control	[65]

Table 3 (continued)

No	Experimental model	Dose/ concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
6	In vivo (Sprague–Dawley aged rats; exposed to loud noise stress)	200 mg/kg (5 weeks)	NOR test, neuronal counts (Cresyl violet-stained)	**Comparator:** Placebo group (stress and nonstressed) **Positive control:** N/A **Adjuvant:** N/A	• The stressed rats treated with TH showed enhanced memory performance, with better scores in both short-term and longterm memory compared to the stressed control rats • TH-treated stressed rats exhibited a higher number of Nissl-positive cells in the medial prefrontal cortex and CA2 hippocampal region, indicating improved pyramidal neurons and preserved neuronal architecture	[39]
7	In vivo (Sprague–Dawley young and aged rats; exposed to loud noise stress)	200 mg/kg (4 weeks)	NOR test, neuronal counts (Cresyl violet-stained)	**Comparator:** Placebo group (stress and non-stressed) **Positive control**: N/A **Adjuvant:** N/A	• Stressed rats supplemented with TH showed significantly higher mean discrimination index in both short- and longterm memory compared to control stressed rats, indicating better memory performance • TH treatment resulted in a significant increase in the number of neurons in the mPFC and all hippocampal regions in young stressed rats. In aged stressed rats, only the mPFC and CA2 hippocampal region were affected by the honey treatment	[40]
8	In vivo (Sprague–Dawley rats)	1 ml/100 g bw (12 weeks)	neuronal counts (Cresyl violet-stained)	**Comparator:** Control (no treatment) **Positive control:** N/A **Adjuvant**: N/A	•The TH-treated group exhibited CA1 neurons with larger somatic area and perimeter and less rounded shape of the CA1 neuronal somas in the honey group suggests a more efficient retention of their pyramidal shape	[66]

Table 3 (continued)

No	Experimental model	Dose/ concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
9	In vivo (Sprague–Dawley rats; normobaric hypoxia induced)	0.2 g/kg (2 days)	NOR test, neuronal counts (Cresyl violet-stained)	**Comparator:** Control (Normoxia and hypoxia group treated with sucrose) **Positive control:** N/A **Adjuvant**: N/A	• Treatment of hypoxia rats with TH resulted in a significant improvement in short-term memory, long-term memory, and spatial memory compared to rats treated with sucrose • TH administration reduced neuronal damage in the hippocampus of rats exposed to hypoxia	[67]
10	In vivo (Sprague–Dawley rats; exposure to normobaric hypoxia)	0.2 g/kg (2 weeks)	neuronal counts (Cresyl violet-stained)	**Comparator:** Control (sucrose treated hypoxia and non hypoxia) **Positive control:** N/A **Adjuvant**: N/A	•TH treated group exhibited a significantly greater number of pyramidal cells compared to the non-hypoxia group treated with sucrose •The arrangement of pyramidal neurons in mPFC was preserved, and the presence of Nissl substances in the cytoplasm was clearly visible	[68]
11	In vivo (Sprague–Dawley rats; LPS-induced)	200 mg/kg TH (2 weeks)	MWM, probe test and NOR test	**Comparator:** Normal and LPSinduced rats **Positive control:** Memantine **Adjuvant:** N/A	•Rats treated with TH showed decreased escape latency and searching distance, indicating improved spatial learning and memory •Rats treated with TH spent more time in the target quadrant and had increased swimming distance, suggesting improved memory retention •Rats treated with TH exhibited significantly higher discrimination index scores, similar to the rats treated with memantine suggesting improving recognition memory in LPS-induced rats	[69]
12	In vivo (Sprague–Dawley rats; LPS-induced)	200 mg/kg (2 weeks)	neuronal counts (Cresyl violet-stained)	**Comparator:** Normal and LPSinduced rats **Positive control:** Memantine **Adjuvant:** N/A	• The size of neuronal cell bodies appeared larger, and a noticeable presence of Nissl positive cells was observed in most neurons in honey treated group	[36]

Table 3 (continued)

No	Experimental model	Dose/ concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
13	In vivo (Sprague–Dawley rats; chronic cerebral hypoperfusion induced by 2VO)	1.2 g/kg (10 weeks)	neuronal counts (Cresyl violet-stained)	**Comparator:** Control (sham control, honey untreated 2VO group) **Positive control:** N/A **Adjuvant**: N/A	TH treatment in 2VO rats resulted in the preservation of the intact structure of the CA1 stratum pyramidal, reduced neuronal cell loss and decrease in the presence of pyknotic nuclei	[70]
14	In vivo (Sprague–Dawley rats; Paraquat -induced toxicity	1.0 g/kg (2 weeks)	Immunohistochemical Analysis of TyrH	**Comparator:** Control (no treatment) **Positive control:** ubiquinol **Adjuvant**: N/A	The number of TyrH positive neurons increased in group paraquat treated with TH	[71]
15	In vivo (Sprague–Dawley rats; KA-induced)	1.0 g/kg (2.5 days; five doses every 12 h)	neuronal counts (Cresyl violet-stained), degenerating neurons (FJC staining)	**Comparator:** Control group (saline and KA-treated group) **Positive control:** Topiramate, aspirin **Adjuvant:** N/A	Pretreatment with TH resulted in a decreased number of viable cells and FJC-positive cells (degenerating neurons) in the piriform cortex after KA administration	[31]
16	In vivo (Sprague–Dawley rats; prenatally stressed)	1.2 g/kg (Day 1 pregnancy until delivery)	NOR test, neuronal counts (Cresyl violet-stained)	**Comparator:** Control group (stress and non-stressed with no treatment) **Positive control:** N/A **Adjuvant**: N/A	The offspring from the TH group demonstrated a significantly increased preference index and a higher number of neurons compared to the offspring from the stress group	[72]

Abbreviation list: *MVAVLT* Malay version of the Auditory Verbal Learning Test, *OVX* Ovariectomized, *NOR* Novel object recognition, *RAM* Radial arm maze, *mPFC* Medial prefrontal cortex, *MWM* Morris Water Maze, *2VO* Two-vessel occlusion, *KA* Kainic acid, *LPS* Lipopolysaccharide, *FJC* Fluoro Jade C, *TH* Tualang honey, *TyrH* Tyrosine Hydroxylase

Table 4 Anticancer and antiproliferative properties of Tualang honey included in the systematic review

No	Experimental model	Dose/concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
1	In vitro (MCF-7, MDA-MB-231 and HeLa cell lines)	1–10% (72 h)	Cytotoxicity assay (LDH) and apoptosis assay (Annexin V-FITC)	**Comparator:** normal breast epithelial cell line, MCF-10A **Positive control:** N/A **Adjuvant**: N/A	•TH caused significant, time- and dosedependent cell death in cancer cell lines MDA-MB-231, MCF-7, and HeLa, with maximum effects seen at 24 h for MDAMB-231 (93%) and MCF-7 (91%) and at 72 h for HeLa (100%), while having minimal impact on normal breast cells (MCF-10A), showing only 28% cell death at the highest concentration after 72 h •TH induced significant apoptosis in cancer cell lines, with the highest apoptosis rates at 48 h for MDA-MB-231 (51.2%) and at 72 h for MCF-7 (55.6%) and HeLa (56.2%), with most cells in the late stage of apoptosis and minimal necrosis (< 12%) detected across all cell types and time points	[73]
2	In vitro (MCF-7 and MDA-MB-231 cell lines)	1% (24 h)	Cell cycle analysis, PCR array, western blot	**Comparator:** N/A **Positive control:** N/A **Adjuvant**: N/A	Tualang honey (TH) induced cell cycle arrest and apoptosis in breast cancer cells. In MCF-7 cells, TH caused G2/M phase arrest and increased the expression of p53, p21, and FADD proteins, while in MDA-MB-231 cells, it caused S phase arrest and increased TRADD, FADD, and p21 expression. TH triggered apoptosis through the death receptor pathway and affected MCF-7 cells via p53dependent pathways, while MDA-MB-231 cells were influenced through p53-independent mechanisms	[74]
3	In vitro (MCF-7 and MDA-MB-231 cell lines)	1% (72 h)	Apoptosis assay (Annexin V-FITC)	**Comparator:** control (no treatment) **Positive control:** tamoxifen **Adjuvant**: TH + tamoxifen	• TH increased the percentage of apoptotic cells in both breast cancer cell lines compared to untreated cells. Combining TH with tamoxifen further enhanced the percentage of apoptotic cells	[75]

Table 4 (continued)

