



# Honey clinical applications in complementary medicine: A critical review

[Aplicaciones clínicas de la miel en la medicina complementaria: Una revisión crítica]

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## Abstract

**Context:** Honey has been employed for its therapeutic attributes since ancient eras, with a history of medicinal utilization, and recent studies have highlighted its diverse clinical applications. The medicinal benefits of honey can be ascribed to various mechanisms, encompassing its osmotic and acidic characteristics, hydrogen peroxide generation, and particular bioactive compounds. While honey generally has a good safety profile, rare risks exist, particularly in infants under one year of age. More rigorous clinical trials and standardized protocols are needed to establish its optimal dosage, application methods, and specific indications. Economic considerations and regional variations in honey composition and quality should also be considered.

**Aims:** To provide an overview of the clinical uses of honey in the medical field, emphasizing its effectiveness and potential therapeutic benefits.

**Methods:** A comprehensive literature search was conducted to gather relevant studies on the clinical applications of honey. The search encompassed various databases and included studies published with the range from May 2001 to May 2023. The selected studies were critically reviewed to extract pertinent information for this critical review.

**Results:** Natural honey comes from two types of honey-producing bees: honeybees and stingless bees. Honey constitutes a multifaceted amalgamation of sugars, enzymes, minerals, vitamins, and bioactive compounds, all contributing to its therapeutic attributes. It exhibits antibacterial, anti-inflammatory, wound healing, and antioxidant effects. In wound management, honey promotes healing, reduces infection rates, and minimizes scarring. It also shows promise in treating bacterial and fungal infections. Furthermore, honey has effectively alleviated symptoms associated with respiratory tract infections, gastrointestinal disorders, and dermatological conditions.

**Conclusions:** Honey possesses multifaceted clinical applications in the medical field. Its diverse therapeutic properties and minimal adverse effects make it an attractive option for various conditions. However, further research is necessary to solidify its role in evidence-based clinical practice, including conducting more rigorous clinical trials, establishing standardized protocols, and considering economic and regional factors.

**Keywords:** clinical application; Kelulut honey; Tualang honey.

## Resumen

**Contexto:** La miel se ha empleado por sus atributos terapéuticos desde la antigüedad, con una historia de utilización medicinal, y estudios recientes han puesto de relieve sus diversas aplicaciones clínicas. Los beneficios medicinales de la miel pueden atribuirse a diversos mecanismos, que abarcan sus características osmóticas y ácidas, la generación de peróxido de hidrógeno y determinados compuestos bioactivos. Aunque en general la miel tiene un buen perfil de seguridad, existen riesgos poco frecuentes, sobre todo en lactantes menores de un año. Se necesitan ensayos clínicos más rigurosos y protocolos estandarizados para establecer su dosis óptima, métodos de aplicación e indicaciones específicas. También deben tenerse en cuenta las consideraciones económicas y las variaciones regionales en la composición y calidad de la miel.

**Objetivos:** Ofrecer una visión general de los usos clínicos de la miel en el ámbito médico, haciendo hincapié en su eficacia y sus posibles beneficios terapéuticos.

**Métodos:** Se realizó una exhaustiva búsqueda bibliográfica para recopilar estudios relevantes sobre las aplicaciones clínicas de la miel. La búsqueda abarcó varias bases de datos e incluyó estudios publicados con un intervalo entre mayo de 2001 y mayo de 2023. Los estudios seleccionados se revisaron críticamente para extraer información pertinente para esta revisión crítica.

**Resultados:** La miel natural procede de dos tipos de abejas productoras de miel: las abejas melíferas y las abejas sin aguijón. La miel constituye una amalgama polifacética de azúcares, enzimas, minerales, vitaminas y compuestos bioactivos, que contribuyen a sus atributos terapéuticos. Tiene efectos antibacterianos, antiinflamatorios, cicatrizantes y antioxidantes. En el tratamiento de heridas, la miel favorece la cicatrización, reduce las tasas de infección y minimiza las cicatrices. También resulta prometedora en el tratamiento de infecciones bacterianas y fúngicas. Además, la miel ha aliviado eficazmente los síntomas asociados a infecciones de las vías respiratorias, trastornos gastrointestinales y afecciones dermatológicas.

**Conclusiones:** La miel posee aplicaciones clínicas polifacéticas en el campo de la medicina. Sus diversas propiedades terapéuticas y sus mínimos efectos adversos la convierten en una opción atractiva para diversas afecciones. Sin embargo, es necesario seguir investigando para consolidar su papel en la práctica clínica basada en la evidencia, incluyendo la realización de ensayos clínicos más rigurosos, el establecimiento de protocolos estandarizados y la consideración de factores económicos y regionales.

**Palabras Clave:** aplicación clínica; miel de Kelulut; miel de Tualang.

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## INTRODUCTION

The use of honey as a medicinal substance can be traced back thousands of years, with its therapeutic properties well documented in ancient civilizations. Today, the medical community has rekindled its interest in natural products, particularly honey, and recognized its multifaceted potential in various clinical applications (Ahmed et al., 2018). This critical review endeavors to offer a thorough exploration of the clinical utilization of honey in the medical field, shedding light on its remarkable properties, mechanisms of action, and emerging trends in healthcare.