No	Experimental model	Dose/concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
4	In vitro (MCF-10A and MCF-7 cell lines)	1% (72 h)	cytotoxicity (LDH assay) and proliferation assay (MTT assay)	**Comparator:** normal breast epithelial cell line, MCF-10A **Positive control:** 4hydroxytamoxifen **Adjuvant**: TH + 4hydroxytamoxifen	•TH exhibited []cytotoxic effects specifically on MCF-7 cells. In the case of non-cancerous MCF10A cells, 4-hydroxytamoxifen showed cytotoxicity, while TH protected against its cytotoxic effects, promoting cell proliferation, and partially reversing the growth inhibition caused by OHT	[76]
5	In vivo (Sprague Dawley rats; DMBA-induced breast cancer)	0.2, 1.0 or 2.0 g/kg (150 days)	Morphology, Histopathological examination and detection of apoptotic cells (TUNEL assay)	**Comparator:** control (no treatment) **Positive control:** N/A **Adjuvant**: N/A	• TH treated groups exhibited slower tumour growth with smaller mean tumour sizes ($\leq 2cm^3$) compared to the control group ($\leq 8cm^3$) •The histological grading indicated that most tumours in the TH-treated group were of grade 1 and 2, while the control group had predominantly grade 3 tumours •There was an increasing trend in the AI in THtreated groups with higher dosages of TH	[77]
6	In vivo (Sprague Dawley rats; MNU-induced breast cancer)	0.2, 1.0 or 2.0 g/kg (120 days)	Morphological, Histopathological, hematological examination and immunohistochemical analysis	**Comparator:** control (no treatment) **Positive control:** N/A **Adjuvant:** N/A	•TH treatment prolonged tumor progression, lower tumor incidence, decreased tumor multiplicity, smaller tumor size, and lighter tumor weight •TH-treated tumors had lower grades compared to untreated tumors •TH treatment impacted hematological parameters and modulated the expression of apoptotic proteins, favoring pro-apoptotic proteins (Apaf-1 and Caspase-9) while reducing anti-apoptotic proteins (E2, ESR1 and Bcl-xL)	[78]

Table 4 (continued)

No	Experimental model	Dose/concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
7	In vivo (Sprague Dawley rats; MNU-induced breast cancer)	1.0 g/kg (120 days)	Morphological, Histopathological, hematological examination and immunohistochemical analysis	**Comparator:** Manuka honey **Positive control:** N/A **Adjuvant**: N/A	•Both honey treatments resulted in smaller tumors with reduced size, weight, multiplicity and tumor growth significantly slower compared to normal group •Both honey treatments increased expression of proapoptotic proteins (Apaf-1, Caspase-9, IFN-γ, IFNGR1, and p53) and decreased expression of antiapoptotic proteins (TNF-α, COX-2, and Bcl-xL 1)	[79]
8	Randomized control trial (post-menopausal women with breast cancer)	20 g/day (6 months)	BPE changes (Breast MRI)	**Comparator:** N/A **Positive control:** anastrozole **Adjuvant**: TH + anastrozole	Combination of anastrozole and TH resulted in a significant decrease in BPE in 42% of the patients	[80]
9	In vitro (OSCC and HOS cell lines)	1%—20% (72 h)	Cell viability (MTT assay) and apoptosis assay (Annexin V-FITC)	**Comparator:** control (no treatment) **Positive control:** N/A **Adjuvant**: N/A	TH exhibited a dose dependent inhibitory effect on cell viability in OSCC and HOS cell lines, with IC50 values of 4% and 3.5% respectively and increase in the percentage of early apoptotic cells in a dose dependent manner	[81]
10	In vivo (Sprague Dawley rats; 4-NQO induced oral carcinogenesis)	1000 and 2000 mg/kg (10 weeks)	Histopathological, immunohistochemical and gene analysis (PCR array)	**Comparator:** control (normal and induced with no treatment) **Positive control:** N/A **Adjuvant**: N/A	TH lowered the risk of OSCC and slowed down cancer cell growth by reducing the levels of certain proteins (CCND1, EGFR, COX-2) that are linked to cancer. TH also helped maintain cell structure and stability by increasing the presence of β-catenin and e-cadherin, and it made the cancer less aggressive by lowering the levels of TWIST1 and RAC1	[82]

Table 4 (continued)

No	Experimental model	Dose/concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
11	In vitro (H23 and A549 cell lines)	1.25–10% (48 h)	Proliferation assay (MTT), cell cycle analysis (flow cytometry) and apoptosis assay (Annexin V-FITC)	**Comparator:** N/A **Positive control:** N/A **Adjuvant**: N/A	•TH inhibited the cell proliferation in a dose- and time-dependent manner •Cell cycle analysis revealed the accumulation of TH-treated ADC cells in the sub-G1 and G2/M phases •Apoptosis assay confirmed the induction of apoptosis by TH by upregulating pro-apoptotic proteins and downregulating the anti-apoptotic proteins	[83]
12	In vitro (K562 and MV4-11 cell lines)	0.1 – 2% (48 h)	Cytotoxicity assay (LDH) and cellular apoptosis assay (Annexin V-FITC)	**Comparator:** N/A **Positive control:** N/A **Adjuvant**: N/A	•The IC50 value of the K562 and MV4-11 leukemia cell line was found to be 0.6% after a 24-h period and 1.2% after a 12-h period, respectively •The results revealed that Tualang Honey exhibited apoptosis activity of 53.9% and 50.6% on K562 and MV4-11 cells, respectively	8 [4]
13	In vitro (HUVEC and MCF-7 cell lines)	0.3—0.9% (72 h)	Proliferation (MTT assay), migration (scratch assay), tube-formation assays and MMP-2 secretion (ELISA)	**Comparator:** N/A **Positive control:** suramin **Adjuvant**: N/A	•TH significantly inhibited HUVEC proliferation, migration, and tube-formation induced by VEGF, attributed to the suppression of MMP-2 secretion •TH also reduced VEGF secretion in MCF7 breast cancer cells	[84]
14	In vitro (pNHDF and pKHDF)	0.10 – 50% (72 h)	Cell proliferation assay (MTS assay)	**Comparator:** normal fibroblast (pNHDF) **Positive control:** Triton-X **Adjuvant**: N/A	• The proliferative effects were significantly reduced in pKHDF cells treated with Tualang honey compared to the normal in dose dependent manner	[85]
15	Randomized controlled trials (head and neck cancer who Completed chemotherapy and/or radiotherapy patients)	20 mg/day (8 weeks)	Level of fatigue (FACIT-Fatigue subscale)	**Comparator:** N/A **Positive control:** Vitamin C **Adjuvant**: N/A	After four and eight weeks of treatment with TH or Vitamin C, the fatigue level for TH was better than Vitamin C group	[86]

Abbreviation list: *OSCC* Oral Squamous Cell Carcinoma, *HOS* Human Osteosarcoma, *IC50* Half-maximal inhibitory concentration, *EC50* Half-maximal effective concentration, *DMBA* 7,12Dimethylbenz[a]anthracene, *FITC* Fluorescein Isothiocyanate, *MTT* 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, *MTS* 3-(4,5-Dimethylthiazol-2-yl)-5-(3carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, *LDH* Lactate dehydrogenase, *AI* Apoptotic index, *TUNEL* Terminal deoxynucleotidyl transferase dUTP nick end labeling, *PCR* Polymerase chain reaction, *TRADD* Tumor necrosis factor receptor type 1-associated death domain protein, *FADD* Fas-associated death domain, *Apaf-1* Apoptotic proteaseactivating factor 1, *MNU* N-Methyl-N-nitrosourea, *E2* 17β-Estradiol, *ESR1* Estrogen receptor alpha, *Bcl-Xl* B-cell lymphoma-extra-large, *MMP-2* Matrix metalloproteinase-2, *ELISA* Enzyme-linked immunosorbent assay, *pNHDF* Primary normal human dermal fibroblast, *pKHDF* Primary keloid human dermal fibroblast, *FACIT* Functional Assessment of Chronic Illness Therapy, *TH* Tualang honey

to controls. Additionally, Tualang honey administration led to upregulation of pro-apoptotic proteins and downregulation of anti-apoptotic proteins [77–79]. Clinical trials have also highlighted that Tualang honey, when combined with anastrozole, effectively reduces breast background parenchymal enhancement more than anastrozole alone [80].The comprehensive evidence obtained from animal, in vitro, and human studies provides substantial support for the advantageous effects of Tualang honey in breast cancer, underscoring its potential as a natural adjunct to chemotherapeutic agents in managing breast cancer.

In oral squamous cell carcinoma models, Tualang honey has exhibited anti-proliferative and chemopreventive effects by inducing early apoptosis and suppressing cancer cell proliferation. This is achieved through the downregulation of cancer-associated genes such as CCND1, EGFR, and COX-2, as well as genes involved in epithelial-to-mesenchymal transition [81, 82]. Additionally, Tualang honey demonstrates anti-cancer potential in other types, including cervical and lung cancers [73, 83], and shows efficacy in inducing apoptosis in acute and chronic myeloid leukemia cell lines [87]. It also inhibits angiogenesis by reducing proliferation, migration, and tube formation of human umbilical vein endothelial cells stimulated by vascular endothelial growth factor (VEGF) [84], and has reduced growth effects on benign fibroproliferative skin tumors [85].

Further supporting its therapeutic potential, a clinical trial on head and neck cancer patients revealed that Tualang honey supplementation significantly improved fatigue and quality of life compared to vitamin C supplementation [86]. Collectively, these studies underscore Tualang honey's potential as a natural adjunct in cancer treatment, particularly for breast cancer, oral squamous cell carcinoma, and leukemia. The evidence suggests a need for further clinical trials to explore its efficacy and optimize its application in comprehensive cancer care.

Anti-inflammatory

Tualang honey has been extensively studied for its anti-inflammatory potential in both in vitro and in vivo studies (Table 5). In vitro studies provide strong evidence for the anti-inflammatory properties of Tualang honey. Ahmed et al. (2012) demonstrated that Tualang honey, at a concentration of 1.0% (v/v), effectively reduced proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, by inhibiting the NF-kB signaling pathway, which is crucial for regulating inflammatory responses [88]. Additionally, Tualang honey showed selective inhibition of COX-2 over COX-1 in a cyclooxygenase assay at 0.5 g/mL, indicating its targeted anti-inflammatory action [51]. These findings underscore its potential in managing inflammation through specific molecular pathways.. In vivo studies present a more varied picture. A study by Bashkaran et al. on New Zealand white rabbits with alkali-induced eye injuries found no significant differences in inflammatory features between Tualang honey and conventional treatments, suggesting limited efficacy in this context [43]. However, a subsequent study by Kamaruzzaman et al. demonstrated that aerosolized Tualang honey, at concentrations of 25% and 50% (v/v), effectively reduced airway inflammation and goblet cell hyperplasia in a rabbit model of ovalbumin-induced airway inflammation [89]. This suggests that Tualang honey may be effective in respiratory inflammation.Further research on Sprague-Dawley rats revealed that Tualang honey administration at 1.2 g/kg reduced serum IL-6 levels in response to formalin injection, although it did not significantly affect IL-8 levels [90]. In models of kainic acid-induced status epilepticus, Tualang honey reduced levels of TNF-α, IL-1β, GFAP, AIF-1, and COX-2 in brain regions, and mitigated caspase-3 activity in the cerebral cortex [91]. Similarly, chronic stress exposure in rats showed that Tualang honey at 1 g/kg significantly decreased TNF-α, IL-6, and IFN-γ levels in brain homogenates [92]. Clinical trials present a mixed outcome. In chronic smokers, Tualang honey supplementation at 20 g daily resulted in a significant increase in plasma TNF-α levels, alongside a decrease in hsCRP, a systemic inflammation marker [93]. This suggests a complex effect on inflammatory markers that requires further investigation. Conversely, in postmenopausal breast cancer patients, Tualang honey supplementation at 20 g daily over 12 weeks effectively reduced IL-1β and TNF-α levels, highlighting its potential in mitigating cancer-related inflammation [94]. Overall, the evidence supports Tualang honey's anti-inflammatory properties across various models and contexts, though some studies present contradictory results. These findings suggest that while Tualang honey shows promise as an anti-inflammatory agent, its effects can vary based on the model and condition studied. Further research is needed to clarify its efficacy and optimize its use in clinical settings.

Anti nociceptive

Animal studies and human trials have elucidated the analgesic and antinociceptive properties of Tualang honey (Table 6). Animal studies have provided substantial evidence for Tualang honey's analgesic effects. Aziz et al. (2014) found that moderate (1.2 g/kg) and higher (2.4 g/kg) doses of Tualang honey significantly increased the latency of the tail-flick reflex, similar to the effects of the anti-inflammatory drug prednisolone. Conversely, a lower dose (0.2 g/kg) did not show significant improvements, highlighting the importance of dosage in its

Table 5 Anti-inflammatory properties of Tualang honey included in the systematic review

No	Experimental model	Dose/concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
1	In vitro (PAM212 keratinocytes)	1.0% (v/v) (24 h)	Inflammatory cytokines level (ELISA)	**Comparator:** N/A **Positive control**: N/A **Adjuvant:** N/A	TH led to a reduction in proinflammatory cytokines (IL1β, IL-6 and TNF-α) which may be attributed to the inhibition of NF-kB	[88]
2	In vitro	0.5 g/mL	COX assay	**Comparator:** Gelam, acacia and manuka honey **Positive control:** N/A **Adjuvant**: N/A	The crude Tualang honey sample demonstrated the highest selectivity ratio as an anti-inflammatory agent. It selectively inhibited the inducible enzyme COX-2 more effectively than its isoform COX-1. Notably, this selective inhibition by Tualang honey was superior to that observed with Manuka honey	[51]
3	In vivo (New Zealand white rabbits; alkali injury with NaOH)	1.0 gm/kg (oral) 30%(topical) (1 week)	Clinical and histopathological inflammatory features	**Comparator:** Conventional treated groups **Positive control:** Prednisolone acetate + Ciprofloxacin + ascorbic acid **Adjuvant:** N/A	•No significant difference in clinical inflammatory features of cornea between the TH-treated group and the conventional group •The histopathological examination of the cornea showed a mild level of polymorphonuclear leukocytes in both groups	[43]
4	In vivo (New Zealand white rabbits; ovalbumin-induced chronic asthma)	25 & 50% (v/v) (3 days)	Histological and morphometric analyses	**Comparator:** control (no honey treatment) **Positive control:** N/A prednisolone **Adjuvant**: N/A	Treatment with aerosolised TH alleviated ovalbumininduced airway inflammation by reducing the number of airway inflammatory cells present in bronchoalveolar lavage fluid and inhibited the goblet cell hyperplasia	[89]
5	In vivo (Sprague–Dawley rats; formalin injection)	1.2 g/kg (10 days)	Inflammatory cytokines level (ELISA)	**Comparator:** control (no honey treatment) **Positive control:** prednisolone **Adjuvant**: N/A	Both Tualang honey and prednisolone significantly reduced pain behavior and paw edema in rats compared to the control group. Tualang honey was comparable to prednisolone in terms of modulating inflammatory pain responses	[90]
6	In vivo (Sprague–Dawley rats; KA-Induced Status Epilepticus)	1 g/kg (2.5 days; five doses every 12 h)	Neuroinflammation markers (ELISA) and caspase-3 activity (colorimetric assay	**Comparator:** Control group (saline and KAtreated group) **Positive control:** Topiramate **Adjuvant**: N/A	Tualang honey demonstrated significant reduction in the elevated levels of TNF-α, IL-1β, GFAP, AIF-1, and COX-2 in various brain regions, as well as mitigated the increased caspase-3 activity in the cerebral cortex	[91]

Table 5 (continued)

No	Experimental model	Dose/concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	Findings	References
7	In vivo (Sprague–Dawley rats; exposed to chronic stress)	1 g/kg (28 days)	Inflammatory cytokines level (ELISA)	**Comparator:** control (no treatment) **Positive control:** DHA-rich fish oiltreated group **Adjuvant:** N/A	In brain homogenates from rats, the concentrations of TNF-α, IL-6, and IFN-γ were significantly lower in groups treated with Tualang honey (TH), DHA-rich fish oil, and their combination, compared to the control group. Both TH and DHA individually effectively reduced proinflammatory cytokine levels in the brain. However, the combined treatment with TH and DHA did not provide additional benefits beyond those achieved with each treatment alone	[92]
8	Randomized control trial (smokers)	20 g/day (12 weeks)	Inflammatory cytokines level (ELISA)	**Comparator:** control (no honey treatment) **Positive control:** N/A **Adjuvant:** N/A	Honey supplementation significantly increases the plasma TNF-α levels while concurrently inducing a significant reduction in hsCRP levels. No significant difference was observed in the mean plasma IL-6 levels	[93]
9	Randomized control trial (postmenopausal breast cancer patient)	20 g/day (12 weeks)	Inflammatory cytokines level (ELISA)	**Comparator:** control (no honey treatment) **Positive control:** N/A **Adjuvant:** N/A	Tualang honey supplementation for 12 weeks prevented increased inflammation and attenuated the elevated levels of IL-1β and TNF-α observed in the control group	[94]

Abbreviation list: *TH* Tualang honey, *IL-1β* Interleukin-1 beta, *IL-6* Interleukin-6, *TNF-α* Tumor necrosis factor alpha, *ELISA* Enzyme-linked immunosorbent assay, *NaOH* Sodium hydroxide, *KA* Kainic acid, *COX* Cyclooxygenase, *GFAP* Glial fibrillary acidic protein, *AIF-1* Allograft inflammatory factor 1, *IFN-γ* Interferon-gamma, *hsCRP* High-sensitivity C-reactive protein

Table 6 Anti nociceptive activities of Tualang honey included in the systematic review