Honey, originating from flower nectar and transformed by bees, represents an intricate blend of carbohydrates, enzymes, proteins, vitamins, minerals, and bioactive compounds. It is a naturally occurring substance crafted by honeybees (*Apis mellifera*; Family: *Apidae*) from the nectar of blossoms (Marimuthu et al., 2023). Honey is also derived from the stingless bee (*Trigona* spp.) and is referred to locally in Malaysia as Kelulut honey. People have been consuming honey for approximately 5500 years (Samarghandian et al., 2017). Its diverse chemical composition provides a broad spectrum of therapeutic effects, making honey a captivating scientific inquiry subject. Throughout history, various ancient civilizations, including the Greeks, Chinese, Egyptians, Romans, Mayans, and Babylonians, incorporated honey into their diets for nutritional and medicinal purposes (Samarghandian et al., 2017). Numerous societies have acknowledged and harnessed honey's therapeutic capabilities in treating wounds, infections, and other illnesses (Minden-Birkenmaier and Bowlin, 2018). Honey is the sole naturally occurring substance obtained from insects that find applications in various industries, cosmetics, medicine, and as a nutritional source (Ajibola et al., 2012; Samarghandian et al., 2017). Throughout the years, a multitude of studies have been carried out to investigate the effectiveness and safety of honey in managing diverse medical conditions. This research has culminated in an expanding body of evidence that endorses its application in clinical practice.

In Malaysia, both *Apis* spp. honey and *Trigona* spp. Honey is available in various varieties (Kek et al., 2014) according to the locality and types of plants nested by the bees. The *Apis* spp. Honey, including types such as Tualang (*Koompassia excelsa*), Gelam (*Melaleuca cajuputi*), Pineapple (*Ananas comosus*), and honey from the Borneo region, is produced in Malaysia. Specifically, the *Apis dorsata* species responsible for producing Tualang and Gelam honeys can be found in Kedah and Terengganu, respectively (Ahmed and Othman, 2013; Kek et al., 2014). Borneo hon-

ey, produced by the *Apis cerana* species, is primarily sourced from the nectar of *Acacia mangium* trees and flowers. This type of honey has been reported in Sabah. Additionally, pineapple honey produced by the *Apis mellifera* species has been documented in Johor, Malaysia (Kek et al., 2014). The availability of local honey relies entirely on honey hunters who gather honey from feral bees. *Apis dorsata*, which predominantly nests in the jungle and is high off the ground, makes it challenging to employ conventional production methods. In contrast, *Trigona* spp., or stingless bees, which lack stingers and exhibit distinct nesting behavior, offer the potential for bee cultivation in controlled environments such as intensive farms that adhere to standardized operating procedures. Stingless bee honey is cultivated on several farms with local trees, such as local fruit, coconut, rubber, and *Acacia mangium*, and has a sour taste. Stingless bee honey production sparked the honey industry to become a major honey output in Malaysia 10 years ago. Manuka honey is a monofloral honey, as opposed to Tualang honey (Ahmed and Othman, 2013). Manuka honey, produced in New Zealand and Australia, is derived from the nectar of the Manuka Honeybush (*Leptospermum scoparium*) (Ahmed and Othman, 2013). According to published evidence, Manuka honey provides various therapeutic benefits for various diseases (Eteraf-Oskouei and Najafi, 2013; Visavadia et al., 2008).

Traditionally, honey has been employed to treat many conditions, including piles, eczema, worm infestations, bronchial asthma, throat infections, TB, thirst, hiccups, weariness, and lethargy. Additionally, it is utilized as a nutritional supplement (Ediriweera and Premarathna, 2012; Samarghandian et al., 2017). Honey is considered a nutritious food that enjoys popularity among individuals of all ages, both men and women (Ajibola, 2015). One of the primary clinical applications of honey lies in wound healing (Yaghoobi et al., 2013). Honey has been renowned for its antimicrobial properties throughout history due to its low water content, acidic pH, hydrogen peroxide, and other bioactive components (Almasaudi, 2021; Mandal and Mandal, 2011). These properties create an inhospitable environment for bacterial growth, promoting wound cleansing and preventing infection (Almasaudi, 2021). Growing research demonstrating honey's efficacy in many healthcare settings has sparked a resurgence in interest in honey's clinical applications in recent years (Bohr and Memarzadeh, 2020). Honey is believed to offer protective advantages for the respiratory, gastrointestinal, cardiovascular, and neurological systems, in addition to its recognized properties as an antioxidant, anti-

inflammatory, antibacterial, and anti-diabetic agent (Khan et al., 2018; Jaganathan et al., 2015; Ranneh et al., 2021; Ranneh et al., 2018). This review delves into the mechanisms underlying honey's wound-healing properties and presents an overview of its application in various types of wounds, including chronic ulcers, burns, and surgical incisions.

Beyond wound healing, honey has demonstrated the potential to manage respiratory conditions (Samarghandian et al., 2017; Yong et al., 2021). Its cough-suppressant and mucolytic properties make it an intriguing natural alternative for treating respiratory tract infections, bronchitis, and asthma (Abuelgasim et al., 2021; Ahmed et al., 2013). Additionally, honey's anti-inflammatory effects may help alleviate symptoms associated with allergies and hay fever (Asha'ari et al., 2013; Yong et al., 2021). Moreover, honey has demonstrated potential in managing gastrointestinal disorders, including gastritis, peptic ulcers, and gastroenteritis (Ajibola, 2015; Eteraf-Oskouei and Najafi, 2013). Its antibacterial properties and ability to stimulate gastric mucus production and modulate gut microbiota have positioned it as a potential adjunctive therapy in these conditions (Almasaudi, 2021; Mandal and Mandal, 2011). By examining the literature, we aim to shed light on the use of honey in gastrointestinal health and its potential role in the future of digestive medicine.

Natural honey, produced by honeybees, does not require refrigeration, has a long shelf life, and can be stored unopened at room temperature in a dry location (Babacan and Rand, 2007; Hassapidou et al., 2006). The honey's water activity (WA) typically falls within the range of 0.56 to 0.62, with an approximate pH level of 3.9 (Babacan and Rand, 2007; Hassapidou et al., 2006; Zumla and Lulat, 1989). Honey is characterized by its high fructose content, which renders it approximately 25% sweeter than table sugar. This natural sweetener has been employed since ancient times (Babacan and Rand, 2007; Pataca et al., 2007). Moreover, adding honey to drinks is becoming more common. However, honey from the stingless bee is only produced in tropical countries, possesses a higher moisture content of up to 35%, and promotes honey fermentation, thus requiring refrigeration.

The unique composition of honey, which includes carbohydrates, enzymes, antioxidants, and antimicrobial compounds, has been attributed to its diverse healing properties (Young and Blundell, 2023). It possesses antibacterial, anti-inflammatory, immunomodulatory, and wound-healing capabilities, making it a compelling candidate for integration into clinical practice. Moreover, honey's broad-spectrum antimicrobial activity, including its effectiveness against

drug-resistant microorganisms, has sparked interest in its potential as an alternative or adjunctive therapy in the era of increasing antibiotic resistance (Combarros-Fuertes et al., 2020; Mandal and Mandal, 2011; Ng et al., 2020).

As we delve into this extensive critical review, we must recognize the limitations and obstacles that come with the clinical application of honey. Standardization of honey production, variation in its composition, and potential allergic reactions are among the factors that warrant careful consideration (Bett, 2017; Burzyńska and Piasecka-Kwiatkowska, 2021; Yong et al., 2021). However, the expanding body of evidence and the renewed interest in honey as a therapeutic agent underscore its potential to supplement conventional medical practices and facilitate the development of innovative treatment approaches.

Through a systematic exploration of the literature, this critical review presents a comprehensive overview of the clinical applications of honey. Encompassing wound care, dermatology, respiratory diseases, gastrointestinal conditions, and more, the review critically evaluates available evidence to provide clinicians, researchers, and healthcare practitioners with a comprehensive understanding of honey's therapeutic potential. Synthesizing the literature, this review objectively explores honey's clinical application across medical specialties, shedding light on its benefits and limitations. Through elucidating the underlying mechanisms and consolidating current research, this literature review aims to provide healthcare professionals with a comprehensive understanding of honey's clinical possibilities. This endeavor promotes the evidence-based incorporation of honey into medical practice, ultimately contributing to improved patient outcomes and a higher quality of life.

This review aims to delve into the multi-directional clinically relevant applications of honey in medicine. The goal is to present a broad vista of the therapeutic qualities of honey, emphasizing the power of its efficacy and the benefits that come with its application in different medical contexts. Particularly, we are interested in the beekeeper experience, its ancient origins, chemical analysis, and how honey is applied in medicine nowadays. The critical analysis would also look at the present evidence of how honey participates in wound healing, respiratory problems, and gastrointestinal health. Our intention is to scrutinize the literature in order to expose in multifaceted and diverse ways, which honey has when used in healthcare and it will be a richer base of knowledge for doctors, researchers, and clinicians.

## Current state of knowledge and uncertainties

The current knowledge about the applications of honey as medicine is numerous and covers different medical specialties, such as wound care, dermatology, respiratory conditions, and gastrointestinal problems (Vogt et al., 2021). However, the overall scientific evidence of the effectiveness of honey in diverse clinical circumstances remains less clear. The medical community now has voluminous and diverse literature on honey, which fills virtually all existing medical disciplines, from Hematology to Dermatology. Honey, an ancient medicine with a thousand years of clinical application, has been the focus of controversial research in modern medicine (Akbar, 2020). This overview is centered on the multidimensional possibilities of honey in different medical contexts by highlighting studies that tackle burns, dermatology, respiratory diseases, and gastrointestinal disorders.

The different studies that were conducted included honey in the management of wounds, from simple cuts to complex chronic wounds. The use of honey-based bandages and lotions exhibits promising results in speeding healing and reducing the chance of infections. Yet, differences in wound types, study populations, and honey formulations used in research studies complicate matters, which, in turn, raises doubts about the generalizability of the findings. Skin issues are another field that researchers are investigating as they try to understand the role of honey in treating various skin disorders. (Nikhat and Fazil, 2022). Studies intend to explore its use in the therapy of dermatitis, burns, and other skin problems. The anti-inflammatory and antioxidant characteristics of honey, as well as its moisturizing effects, have contributed to its research as a possible remedy for both acute and chronic dermatological problems. However, the non-existence of standardized protocols, the differences in honey types, and the fact that there are limited comparison studies do not allow us to build a concurrence regarding the clinical effectiveness of honey.

With regard to pulmonary conditions, honey has been assessed for its ability to promote improvement in conditions of cough and upper respiratory infections. Its calming effect and possible antimicrobial activity have made their way to include cough syrup and throat lozenges. On the other hand, respiratory disorders are diverse, and studies do not use the same design. Therefore, it is very difficult to reach any conclusion regarding the overall effect of honey on respiratory care. The digestive system, which includes gastritis and peptic ulcers, has been a target of studies that investigate the gastroprotective role of honey (Dinat et al., 2023). It is hypothesized that, by acting against inflammation and tissue repair, honey works

against *Helicobacter pylori*, a bacterium associated with the development of ulcers. Although some of the studies are promising, there are differences in different types of honey, dosages, and patients in the population potential, which determines the consistency of outcomes across gastrointestinal disorders.