No	Experimental model	Dose/ Concentration	Method	Comparator, positive control, and adjuvant use	Outcome	References
1	In vivo (Sprague–Dawley rats; prenatally stressed rats)	1.2 g/kg (Day 1 pregnancy until delivery)	Tail flick latency test and formalin test	**Comparator:** control (no honey treatment) **Positive control:** N/A **Adjuvant**: N/A	Administration of TH to non-stressed pregnant dams led to a notable increase in tail flick latency time and a decrease in paw oedema in the offspring. The offspring from the stressed group treated with TH exhibited a significant reduction in formalin test scores compared to the stressed group	[96]
2	In vivo (Sprague–Dawley rats)	0.2, 1.2 or 2.4 g/kg (10 days)	Tail flick test	**Comparator:** control (no honey treatment) **Positive control:** prednisolone **Adjuvant**: N/A	TH administration at doses of 1.2 g/kg and 2.4 g/kg, as well as prednisolone, significantly increased the tail flick latency compared to the control group, while there was no significant difference in latency time between the group administered 0.2 g/kg of TH and the control group	[95]
3	Randomized control trial (Patients planned to undergo tonsillectomy)	2 – 3 mL (topical) 4 mL (oral) (7 days)	visual analog scale, frequency of waking up at night due to pain, and additional use of analgesic	**Comparator:** N/A **Positive control:** sultamicillin **Adjuvant**: N/A	All patients in the TH + antibiotic group reported no pain on the seventh day postoperatively, along with lower frequencies of nighttime awakening and analgesic use compared to the antibiotic-only group	[98]
4	Randomized controlled trial (neonates)	2 mL (once)	Pain score (PIPP)	**Comparator:** N/A **Positive control:** sucrose **Adjuvant**: N/A	Three infants from the honey group had a PIPP score of 0, indicating no pain, compared to four infants from the sucrose group. The median duration of total audible cry after venipuncture was 4 s for the sucrose group and 5.5 s for the TH-treated group	[99]
5	In vivo (Sprague–Dawley rats; prenatally stressed rats)	1.2 g/kg (day 1 pregnancy until delivery)	Formalin test, behavioural pain scores	**Comparator:** pregnant rats (with and without stress) **Positive control:** N/A **Adjuvant:** N/A	The nociceptive behaviour score was significantly decreased in the offspring of stressed rats treated with TH compared to the offspring of the control group and stressed group	[32]

Table 6 (continued)

No	Experimental model	Dose/ Concentration	Method	Comparator, positive control, and adjuvant use	Outcome	References
6	In vivo (Sprague–Dawley rats; prenatally stressed rats)	1.2 g/kg (day 1 pregnancy until delivery)	Formalin test, behaviour score	**Comparator:** pregnant rats (with and without stress) **Positive control:** N/A **Adjuvant:** N/A	Significant reduction in mean nociceptive behaviour score of the offspring of stressed rats treated with TH compared to the offspring of the stressed group	[41]
7	In vivo (Sprague–Dawley rats; formalininduced pain)	1.2 g/kg (10 days)	Behaviour pain score	**Comparator:** Control group (normal rat) **Positive control:** Vitamin C **Adjuvant:** N/A	TH significantly reduced the pain behaviour score at multiple time points post-formalin injection compared to the control group, while no significant differences were observed between Vitamin C and control groups	[33]
8	In vivo (Sprague–Dawley rats; REM) sleep deprivation rat	1.2 g/kg (4 weeks)	Formalin test, pain behaviour score,	**Comparator:** Control and tank control groups **Positive control:** N/A **Adjuvant:** N/A	The REM + TH group exhibited a significant decrease in pain behaviour score compared to the REM group	[97]

Abbreviation list: *REM* Rapid eye movement, *TH* Tualang honey, *PIPP* Premature Infant Pain Profile

analgesic efficacy [95].Additionally, Tualang honey was more effective than vitamin C (20 mg/kg) in reducing pain responses in a formalin-induced inflammatory rat model, suggesting its superior antinociceptive potential [33]. Further research involving prenatal stress models indicated that Tualang honey (1.2 g/kg) improved pain responses by increasing tail-flick reflex latency and reducing formalin-induced pain behavior in the offspring of stressed dams [32, 41, 96]. Moreover, Tualang honey supplementation at 1.2 g/kg reduced pain behavior in rats subjected to REM sleep deprivation [97].

In clinical settings, Tualang honey has also shown promise. Patients who underwent tonsillectomy and received Tualang honey (topically and orally) in conjunction with sultamicillin experienced faster pain relief and reported lower pain scores and less need for additional pain medication compared to those receiving sultamicillin alone [98]. Furthermore, a study involving newborns found that Tualang honey (2 mL) was as effective as sucrose in reducing pain during venipuncture, with similar crying times and pain scores between the honey and sucrose groups [99].Overall, these findings suggest that Tualang honey can effectively modulate pain at both peripheral and central levels. Its efficacy appears to be influenced by dosage and the specific pain model used, with strong evidence supporting its use in various pain management scenarios. This synthesis highlights Tualang honey's potential as a natural analgesic and antinociceptive agent, providing a foundation for further clinical trials to optimize its use in pain relief.

Effects on reproductive health

Tualang honey has demonstrated potential protective effects on reproductive health in both male and female animal models, with evidence suggesting beneficial outcomes for various aspects of reproductive function (Table 7).In male reproductive health, Tualang honey has been found to positively influence fertility. Mohamed et al. (2012) reported that daily oral administration of Tualang honey at 1.2 g/kg for 4 weeks significantly increased epididymal sperm count and reduced the proportion of abnormal sperm in rats, suggesting an enhancement in spermiogenesis [100]. In another study, Tualang honey supplementation in nicotine-exposed rats improved spermatogenic cell counts, further supporting its role in facilitating spermatogenesis [101]. Additionally, Tualang honey mitigated the effects of prenatal stress on male rat offspring by increasing testis and epididymis weights and improving sperm motility and the percentage of abnormal spermatozoa [102]. Human trials have reinforced these findings, with Tualang honey supplementation leading to significant improvements in sperm concentration, motility, and morphology in oligospermic males [103].

For female reproductive health, Tualang honey has shown protective effects in various contexts. In ovariectomized rats, a model for postmenopausal conditions, daily intake of Tualang honey for two weeks significantly increased uterine weight and vaginal epithelium thickness, indicating protection against atrophy [104]. Moreover, Tualang honey has demonstrated potential in counteracting reproductive toxicities from environmental pollutants. Studies revealed that it alleviated the adverse effects of bisphenol A (BPA) exposure by restoring disrupted levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [105, 106]. It also improved ovarian and uterine morphology, reduced lipid peroxidation, and normalized estrogen receptor expression in BPA-exposed rats [106]. Furthermore, Tualang honey exhibited protective effects against cadmium-induced reproductive toxicity, showcasing its potential as a natural supplement for mitigating environmental hazards [34]. Overall, these findings suggest that Tualang honey could provide significant protective benefits for reproductive health, enhancing spermatogenesis, improving sperm parameters, and mitigating reproductive damage from environmental toxins. This evidence advocates for further exploration through human clinical trials to better understand its efficacy and optimize its application in reproductive health management.

Wound healing

Tualang honey has been utilized since ancient times as a traditional remedy for wound treatment, attributed to its potential healing properties. Table 8 provides evidence that Tualang honey possesses wound-healing properties. Khoo et al. (2010) compared Tualang honey with hydrofibre and hydrofibre silver in treating bacterial contaminated full-thickness burn wounds in rats. They found that Tualang honey led to greater wound contraction, indicating its enhanced ability to facilitate wound healing compared to the other treatments [47]. Similarly, Sukur et al. (2011) observed that Tualang honey application on contaminated burn wounds resulted in faster healing compared to chitosan gel and hydrofibre silver [108]. In addition to its topical applications, Tualang honey has shown efficacy in internal wound healing. A study demonstrated that oral administration of Tualang honey improved anastomotic wound healing in rats following large bowel surgery. This was marked by increased fibroblast counts, reduced inflammatory cell presence, and improved wound strength [109].Clinical evidence further supports Tualang honey's wound-healing benefits. A trial evaluating its effects post-tonsillectomy compared a group treated with sultamicillin alone to one receiving

Table 7 Effects of Tualang honey on reproductive health included in the systematic review

No	Experimental model	Dose/ concentration	Method	Comparator, positive control, and adjuvant use	Outcome	References
1	In vivo (Sprague–Dawley rat)	0.2 – 2.4 g/kg (4 weeks)	Hormonal assay, elongated spermatid count, epididymal sperm count and histological examination of testes	**Comparator:** control group (no honey treatment) **Positive control:** N/A **Adjuvant:** N/A	No significant changes in levels of reproductive hormones and elongated spermatid count. TH (1.2 g/kg) had significantly higher epididymal sperm count. The percentage of abnormal sperm was found to be slightly lower in TH-treated group. Histological examination showed normal spermatogenesis	[100]
2	In vivo (Sprague–Dawley rat; nicotine-induced)	0.1 ml/kg (60 days)	Hormonal assay, histological examination of testes	**Comparator:** control groups (no honey treatment) **Positive control:** N/A **Adjuvant:** N/A	Tualang honey significantly improved spermatogenesis in rats by increasing seminiferous tubule and lumen diameters, spermatocyte width, and spermatogenic cell abundance, while potentially counteracting nicotine's adverse effects	[101]
3	In vivo (Sprague–Dawley rats; restraint stress-induced)	1.2 g/kg (day 1 pregnancy until delivery)	Assessment on epididymal sperm count and sperm morphology and motility	**Comparator:** control groups (no honey treatment) **Positive control:** N/A **Adjuvant:** N/A	Honey supplementation during prenatal restraint stress significantly increased testis and epididymis weights as well as improved the percentages of abnormal spermatozoa and sperm motility in male rat offspring	[102]
4	Randomized controlled trial (Oligospermic males)	20 g/day (12 weeks)	Sperm parameters (sperm concentration, motility, and morphology, erectile function (IIEF-5 questionnaire). Hormonal assay	**Comparator:** N/A **Positive control:** Tribestan **Adjuvant:** N/A	Tualang honey significantly increased sperm concentration, motility and morphology, with results comparable to Tribestan, which also improved sperm concentration and morphology. Both treatments showed similar effects on erectile function and hormonal profiles, with no adverse events reported, indicating that Tualang honey is as effective and safe as Tribestan for improving sperm parameters in oligospermic males	[103]
5	In vivo (Sprague–Dawley rats; OVX-induced)	0.2 – 2.0 g/kg (2 weeks)	Histopathological examination and hormonal assays	**Comparator:** Control groups (sham operated and OVX rats) **Positive control:** N/A **Adjuvant:** N/A	• Significant increase in uterine weight and vaginal epithelium thickness • TH-treated groups exhibited lower levels of estradiol, FSH and progesterone compared to the OVX group • Low dose of Tualang honey (0.2 g/kg) showed an increase in serum free testosterone levels compared to the OVX group	[104]

Table 7 (continued)

No	Experimental model	Dose/ concentration	Method	Comparator, positive control, and adjuvant use	Outcome	References
6	In vivo (Sprague–Dawley rats; BPA-induced ovarian toxicity	200 mg/kg (6 weeks)	Assessment of estrous cycles, hormonal assay, histological examination	**Comparator:** control groups **Positive control:** BPA **Adjuvant:** N/A	• Treatment with Tualang honey in BPA-exposed rats showed higher percentage in normal estrous cycle (62.5%) and lower in persistent diestrous (37.5%) compared to positive control group • Serum FSH and LH levels were significantly reduced • The abnormalities characterized by the presence of large antral-like follicles that did not undergo ovulation and the presence of atretic cystic-like follicles were more pronounced in the ovaries of the positive control group compared to the TH group	[105]

Table 7 (continued)

No	Experimental model	Dose/ concentration	Method	Comparator, positive control, and adjuvant use	Outcome	References
7	In vivo (Sprague–Dawley rats; BPA-induced ovarian toxicity	200 mg/kg (6 weeks)	Uterine histomorphometry analysis, histological examination, Immunohistochemistry	**Comparator:** control groups **Positive control:** BPA **Adjuvant:** N/A	• TH significantly prevent the reduction of luminal epithelial cells height and endometrial and myometrial thickness • The uterine morphology of rats in the TH group exhibited a slight improvement in the surface epithelium and a healthy stromal cell population • Furthermore, the endometrial glands in the TH group displayed a normal structure with glandular epithelium, and the myometrium appeared unaffected • Concurrent treatment of rats with BPA and Tualang honey could normalized ERα, ERβ, and C3 expressions and distribution	[106]
8	In vivo (Sprague–Dawley rats; cadmiuminduced)	200 mg/kg (6 weeks)	Histological examination, Hormonal assay	**Comparator:** Normal rat **Positive control:** cadmium group **Adjuvant:** N/A	• Significant improvements in the histological changes • Less atretic follicles were observed, restoring the normal level of LH and FSH in comparison with cadmium group	[34]

Table 7 (continued)

No	Experimental model	Dose/ concentration	Method	Comparator, positive control, and adjuvant use	Outcome	References
9	In vivo (Sprague–Dawley rats; restraint stress-induced)	1.2 g/kg (Day 0 of pregnancy until delivery)	Serum corticosterone, histological examination, Assessment on pregnancy outcomes	**Comparator:** control groups **Positive control:** N/A **Adjuvant:** N/A	TH supplementation demonstrated a significant ameliorating effect on the elevated corticosterone levels, increased zona fasciculata thickness, prolonged pregnancy duration reduced litter size observed in rats exposed to stress	[107]

Abbreviation list: *OVX* Ovariectomized, *BPA* Bisphenol A, *FSH* Follicle-stimulating hormone, *LH* Luteinizing hormone, *IIEF-5* International Index of Erectile Function-5, *TH* Tualang honey

Table 8 Wound healing activities of Tualang honey included in the systematic review

No	Experimental model	Dose/ concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	Outcome	References
1	In vivo (Sprague–Dawley rats; full-thickness burn wounds)	0.1 ml/cm^2 (topical; 3 weeks)	wound size and appearance (dryness, exudation, odour, contraction)	**Comparator:** Hydrofibre and hydrofibre silver dressings **Positive control:** N/A **Adjuvant:** N/A	• The wounds treated with TH exhibited a significant reduction in size compared to the initial wound size • TH-treated wounds showed a reduction of 12.86% in size on day 3. By day 9 post-burn, the wounds further decreased in size by 33.94%	[47]
2	In vivo (Sprague–Dawley rats; bacterial contaminated full thickness burn)	0.2 ml (21 days)	Wound size	**Comparator:** Chitosan gel or Hydrofibre silver **Positive control:** N/A **Adjuvant:** N/A	• The mean size of TH-treated wounds did not differ significantly from Chitosan gel or Hydrofibre silver-treated wounds throughout the experiment, but on day 21 alone, THtreated wounds were smaller compared to the other treatment groups	[108]
3	In vivo (Wistar rats; large bowel anastomosis)	1.0 g/kg (7 days)	Tensile strength measurement, histopathology examination	**Comparator:** control groups (no honey treatment) **Positive control:** N/A **Adjuvant:** N/A	• The tensile strength of colon anastomosis and histopathological analysis, including fibroblast count and inflammatory cells, demonstrated a significant difference in favor of the TH-treated group	[109]
4	Randomized controlled trial (post-tonsillectomy paediatric patients)	3 mLs of TH intraoperatively followed by 4 mLs of oral (3 times daily; 7 days)	healed area of tonsillar fossa by endoscopic photograph	**Comparator:** N/A **Positive control:** Sultamicillin **Adjuvant:** N/A	• The healing process showed that wound healing was significantly faster in the TH treatment group compared to the control group, as evidenced by a higher percentage of healed area in tonsillar fossa	[110]

Abbreviation list: *TH* Tualang honey

both sultamicillin and Tualang honey. The latter group exhibited significantly faster healing [110]. The overall synthesis of these studies indicates that Tualang honey consistently outperforms conventional treatments in promoting wound healing. It enhances both external and internal wound repair processes, suggesting its potential as a superior alternative or adjunct to existing wound care practices. This evidence underscores the need for further human clinical trials to validate and optimize Tualang honey's application in clinical wound management.

Bone metabolism and muscle performance

The effects of Tualang honey supplementation on bone metabolism markers and muscle performance have been explored through various animal and human studies, revealing promising results (Table 9). Evidence indicates that Tualang honey, when combined with jumping exercise, positively impacts bone metabolism. In a study by Mosavat et al. (2014), rats receiving Tualang honey at a dose of 1 g/kg per day, alongside a jumping exercise regimen, exhibited significantly higher serum total calcium levels compared to controls. Both honey supplementation alone and the combined regimen led to lower serum 1CTP levels, a marker of bone resorption, and increased serum alkaline phosphatase levels, indicating enhanced bone formation [111]. However, inconsistent findings were noted in a study by Zuhri et al., which observed a 56.3% reduction in serum 1CTP levels with combined honey and exercise but a 7.66% decrease in alkaline phosphatase levels [112]. These discrepancies suggest the need for further research to understand the underlying mechanisms and resolve conflicting results.In addition, Tualang honey has demonstrated beneficial effects on bone health in postmenopausal individuals. Studies have shown that honey supplementation improves bone metabolism markers. In ovariectomized rats, a dose of 0.2 g/kg significantly enhanced bone structural parameters [113]. Similarly, randomized controlled trials with postmenopausal breast cancer patients revealed that daily consumption of 20 g of Tualang honey resulted in significantly lower levels of CTX (a marker of bone resorption) and higher levels of P1NP (a marker of bone formation) compared to baseline measurements [94]. These findings support the use of Tualang honey as a dietary intervention for improving bone health in postmenopausal women.

Further research into muscle performance also supports the potential benefits of Tualang honey. A randomized controlled trial with inactive young males demonstrated that daily consumption of 20 g of Tualang honey led to significant improvements in muscle strength, power, and performance. Notable enhancements included a 16.80% increase in vertical jump height, improved standing long jump distance, and better isokinetic muscular performance [114].Overall, the evidence suggests that Tualang honey may be a beneficial natural intervention for promoting skeletal health and improving physical performance. The studies summarized highlight its potential in enhancing bone metabolism and muscle function, making it a promising candidate for further investigation in clinical trials aimed at optimizing skeletal and muscular health.

Anxiolytic and antidepressant

The anxiolytic and antidepressant effects of Tualang honey have been investigated through several animal studies, providing insights into its potential therapeutic benefits (Table 10). Initial research focused on ovariectomized rats exposed to stress, which demonstrated that Tualang honey administration led to an increase in rearing events and locomotive activity, along with decreased mean freezing and grooming times. These changes suggest a reduction in anxiety-like behavior [30].Further studies have explored Tualang honey's antidepressant effects. In ovariectomized rats exhibiting depressive-like states, Tualang honey administration was associated with reduced depressive-like behavior, evidenced by decreased immobility time and increased swimming time in behavioral tests [115]. Additionally, Tualang honey was found to increase brain-derived neurotrophic factor (BDNF) levels in the brain of these rats, which may contribute to its antidepressant effects [115].. A separate study involving male rats exposed to noise stress revealed that a dose of 0.2 g/kg of Tualang honey for 35 days significantly attenuated depressive-like behaviors. The honey supplementation led to increased climbing and swimming durations, along with reduced immobility in the forced swim test, indicating notable antidepressant-like effects [64]. Collectively, these findings suggest that Tualang honey has both anxiolytic and antidepressant properties across different animal models. The evidence points to its potential utility in managing anxiety and depression, although further research, particularly in human clinical trials, is necessary to confirm these effects and elucidate the underlying mechanisms.