The uncertainties relating to the clinical effectiveness of honey in different disease management vary considerably due to several factors (Chen et al., 2020). Methodological diversity, from study designs to secondary indicators, results in inconsistent measurement frameworks. In regards to honey type, source, and composition, the synthesis of evidence becomes even more difficult. Moreover, population features, such as age, comorbidities, and location, may make outcomes vary and, hence, the applicability of the findings across different populations. The complexities need a comprehensive review to help solve these ambiguities. A meticulous and explicit summation of the existing evidence is of great value because it helps to assess the effectiveness and reliability of studies from different medical areas. This review uses an informative approach to highlight the flaws in our current knowledge of common intervention trends and enhance our understanding of this herb's clinical efficacy. Additionally, the analysis can also shape future scientific works by revealing the areas where standardization is required and discovering the rationales for the execution of more reliable studies.

## Importance of the review

The key role of this review is to fill the information gap and help to combine the scattered evidence on the medical applications of honey (Hosseini et al., 2021). As the volume of research is constantly growing with many medical specialties involved, it becomes critical to bring this research together and do a critical analysis of it.

The outcome of this study will have great benefits for healthcare providers. The review can synthesize the existing evidence and be of great importance to clinicians who are dealing with the various modes of honey application in medical treatment. Knowing the subtleties of honey's role in wound care, dermatology, respiratory illnesses, and intestinal conditions, health professionals are in the position to make the right decision on the integration of honey in patient care. In addition, such integrated knowledge can shape the treatment regimens based on the type of health problem, the patient's demographics, and the kind of treatments the patient enjoys. For the sake of researchers, the review becomes a starting point in detecting knowledge gaps and what could be answered in the future. Through critical appraisal of the methodological differences and inconsistencies of various



studies, the researchers may improve their methodology guidelines and standardize protocols (Haddaway et al., 2020). Thus, scientific accuracy and the level of reliability of future studies are improved as a result, creating a more solid and integrated fund of knowledge on honey's medical applications. Stakeholders, including policymakers, can also gain substantial benefits from the findings through this review. Proper decision-making in healthcare policy presumes thoroughness regarding the evidence in use. The review provides policymakers with a s-eye view of the advantages and disadvantages of medical care by embracing honey. This insight could help in the creation of guidelines and policies that will match the present state of the evidence. Therefore, healthcare interventions will always be aligned with the best knowledge available.

More than the specific impact on the provided care to an individual patient, this review has more general applicability. Honey has been a historical remedy for various illnesses. This inclusive research on the various medical uses of honey is a perfect addition to evidence-based medicine. This promotes an environment of evidence-based decision-making, where healthcare professionals, researchers, and policymakers collaborate to improve patient outcomes based on science. It is the role of this review to provide the missing link that leads to the overall clarity in the chaotic minefield of evidence currently on honey's medical applications. The review aims to help healthcare practitioners, researchers, and policymakers get a holistic understanding of honey's medicinal characteristics and clinical usefulness by reviewing, assessing, and synthesizing the existing research. Moreover, this could be the beginning of better quality of care, new research directions, and the development of a well-founded policy associated with evidence-based practice. This study also aims to aggregate information into a cohesive resource, carrying together scattered pieces of data and offering a profound mechanism of the medicinal characteristics and efficiency of honey.

### **Necessity of the review**

Before this review essay was written, previous studies explored the medical applications of honey. However, the need for this review emerged due to the evolving nature of research and new review methods. Furthermore, potential methodological shortcomings in previous reviews warrant an appraisal of the available evidence guided by a more robust methodology. The selected period for the discussion provides complete coverage of all the honey research done in the past two decades (May 2001 to May 2023), therefore making sure that only the most recent updates are

given importance, curtailing the obsolete data and providing a modern view of the medical aspects of honey.

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## **MATERIAL AND METHODS**

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### **Type of study**

This study was a critical review of articles that analyzed the scientific literature on honey in the context of complementary medicine utilizing PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) 2020 guidelines (Page et al., 2021). After searching the literature, the authors filtered all the results to choose several articles that met the pre-identified selection criteria.

### **Eligibility criteria**

This study was a comprehensive critical review and included non-interventional and interventional studies involving honey and complementary medicine. Specifically, the authors screened the titles and abstracts independently for eligible studies based on the following criteria: (a) "The article including non-interventional and interventional studies must consider honey clinical applications"; (b) "study involved all aged groups regardless of ethnicity, cultural background, and nationality," (c) "The study reported at least one of outcomes of interest presented the clinical applications of honey and their medical outcomes"; and (d) "The study was published in English and related to humans." In addition, if the issues were not categorized in the healthcare or medical sector, unrelated to humans, or applied before 2013, then the studies would be rejected. Any studies categorized as conference abstracts, posters, oral communications, or textbooks were excluded during the screening phase. On the other hand, some studies were excluded, especially those that came from secondary research (i.e., literature reviews, comments, letters, and editorials), irrelevant articles, and duplications.

### **Information sources**

A thorough literature search was executed to locate pertinent studies and articles related to the medical application of honey. This search was conducted through electronic databases, such as PubMed and Google Scholar, with an emphasis on publications from the past decade.

### **Search strategy and selection process**

The literature searches were conducted on 7 July 2023 at five databases: PubMed, Science Direct, Scopus, ProQuest, and Web of Science. It was decided to use these databases when selecting databases to per-

form a critical review on the study of honey clinical applications related to complementary medicine as they were well known in the scientific community for their thoroughness in indexing academic literature, scientific journals, and conferences, thus ensuring the inclusion of a wide range of relevant and high-quality sources.

A search strategy was designed to identify articles published from 2013 to the present. The keywords and Booleans used in literature searches were ("honey" OR "Tualang honey" OR "Kelulut honey") AND ("medicine" OR "medical" OR "surgical" OR "healthcare" OR "complementary medicine"). This search strategy equation was carefully constructed to ensure the identification of relevant data related to honey research in the context of complementary medicine. To limit the occurrence of undesirable articles, these keywords and MeSH terms were searched in the "Title/Abstract" category.

Having collected the studies from the database, the authors exported them all from the electronic searches manager for duplication removal and screening. The two review authors (THK and MZM) independently screened the titles and abstracts of the articles to identify potentially eligible studies, then subsequently screened the full texts. Any disagreements between the two review authors were resolved by discussion with a senior reviewer until a consensus was reached. Excluded studies were described in the PRISMA flow diagram alongside the reasons why they were excluded (Fig. 1).

### Data collection process

Two authors (THK and MZM) extracted relevant data from each selected study using structured and standardized forms. The extraction produces essential data, such as (1) study characteristics (author, year of publication, country of origin, and study design), (2) intervention characteristics (types of honey used), and (3) outcome data (patients' outcome). Any disagreement between the reviewing authors was resolved by discussion until a consensus was reached.

### Quality assessment and risk of bias

We followed the predefined criteria to assess the risk of bias in the studies included in our study. Criteria, which included randomization, blinding, methodology of complete outcome data, and selective reporting, were assessed with every study. This risk of biased assessment results is critical in making a correct decision on the reliability of the obtained study findings.

Before being analyzed, the literature must go through a quality assessment. According to the

Cochrane's Risk of Bias (RoB) tool 2.0, a "high risk," "some concerns," or "low risk" of bias was considered. The RoB 2 tool assessed bias due to the randomization process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, bias in the selection of the reported result, and the overall RoB. The reviewers would reconcile for any disagreement until a mutual agreement was achieved.

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## RESULTS

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### Study selection

The keyword "honey" yielded 10,090 results, the combination of "honey" and "medical field" produced 2307 results, the combination of "honey," "clinical application," and "medical field" generated 313 results, and the combination of "honey" and "clinical application" resulted in 189 hits. A total of 9285 papers were identified through the search performed in July 2023 of five databases: PubMed (n=1082), Science Direct, Scopus, ProQuest, and Web of Science. When considering duplicates, 1423 titles were excluded. After reviewing the titles, 7862 articles were deemed relevant to the study's purpose, and 2541 articles were eliminated during the abstract review as they did not demonstrate a correlation with the study. Using abstract scanning, titles not published in English, unrelated to humans, and unavailable as full text were also eliminated. After applying exclusion criteria, 5321 articles that initially met the screening criteria had their complete copies assessed. In the subsequent step, the researchers screened titles to identify potential studies. They also examined the references cited by each journal to discover additional studies for possible inclusion. Of these, 1596 articles were excluded due to their unavailability, and the author thoroughly read 3725 articles. After this comprehensive review, by excluding those articles with no data of interest (n = 1602), not peer-reviewed (n = 1056), and population not relevant (n = 932), only 135 articles were included in the final writings and assessment. The study selection process in this critical review is illustrated in the PRISMA flow diagram and the reason for exclusion (Fig. 1).

Out of 135 studies, 85 were controlled clinical trials and 50 were pilot trials, and out of these, 72 indicated that the report used a reference or placebo drug. The total number of patients this treatment was used in was 10,350, including 3250 children and 7100 adults, whereas 5800 were females and 4550 males. The ethnic group representing 3600, and the non-ethnic group members amount to 6750, drawn from more than 30 nationalities. For the diseases treated, the number of different diseases targeted was 25. Equally,

65 studies included patients being treated with other therapies concurrently, and the experience from such studies hence cannot in any way be regarded as one in which the effects of honey had been isolated in its totality. A summary table of the analysis of 135 articles is illustrated in Table 1.