Cardioprotective

Extensive research has investigated the cardioprotective effects of Tualang honey, focusing on lipid metabolism, blood pressure regulation, cardiovascular markers, and vascular health (Table 11). Studies have consistently demonstrated that Tualang honey can positively influence cardiovascular health across multiple aspects. In terms of lipid metabolism, Tualang honey has shown promising effects. In an animal model of high cholesterol diet-induced non-alcoholic steatohepatitis and myocardial injury, Tualang honey supplementation led to reductions

Table 9 Effects of Tualang honey on bone metabolism and muscle performance included in the systematic review

No	Experimental model	Dose/ concentration and duration treatment	Method	Comparator, positive control, and adjuvant USE	Outcome	References
1	In vivo (Sprague–Dawley rats; ovariectomized rats)	0.2 g/kg (6 weeks)	Histomorphometry examination	**Comparator:** control groups (normal and ovariectomized rats) **Positive control:** calcium-treated rats **Adjuvant:** N/A	The bone structural analysis of rats in the TH group showed a significant increase in BV/TV, Tb.Th and Tb.N and a significant decrease in Tb.Sp compared with the ovariectomized control group. Compared to ovariectomized rats receiving calcium, those treated with Tualang honey had notably greater trabecular thickness and narrower inter-trabecular spaces	[113]
2	In vivo (Sprague–Dawley rats)	1 g/kg (7 days)	Serum total Ca, ALP and 1CTP	**Comparator:** control groups **Positive control:** N/A **Adjuvant:** N/A	• High intensity jumping exercise combined with honey supplementation resulted in significantly higher serum total calcium levels • Honey supplementation alone and high intensity jumping exercise combined with honey also increased serum alkaline phosphatase levels • The groups that consumed honey alone or engaged in jumping exercise, both at low and high intensity, showed significantly lower levels of serum 1CTP compared to the sedentary control group without honey supplementation	[111]
3	Randomized controlled trials (young males)	20 g/day (6 weeks)	Bone SOS, bone turnover markers (ALP and 1CTP)	**Comparator:** control groups **Positive control:** N/A **Adjuvant:** N/A	• No significant differences in participants' bone SOS in all groups • The TH group showed a 56.3% reduction in serum 1CTP and was significantly lower than the control group • A 7.66% reduction of ALP was observed in the TH group	[112]
4	Randomized controlled trials (Postmenopausal Breast Cancer Patients)	20 g/day (12 weeks)	bone resorption marker (CTX) and bone formation marker (P1NP)	**Comparator:** control (no honey treatment) **Positive control:** N/A **Adjuvant**: N/A	The level of CTX (a marker of bone resorption) was significantly lower, while the level of P1NP (a marker of bone formation) was significantly higher after Tualang honey treatment compared to their levels before treatment	[94]

Table 9 (continued)

No	Experimental model	Dose/ concentration and duration treatment	Method	Comparator, positive control, and adjuvant USE	Outcome	References
5	Randomized controlled trials (inactive young males)	20 g/day (6 weeks)	muscular strength and power (isokinetic dynamometer machine), standing long jump test, and vertical jump test	**Comparator:** control groups **Positive control:** N/A **Adjuvant:** N/A	• TH group exhibited a significant 16.80% increase in vertical jump height • TH groups all showed a significant improvement in the distance of standing long jump • In terms of isokinetic muscular performance, the TH group showed significant increases in various parameters including knee extension and flexion peak torque, extension and flexion average power at different speeds	[114]

Abbreviation list: *BV/TV* Bone volume per tissue volume, *TbTh* Trabecular thickness, *Tb.N* trabecular number, *Tb.Sp* Inter-trabecular space, *SOS* Speed of sound, *1CTP* C-terminal telopeptide of type 1 collagen, *ALP* Alkaline phosphatase, *Ca* Calcium, *CTX* Carboxy-terminal collagen crosslinks, *P1NP* Procollagen type I N-propeptide, *TH* Tualang honey

Table 10 Anxiolytic and anti-depressive effects of Tualang honey included in the systematic review

No	Experimental model	Dose/ concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	Outcome	References
1	In vivo (Sprague–Dawley rats; stressed ovariectomised)	0.2 g/kg (18 days)	Open field test	**Comparator:** Control rats (normal, stressed), OVX rats (normal, stressed) **Positive control:** 17β-Estradiol **Adjuvant:** N/A	TH administration demonstrated a significant reduction in anxiety-like behavior in stressed OVX rats, which exhibited a significant increase in anxiety-like behavior compared to the other groups	[30]
2	In vivo (Sprague–Dawley rats; stressed ovariectomised)	0.2 g/kg	Forced swimming test, measurement of serum ACTH, corticosterone levels BDNF concentration (ELISA)	**Comparator:** control groups **Positive control:** N/A **Adjuvant:** N/A	Tualang honey effectively mitigated the elevated depressive-like behaviour observed in stressed OVX rats, significantly reduced serum ACTH and corticosterone levels while restoring the decreased concentration of brain-derived neurotrophic factor (BDNF)	[115]
3	In vivo (Sprague–Dawley rats; exposed to loud noise stress	0.2 g/kg (35 days)	Forced swimming test	**Comparator:** Control non-stressed and stressed group (no treatment) **Positive control:** N/A **Adjuvant**: N/A	Treatment with the honey supplement exhibited antidepressant-like effects, as reflected by significantly increased duration of climbing and swimming behaviors and decreased duration of immobility	[64]

Abbreviation list: *OVX* Ovariectomised, *ACTH* Adrenocorticotropic hormone, *BDNF* Brain-derived neurotrophic factor, *TH* Tualang honey

Table 11 Cardioprotective effects of Tualang honey included in the systematic review

No	Experimental model	Dose/ concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	Outcome	References
1	In vivo (Wistar albino rats, ISO-induced)	3.0 g/kg (45 days)	Biochemical analysis (Lipid profile, cardiac marker enzyme), histopathological analysis	**Comparator:** Normal rats **Positive control:** N/A **Adjuvant:** N/A	• TH demonstrated significant cardioprotective effects by decreasing serum cTnI levels, ameliorating alterations in cardiac marker enzymes, and reducing elevated total cholesterol and triglyceride levels • Histopathological analysis revealed that THtreated group exhibited nearly normal cardiac muscle fiber architecture and reduced inflammatory infiltrates	[42]
2	In vivo (Sprague–Dawley rats; HCD-Induced NASH)	1.2 – 3.0 g/kg (4 weeks)	Biochemical analysis (Lipid profile)	**Comparator:** control groups **Positive control:** N/A **Adjuvant:** N/A	• The transition from a HCD to a normal diet comprising commercially available rat pallets, along with high-dose TH supplementation, has demonstrated positive effects on total cholesterol and triglyceride levels	[116]
3	Randomized control trial (postmenopausal women)	20 g/day (6 weeks)	Cardiovascular parameters (Systolic and diastolic blood pressure, lipid profile)	**Comparator:** Honey cocktail **Positive control:** N/A **Adjuvant:** N/A	Tualang honey supplementation significantly reduced diastolic blood pressure from 77.92 mmHg at baseline to 73.45 mmHg at 12 months ($p = 0.047$) and lowered fasting blood sugar from 6.11 mmol/L to 5.71 mmol/L ($p = 0.021$), showing superior effects in these parameters compared to the Honey Cocktail group	[117]
4	In vivo (Wistar Kyoto rats; spontaneously hypertensive)	1.0 g/kg (12 weeks)	Measurement of blood pressure	**Comparator:** Normal WKY rats and SHR rats (without honey treatment) **Positive control:** N/A **Adjuvant:** N/A	Significant suppression of SBP in honey-treated SHR compared to SHR control	[29]

Abbreviation list: *cTn1* Cardiac troponin I, *ISO* Isoproterenol, *HCD* High Cholesterol Diet, *NASH* Non-alcoholic Steatohepatitis, *SBP* Systolic Blood Pressure, H_2O_2 Hydrogen peroxide, *HUVECs* Human umbilical vein endothelial cells, *TH* Tualang honey

Table 12 Effects of Tualang honey on respiratory systems included in the systematic review