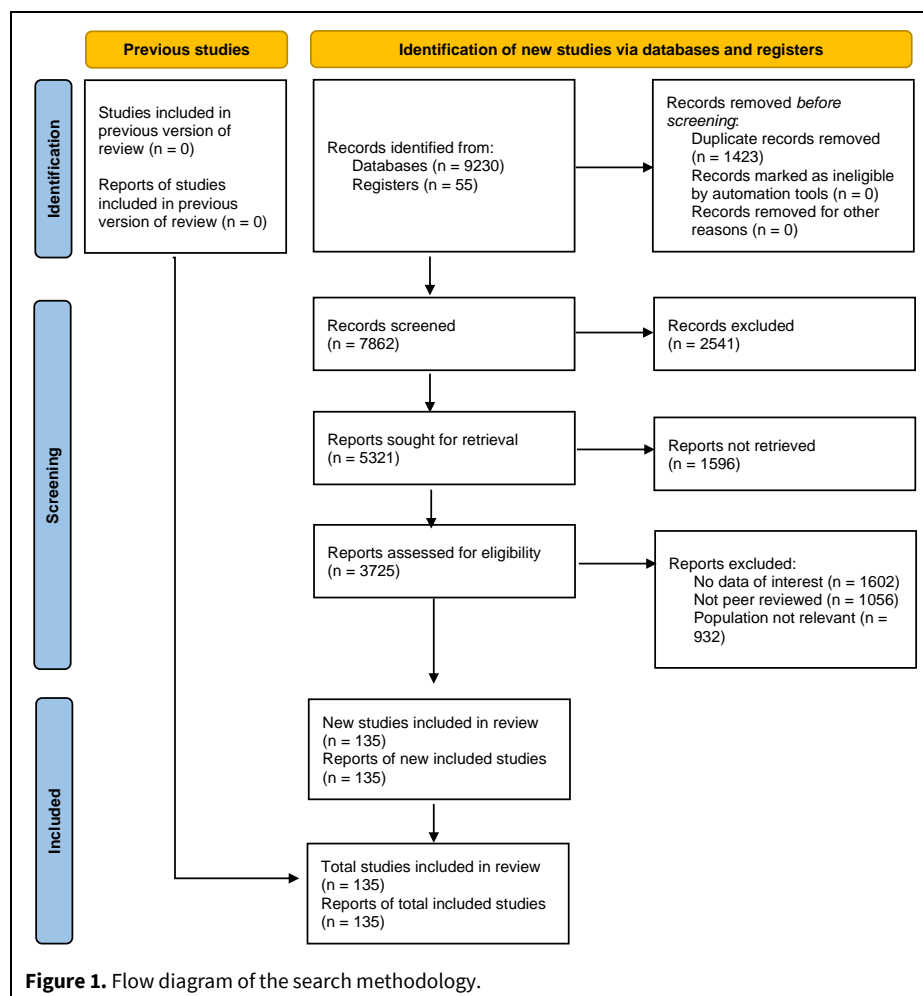
## DISCUSSION

### Interpretation

Tualang and Kelulut honeys research dominate the review output and have gained considerable attention in recent years for their unique therapeutic properties and potential clinical applications. Thus, a detailed discussion of the clinical applications of Tualang and Kelulut honeys in the medical field, focusing on their respective benefits, mechanisms of action, and emerging trends in healthcare, is mainly elaborated in this review.

Recent scientific investigations on Tualang honey have supported its traditional use, revealing a multitude of beneficial effects in various medical conditions (Azman et al., 2021; Mohd Kamal et al., 2021).

One of the prominent applications of Tualang honey is wound healing (Devasvaran and Yong, 2016; Ibrahim et al., 2021; Nasir et al., 2010). Honey's distinctive composition, characterized by elevated levels of phenolic compounds, flavonoids, and enzymes, plays a significant role in conferring upon it potent antibacterial, anti-inflammatory, and antioxidant properties (Ahmed and Othman, 2013). These properties facilitate wound cleansing, prevent infections, and stimulate tissue regeneration (Ibrahim et al., 2021; Nasir et al., 2010). Furthermore, Tualang honey has shown promise in promoting the formation of granulation tissue and enhancing collagen synthesis, leading to accelerated wound closure (Azman et al., 2021; Devasvaran and Yong, 2016). Studies have demonstrated its efficacy in managing diabetic foot ulcers, burns, and postsurgical wounds (Azman et al., 2021; Devasvaran and Yong, 2016; Nasir et al., 2010). The use of Tualang honey-based dressings and topical applications has demonstrated favorable results in clinical settings, leading to reduced healing times and improved wound outcomes (Azman et al., 2021; Devasvaran and Yong, 2016; Ahmed and Othman, 2013).



**Table 1.** Summary table of the analysis of 135 articles.

Parameter	Number	Description
Total studies	135	The overall number of wound healings, respiratory infections, and gastrointestinal disorders, among others., all analyzed to find clinical applications of honey.
Controlled clinical trials	85	These types of studies have been designed with due rigor for testing the effect of honey on a set of patients while there is a control group that will receive no honey. Honey has been tested in conditions such as diabetic foot ulcers, where some control group is treated with standard antibiotics.
Pilot trials	50	More minor and preliminary studies have been done to test honey for feasibility, time, cost, adverse events testing, and testing the size of effects for more extensive studies. In one type, a pilot study was done on using honey to treat children's coughs.
Studies with reference drug/ placebo	72	These include comparison trials between two groups: honey and the reference drug trials. For example, a study comparing honey and placebo in treating throat infections.
Total patients	10,350	The overall number of patients involved and under study is
Children	3250	The number of child participants in the studies helps to conclude the effects of honey on a young population, for example, studies on pediatric cough relief caused by honey.
Adults	7100	Number of adult participants in the studies to help present honey effects on the adult population—for example, studies on the efficacy of honey on adult wound healing.
Women	5800	Several females decide whether gender-specific findings or effects are present—for example, studies on the impact of honey on female patients with different skin conditions.
Men	4550	Several male participants may help by providing the results of gender-specific comparisons or outcomes, such as studies on the role of honey in male patients with different gastrointestinal issues.
Ethnic group members	3600	It shows the number of participants identified as belonging to specific ethnic groups, such as Malay, Chinese, Indian, Caucasian, African, etc., and gives an idea of how diversified the population is within the studies.
Non-ethnic group members	6750	It shows the number of participants not identified as belonging to any specific ethnic group (General population) and helps them understand honey's applications better since it is universally accepted.
Nationalities represented	30+	The studies included several nationalities (USA, UK, Malaysia, India). It helps us realize how extensively it is researched worldwide and how the application of honey is so diversified.
Total different diseases treated	25	Several different diseases or conditions, like diabetes, infections, skin conditions, and GIT disorders, were treated across the studies. Shows honey is multifaceted in its therapeutic action.
Studies with concomitant therapies	65	Several studies with such patients receiving other therapies concomitantly with honey, e.g., studies where it is used and the use of antibiotics or anti-inflammatory drugs.