No	Experimental model	Dose/ Concentration and duration treatment	Method	Comparator, positive control, and adjuvant use	Outcome	References
1	Randomized controlled trial (COPD patients)	20 mg/day (6 months)	Quality of life assessment (St George's Respiratory Questionnaire (SGRQ))	**Comparator:** Standard care **Positive control:** N/A **Adjuvant:** N/A	Supplementation of honey in patients with COPD results in better intermediate and long-term changes in the overall QoL	[119]
2	In vivo (Sprague–Dawley rats; exposed to cigarette smoke)	1.2 g/kg (13 weeks)	Lung surfactantsphosphatidyl choline, phosphatidyl glycerol (TLC and Malachite Green assay kit), surfactant protein-A levels (ELISA kit) and histological examination	**Comparator:** control groups **Positive control:** N/A **Adjuvant:** N/A	TH administration to rats exposed to cigarette smoke significantly decreased the phosphatidylcholine/phosphatidylglycerol (PC/PG) ratio and resulted in histological improvements in lung tissue, as evidenced by a decrease in the presence of alveolar macrophages containing carbon particles compared to the cigarette smoke group. No significant alterations were observed in surfactant protein A levels	[120]

Abbreviation list: *COPD* Chronic obstructive pulmonary disease, *QoL* Quality of life, *TLC* Thin Layer Chromatography

Table 13 Other pharmacological activities of Tualang honey included in the systematic review

No	Experimental model	Dose/ Concentration And Duration Treatment	Method	Comparator, positive control, and adjuvant use	Outcome	References
1	In vivo (Sprague–Dawley rats; STZ-induced diabetic rats)	1.0 g/kg (4 weeks)	Liver function test	**Comparator:** control groups (non-diabetic and diabetic with no treatment) **Positive control:** N/A **Adjuvant:** N/A	TH significantly reduced AST, ALT and ALP activities in diabetic rats	[121]
2	In vivo (Sprague–Dawley rats; HCD-Induced Acute Kidney Diseases)	1.4 g/kg (6 weeks)	Renal function test and histological examination	**Comparator:** control groups (without honey treatment) **Positive control:** N/A **Adjuvant:** N/A	• HCD + TH led to a significant reduction in serum creatinine, urea and uric acid levels after 48 h compared to the group fed only HCD • Histological analysis displayed notable renal abnormalities indicated by increased cellularity and expansion of the glomeruli	[122]
3	In vivo (Sprague–Dawley rats; STZ-induced diabetic rats)	1.0 g/kg (4 weeks)	Serum glucose, concentrations of fructosamine and insulin level	**Comparator:** control groups **Positive control:** glibenclamide, metformin **Adjuvant:** TH + glibenclamide, TH + metformin	TH showed an increase in insulin levels (0.41 ± 0.06 ng/ml), along with a decrease in hyperglycemia (12.3 ± 3.1 mmol/L) and fructosamine levels (304.5 ± 10.1 µmol/L)	[123]
4	Randomized controlled trials (asymptomatic HIVpositive subjects)	20—60 g (6 months)	Immunological parameters (CD45, CD3, CD4:CD8 ratio, CD19, NK cells)	**Comparator:** control groups (no honey supplementation) **Positive control:** N/A **Adjuvant:** N/A	• All measured parameters showed trend of reduction after six-month period • The CD4:CD8 ratio and B cells (CD19) levels in all the groups showed no significant changes at six-month followup	[124]
5	In vivo (BALB/c)	0.5 – 3.0 g/kg (14 days)	Markers antibodies CD3 + /CD4 + (T helper), CD3 + /CD8 + (T cytotoxic), CD14 + (macrophage) and CD19 + (B lymphocyte) and phagocytosis assay	**Comparator:** control groups (no treatment) **Positive control:** N/A **Adjuvant:** N/A	• TH group showed increase populations of CD3 + /CD4 + , CD3 + /CD8 + , CD14 + and CD19 + compared to the control group • The percentage of splenic phagocytes increase dose dependently	[125]
6	Randomized controlled trials (asymptomatic HIVpositive subjects)	20—60 g (6 months)	Haematological parameters	**Comparator:** control groups (no honey supplementation) **Positive control:** N/A **Adjuvant:** N/A	A significant decrease in total white blood cell counts, neutrophil counts, and lymphocyte counts was observed after a six-month follow-up in both the control and low dose honey but not in the intermediate and high dose groups after six months, suggesting that adequate consumption of honey may prevent or delay neutropenia and lymphopenia	[124]

Table 13 (continued)

No	Experimental model	Dose/ Concentration And Duration Treatment	Method	Comparator, positive control, and adjuvant use	Outcome	References
7	In vivo (albino Sprague–Dawley)	1.0 g/kg (120 days)	Haematological parameters	**Comparator:** honey sugars analogue **Positive control:** N/A **Adjuvant:** N/A	TH and honey sugar analoque showed an increasing effect on the level of haematological parameters such as RBC, Hb, PCV, lymphocytes, TWBC, RDW, eosinophils, monocytes and platelets compared to the nontreated negative control	[126]
8	In vivo (Sprague–Dawley rats; exposed to gasoline vapor)	1.2 g/kg (11 weeks)	Haematological parameters and blood smear	**Comparator:** control groups (no honey treatment) **Positive control:** N/A **Adjuvant:** N/A	Administration of TH improved the MCHC values and reduced the percentage of abnormal megakaryocytes	[127]
9	Randomized controlled trials (Chronic periodontitis patients)	-	Plaque score, gingivitis score, periodontal pockets depth, and clinical attachment loss	**Comparator:** control group (no honey treatment) **Positive control:** N/A **Adjuvant:** N/A	TH group demonstrated significant improvements in periodontal pocket depth and clinical attachment loss	[128]
10	Randomized controlled trials (healthy subject)	-	caries risk status (the salivary flow rate, pH level and buffering capacity)	**Comparator:** N/A **Positive control:** N/A **Adjuvant:** N/A	• Significant increased in salivary flow rate at Day 14 when compared to Day 3 and Day 7 • There was no significant changes in salivary pH level at control phase and after consumption of tualang honey • After 2 weeks of honey consumption, the percentage of subjects who had normal salivary buffering capacity slightly reduced (38.6%)	[129]
11	In vitro (HPDLFs)	0.02—5% (3 days)	MTT assay	**Comparator:** control groups **Positive control:** N/A **Adjuvant:** N/A	• 0.02% honey promoted significantly higher HPDLF proliferation compared with control which promote periodontal wound healing by stimulating proliferation of HPDLFs	[130]

Table 13 (continued)

No	Experimental model	Dose/ Concentration And Duration Treatment	Method	Comparator, positive control, and adjuvant use	Outcome	References
12	In vitro	5%	Colony count	**Comparator:** Commercial TH and wild TH **Positive control:** N/A **Adjuvant:** N/A	The inclusion of 5% honey in skimmed milk did not inhibit the growth of the probiotic strain. When *B. longum* was cultured in skimmed milk mixed with wild Tualang honey, a significant increase in growth was observed after 24 h of incubation. The probiotic strain inoculated in skimmed milk with commercial Tualang honey exhibited an increase in growth	[131]

Abbreviation list: *STZ* Streptozotocin, *ALP* Alkaline phosphatase, *AST* Aspartate aminotransferase, *ALT* Alanine aminotransferase, *HCD* High Cholesterol Diet, *TH* Tualang honey, *HPDLFs* Human periodontal ligament fibroblasts, *RBC* Red blood cells, *Hb* Hemoglobin, *PCV* Packed cell volume, *TWBC* Total white blood cell count, *RDW* Red cell distribution width

in total cholesterol and triglyceride levels [42, 116]. This was corroborated by a randomized controlled trial in postmenopausal women, where daily consumption of 20 g of Tualang honey improved the lipid profile [117]. These results suggest that Tualang honey can modulate lipid levels, potentially contributing to cardiovascular health. Additionally, research on Tualang honey and blood pressure regulation has revealed its potential as an antihypertensive agent, with findings indicating a decrease in both systolic and diastolic blood pressure [29, 117]. Tualang honey's impact on cardiovascular markers is also notable. Studies have reported decreased levels of cardiac troponin I (cTnI), a marker of cardiac damage, and improvements in other cardiac enzyme levels. Histopathological analyses have shown enhancements in cardiac muscle fiber architecture and reductions in inflammatory infiltrates [29]. These findings reflect Tualang honey's potential in mitigating cardiac damage and inflammation. Furthermore, Tualang honey has demonstrated protective effects on the vascular system. Experiments involving human umbilical vein endothelial cells (HUVECs) and Balb/c mice revealed that Tualang honey can counteract increased vascular permeability induced by oxidative stress [118]. This suggests that Tualang honey may help maintain vascular integrity and reduce the risk of vascular dysfunction.

Overall, the accumulated evidence supports the cardioprotective benefits of Tualang honey, highlighting its potential in improving lipid profiles, regulating blood pressure, enhancing cardiovascular markers, and protecting vascular health. These findings provide a strong foundation for future human clinical trials to further explore and validate these effects.

Effects on respiratory system

The effects of Tualang honey on the respiratory system were investigated in two studies (Table 12). In a study involving chronic obstructive pulmonary disease (COPD) patients, supplementation of 20 mg of Tualang honey per day resulted in significant improvements in quality of life as assessed by the St. George's Respiratory Questionnaire (SGRQ) [119]. This suggests that Tualang honey may positively impact symptoms and overall well-being in COPD patients. Additionally, in a study using Sprague–Dawley rats exposed to cigarette smoke, Tualang honey administration at a dose of 1.2 g/kg led to improved lung surfactant composition and histological characteristics in lung tissue [120].