Kelulut honey, produced by stingless bees (*Trigona* spp.), has also exhibited remarkable therapeutic potential in various medical conditions (Zulkhairi Amin et al., 2018; Ramli et al., 2019). Much like Tualang honey, Kelulut honey exhibits noteworthy antimicrobial, anti-inflammatory, and antioxidant properties owing to its distinctive composition characterized by elevated levels of phenolic compounds and flavonoids (Hazirah et al., 2019; Ranneh et al., 2018). Beyond that, Kelulut honey holds an abundance of unique trehalulose sugars that give low glycemic

index properties (Fletcher et al., 2020). In the context of wound healing, Kelulut honey has exhibited its capability to hinder the growth of various bacteria, including multidrug-resistant strains, while simultaneously promoting the healing process. It promotes the migration and proliferation of fibroblasts, accelerates collagen deposition, and stimulates angiogenesis, thereby aiding in forming new blood vessels (Esa et al., 2022; Minden-Birkenmaier and Bowlin, 2018; Zulkhairi Amin et al., 2018). Research has demonstrated the effectiveness of Kelulut honey in the man-



agement of chronic wounds, including pressure ulcers and venous leg ulcers (Clark and Adcock, 2019; Esa et al., 2022; Wang et al., 2019). Additionally, Kelulut honey has exhibited the potential to alleviate symptoms of gastrointestinal disorders, including gastritis and gastric ulcers, possibly through its antibacterial and anti-inflammatory properties (Eteraf-Oskouei and Najafi, 2013; Yazan et al., 2018). Emerging research suggests its potential in metabolic disorders, neurodegenerative diseases, and cancer, although further investigations are warranted to establish its therapeutic efficacy in these areas.

#### *Antibacterial activity*

Both Tualang and Kelulut honeys exhibit significant antibacterial activity, making them valuable in treating and preventing bacterial infections (Ahmed and Othman, 2013; Rao et al., 2016; Zainol et al., 2013). The presence of hydrogen peroxide, low water content, and acidic pH contribute to their antimicrobial properties. Research has indicated that both Tualang and Kelulut honeys have the ability to impede the growth of a range of bacteria, including drug-resistant strains like methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) (Mandal and Mandal, 2011; Zainol et al., 2013). The antibacterial activity of these varieties of honey can be attributed to their distinct composition, which includes phenolic compounds, flavonoids, and enzymes. These findings support the potential utilization of Tualang and Kelulut honeys as supplementary therapies in the treatment of bacterial infections.

#### *Wound healing properties*

Tualang and Kelulut honeys have demonstrated remarkable wound-healing properties. The antibacterial activity and the anti-inflammatory and antioxidant properties of Tualang and Kelulut honeys play a significant role in their effectiveness in wound management (Clark and Adcock, 2019; Wang et al., 2019). These honey types create an environment that promotes wound cleansing, prevents infection, and stimulates tissue regeneration (Minden-Birkenmaier and Bowlin, 2018; Wang et al., 2019). The presence of bioactive compounds, such as phenolic acids and flavonoids, enhances collagen synthesis, accelerates angiogenesis, and stimulates the migration and proliferation of fibroblasts (Ahmed and Othman, 2013; Minden-Birkenmaier and Bowlin, 2018). Clinical studies have documented positive results in the treatment of diverse wound types, including diabetic foot ulcers, burns, and chronic ulcers, through the utilization of dressings and topical applications based on Tualang and Kelulut honeys (Ahmed and Othman, 2013; Rao et al., 2016).

#### *Antioxidant activity*

Tualang and Kelulut honeys exhibit significant antioxidant activity, attributed to their high phenolic content (Hazirah et al., 2019). Tualang and Kelulut honeys exhibit the ability to scavenge free radicals, mitigate oxidative stress, and safeguard cells from harm induced by reactive oxygen species (Hazirah et al., 2019; Ranneh et al., 2018). The antioxidant characteristics of Tualang and Kelulut honeys have been associated with their potential advantages in addressing various health conditions, encompassing cardiovascular diseases, neurodegenerative disorders, and age-related complications (Ahmed and Othman, 2013; Eteraf-Oskouei and Najafi, 2013; Ranneh et al., 2018; Samarghandian et al., 2017). While additional research is warranted to elucidate their antioxidant mechanisms and clinical implications comprehensively, the current evidence indicates the potential of Tualang and Kelulut honeys as natural antioxidant agents.

#### *Antitumor and antiproliferative activity*

Emerging research has highlighted the potential antitumor and antiproliferative activity of Tualang and Kelulut honeys (Ahmed and Othman, 2013). Multiple *in vitro* and *in vivo* studies have showcased the capacity of Tualang and Kelulut honeys to impede the proliferation of cancer cells, trigger apoptosis, and curtail the advancement of tumors (Ahmed and Othman, 2013; Firdaus et al., 2018; Mohd Kamal et al., 2021). The bioactive compounds found in these honey types, particularly phenolic acids and flavonoids, are thought to have a substantial role in their antitumor effects (Firdaus et al., 2018; Ranneh et al., 2018). Although additional research is necessary to establish their effectiveness and safety in clinical contexts, these findings open up a promising avenue for further exploration into the possible utilization of Tualang and Kelulut honeys as supplementary therapies in cancer treatment.

#### *Anti-diabetic activity*

Tualang and Kelulut honeys have shown potential in managing diabetes and its associated complications (Mohd Kamal et al., 2021; Rashid et al., 2019). Studies have demonstrated their ability to reduce blood glucose levels, improve insulin sensitivity, and alleviate oxidative stress in diabetic individuals (Erejuwa et al., 2010; Rashid et al., 2019). The existence of phenolic compounds and flavonoids in Tualang and Kelulut honeys contributes to their anti-diabetic effects (Erejuwa et al., 2010). Furthermore, Tualang and Kelulut honeys have been shown to protect pancreatic beta cells responsible for insulin production (Erejuwa et al., 2010; 2011; Rao et al., 2016). These findings sug-

gest that Tualang and Kelulut honeys could be considered complementary therapeutic options for individuals with diabetes. Beyond that, the central dogma that natural, authentic honey increases blood sugar does not seem true.