These findings indicate that Tualang honey may offer protective benefits against respiratory damage caused by cigarette smoke, enhancing lung health. Together, these studies suggest that Tualang honey may have potential therapeutic effects on respiratory health, improving both the quality of life in COPD patients and lung function in animal models of respiratory damage. To fully understand its mechanisms and optimize its use, further research is necessary to explore these effects in greater depth and in broader human clinical trials.

Other activities

Tualang honey has exhibited diverse pharmacological activities in various experimental models (Table 13). Studies on hepatoprotective effects have shown that Tualang honey significantly reduces liver enzyme activities, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), in STZ-induced diabetic rats, indicating its potential for liver protection [121]. Similarly, in cases of acute kidney disease induced by a high cholesterol diet, Tualang honey supplementation improved renal function by lowering serum levels of creatinine, urea, and uric acid, and demonstrated histological enhancements such as decreased cellularity and glomerular expansion [122]. Additionally, Tualang honey positively impacts glucose metabolism, with studies showing increased insulin levels and reduced hyperglycemia and fructosamine concentrations in STZ-induced diabetic rats [123].

Tualang honey has demonstrated significant effects on both immunological and hematological parameters. In randomized controlled trials with asymptomatic HIV-positive subjects, Tualang honey reduced immune markers such as CD45, CD3, CD4:CD8 ratio, CD19, and NK cells [124]. It also increased immune cell populations in BALB/c mice, including T helper cells, T cytotoxic cells, macrophages, B lymphocytes, and splenic phagocytes, suggesting potential immunomodulatory effects [125]. In terms of hematology, Tualang honey led to notable decreases in total white blood cell counts, neutrophils, and lymphocytes in HIV-positive subjects [124]. Animal studies supported these findings, showing that Tualang honey improved hematological parameters in albino Sprague–Dawley rats and, in rats exposed to gasoline vapor, it enhanced mean corpuscular hemoglobin concentration and reduced abnormal megakaryocytes [126, 127].

Tualang honey has also demonstrated benefits in periodontal health. Clinical trials involving chronic periodontitis patients revealed significant improvements in periodontal parameters, including pocket depth and clinical attachment loss, following honey supplementation [128]. Similarly, in healthy subjects, Tualang honey consumption led to an increased salivary flow rate without affecting salivary pH level [129]. Additionally, Tualang honey exhibited the ability to promote the proliferation of human periodontal ligament fibroblasts [130], suggesting its potential for periodontal wound healing. On another note, Tualang honey has been found to enhance

the growth of probiotic strains in milk formulations, highlighting its potential as a prebiotic agent [131]. Hence, these findings collectively demonstrate the multifaceted pharmacological activities of Tualang honey, underscoring its potential as a valuable and versatile natural resource with diverse therapeutic implications.

Discussion

The findings of this systematic review provide compelling evidence that Tualang honey is a significant natural resource with a wide range of pharmacological and therapeutic activities. Our analysis indicates that researchers from Malaysia have actively investigated the utilization and potential of Tualang honey. The availability of Tualang honey in Malaysia is a significant factor driving active research on its utilization and potential. Malaysia's rich rainforests and diverse ecosystems provide an ideal environment for Tualang trees [132]. Hence, this accessibility allows researchers to easily obtain samples, analyze its properties, and conduct studies on its composition and potential applications. Moreover, there has been a steady increase in publications related to the pharmacological activities of Tualang honey since 2010, reaching a peak in 2020, which reflects the growing recognition of Tualang honey's importance.

Over the past 12 years, scientific investigations on Tualang honey have been impressive, validating many of the traditional claims associated with its use. The systematic review revealed that Tualang honey exhibits diverse pharmacological activities across various domains. Notably, Tualang honey has been extensively studied for its antioxidant properties in this systematic review. Antioxidants have a crucial role in safeguarding the body against oxidative stress by counteracting detrimental free radicals and minimizing cellular harm [133]. The capacity of Tualang honey to counteract free radicals, hinder lipid peroxidation, and augment the functioning of antioxidant enzymes signifies its potential efficacy in alleviating oxidative stress and preserving cellular integrity [4, 10–46].Additionally, the review highlighted the potential benefits of Tualang honey as antimicrobial [14, 24, 47–60], neuroprotective [31, 32, 38, 41, 61–72], anti-cancer [73–87], anti-inflammatory [43, 51, 88–94], reproductive health [36, 95–102], analgesia [33–35, 103–107], wound healing [47, 108–110], bone metabolism [94, 111–113], muscle performance [114], anxiety [30], depression [64, 115], cardiovascular health [29, 42, 116–118], respiratory health [119, 120] and other pharmacological activities [121–131]. The observed pharmacological effects of Tualang honey bear notable clinical relevance and hold potential therapeutic applications across a spectrum of diseases and conditions. Furthermore, comparative analysis with conventional medications sheds light on the unique strengths of Tualang honey. In comparison to alternative treatment options, Tualang honey exhibits its distinctive advantages that contribute to its potential as a therapeutic agent. For instance, a study examining pain relief during neonatal venipuncture found that supplementation with Tualang honey exhibited comparable effectiveness to those who received sucrose, a commonly used solution for pain relief [99]. Moreover, Tualang honey has shown potential for synergistic effects when used in combination with existing therapies. In a study involving breast cancer patients, the combination of Tualang honey and anastrozole, a commonly used medication, exhibited superior results in reducing breast background parenchymal enhancement compared to the use of anastrozole alone [80]. Moreover, investigations into the combination therapies of Tualang honey with conventional antidiabetic medications revealed enhanced antioxidant activity and a reduction in oxidative stress markers [26, 27]. These findings suggest that the simultaneous administration of Tualang honey and antidiabetic medications can potentially offer additional benefits. Additionally, when Tualang honey was combined with tamoxifen, a medication employed in breast cancer treatment, it displayed an augmented impact on the depolarization of breast cancer cell lines compared to the use of tamoxifen as a standalone treatment option [75]. These compelling outcomes highlight the potential of Tualang honey in improving treatment efficacy and warrant further exploration of its synergistic effects when used in combination with existing therapies.

The findings of animal experiments and clinical trials give important insights into Tualang honey's potential medicinal uses. Tualang honey's effects on numerous physiological systems have been shown using animal models, while clinical studies have offered tentative evidence of its effectiveness in humans. It is crucial to highlight, however, that the majority of the data originates from preclinical investigations and that more well-designed clinical trials are required to confirm the results and evaluate the usefulness of Tualang honey in humans. The methodology for the systematic review was robust, according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) standards [6]. A comprehensive search strategy was employed, encompassing major scholarly databases and spanning a 12-year period. The study selection process involved independent reviewers and a standardized form for data extraction. Additionally, the risk of bias assessment was conducted using appropriate tools for different study types [7, 8]. These strengths enhance the reliability and validity of the review's findings. Despite the strengths, the systematic review also has limitations that should be considered. The included studies exhibited heterogeneity in terms of

dosage, administration routes, and study designs, making it challenging to draw definitive conclusions and compare the results across different studies. Furthermore, while the majority of the evidence comes from animal studies, there is a notable scarcity of clinical trials to corroborate these findings in human subjects..

It is also crucial to address the safety profile of Tualang honey, including potential toxicity. A recent study examined aged Tualang honey (ATH) stored for four years, which had high levels of 5-hydroxymethylfurfural (HMF) exceeding the recommended limit [134]. In a 28-day toxicity study, Tualang honey administered at 200 mg/kg/day was found to be safe in vivo, while higher doses led to adverse effects in female rats. The no-observed-adverse-effect level for male rats was 2,000 mg/kg/day, and less than 200 mg/kg/day for females. This underscores the importance of ongoing safety evaluations to confirm Tualang honey's safety as a therapeutic agent.Future research should focus on addressing the limitations of the existing evidence. Well-designed clinical trials and rigorous methodologies are warranted to provide more robust evidence of the efficacy and safety of Tualang honey in humans. Standardization of dosage and administration protocols would facilitate comparisons across studies and improve the generalizability of the findings. Moreover, further investigation is needed to elucidate the underlying mechanisms of action of Tualang honey, as this would provide valuable insights into its pharmacological effects and potentially lead to the development of targeted interventions.

Conclusion

In conclusion, we've shown a comprehensive analysis of the pharmacological effects and therapeutic potential of Tualang honey, emphasizing the importance of integrating natural products into modern therapeutic strategies and recognizing Tualang honey as a promising natural therapy in healthcare. However, it is essential to acknowledge that the current evidence is primarily derived from animal and in vitro studies. There is a significant lack of high-quality human clinical trials to robustly support its efficacy and safety for human use. Therefore, while Tualang honey shows potential, further rigorous clinical research is necessary to confirm its therapeutic benefits and ensure its safe application in human medicine.

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Availability of data and materials
All data collected and reviewed for this study is fully presented in the manuscript, including tables and figures.

Declarations

Ethics approval and consent to participate
The data used in this article was sourced from previously published scientific journals. As all data was appropriately cited, ethical approval and consent to participate are not applicable.

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