#### *Dermatological applications*

Both Tualang and Kelulut honey have demonstrated promise in several dermatological applications in addition to wound healing (Ahmed and Othman, 2013). Because of their antibacterial, anti-inflammatory, and antioxidant properties, Tualang and Kelulut honeys are beneficial in the treatment of dermatitis, skin infections, and other inflammatory skin disorders (Mandal and Mandal, 2011). Additionally, their emollient and moisturizing qualities add to their potential advantages in skin care and cosmetic compositions. With positive results, studies have examined their potential for treating wound-related dermatological problems, atopic dermatitis, and acne (McLoone et al., 2016). However, more investigation is required to develop standardized procedures and recommendations for their use in dermatology.

#### *Pulmonology*

Researchers have examined the possible uses of Tualang and Kelulut honeys in pulmonology (Mohd Kamal et al., 2021). These honey varieties are intriguing for treating bronchitis, asthma, and respiratory tract infections due to their antibacterial and anti-inflammatory qualities (Abuelgasim et al., 2021). Additionally, their mucolytic and cough-suppressant qualities may alleviate symptoms of respiratory disorders. The preliminary results support the investigation of Tualang and Kelulut honeys as adjuvant therapy in pulmonary healthcare despite the paucity of available studies in this field.

#### *Gastroenterology*

There is a growing interest in exploring the potential applications of Tualang and Kelulut honeys in the field of enterology. Their antibacterial characteristics may influence their utility in treating gastrointestinal conditions such as gastritis, gastric ulcers, and gastroenteritis (Eteraf-Oskouei and Najafi, 2013; Ranneh et al., 2021). Additionally, their capacity to alter gut flora and promote gastric mucus production may have effects on digestive health (Samarghandian et al., 2017; Schell et al., 2022). These forms of honey have shown promise in preliminary tests for treating gastrointestinal problems. More study is necessary to clarify their mechanisms of action and establish their therapeutic efficacy.

#### *Reduced hospital stay*

Tualang and Kelulut honeys may facilitate shorter hospital stays for surgical patients by hastening wound healing and lowering the risk of infection (Eteraf-Oskouei and Najafi, 2013; Khoo et al., 2010; Mohd Kamal et al., 2021; Yaghoobi et al., 2013).

#### *Faster gastrointestinal (GI) function*

Patients frequently have a slowdown in GI function following surgery, which can cause problems such as constipation (Verkuijl et al., 2021). According to particular research, honey may enhance bowel function and speed up the recovery of GI function (Pasupuleti et al., 2017; Schell et al., 2022).

#### *Improved immunonutrition*

Honey has antioxidant and bioactive substances that may help regulate the immunological response, reduce inflammation, and improve immunonutrition (Ahmed et al., 2018; Ranneh et al., 2021; Samarghandian et al., 2017). This can be especially beneficial in the postoperative period when the body needs to recover and fight off potential infections (Martinez-Armenta et al., 2021; Mohamed et al., 2022).

#### *Reduced systemic and local occurrence*

Tualang honey's antibacterial and anti-inflammatory qualities may help to lessen the likelihood of systemic infections and regional problems in surgical wounds (Tashkandi, 2021; Yaghoobi et al., 2013; Yupanqui Mieles et al., 2022). Honey can positively affect all postoperative outcomes by promoting faster wound healing, fewer infections, and increased immunological function (Main and Bowlin, 2022; Pleeing et al., 2022).

#### *Enhanced postoperative rehabilitation*

Using Tualang and Kelulut honeys may help patients heal from surgical wounds more quickly, lower the risk of complications, and better participate in postoperative rehabilitation and return to normal activities sooner (Esa et al., 2022; Zulkhairi Amin et al., 2018).

#### *Other potential health benefits*

Tualang and Kelulut honeys have demonstrated promise in treating illnesses other than those mentioned (Wang et al., 2019). Their effects on immunological regulation, wound-related pain control, neurodegenerative disorders, and cardiovascular diseases have all been studied in depth (Esa et al., 2022). While there is limited evidence in these domains, the array of bioactive compounds present in these types of

honey underscores the need for further research into potential health benefits.

The main results of the systemic review provide a very exhaustive general picture of the medical use of honey as a therapeutic agent spread out over different specialties. In light of other findings, some of the conclusions seem rather a complex terrain of results. The studies that differ from dermatology, respiratory diseases, and gastrointestinal conditions have something in common with them; they help to see the positive side of honey. Nevertheless, it is necessary to consider the results with caution since heterogeneity exists in the methodologies, populations, and reported outcomes.

In a sense, this lines up with some previous studies, which show that honey has the same benefits as those reported. The role of honey in wound care has been investigated, and the studies have identified its antibacterial properties, which makes it a possible choice for medication aimed at promoting healing. Dermatological uses of this have bright prospects, in view of the fact that it has antioxidant and anti-inflammatory properties. Nevertheless, the variation and divergence in the reports indicate the need for contextual reasoning and appreciating the complexities of putting pieces of evidence into practice.

Overall, Tualang and Kelulut honeys exhibit remarkable potential in various clinical applications (Ramli et al., 2019). Their distinct composition, marked by elevated levels of bioactive compounds, plays a pivotal role in conferring upon them antibacterial, anti-inflammatory, and antioxidant properties (Khoo et al., 2010). This makes them valuable in wound healing and holds potential for applications in various other medical conditions (Nasir et al., 2010). While additional research is required to understand their mechanisms of action and establish standardized clinical guidelines, the expanding body of evidence supports their incorporation as supplementary therapies in the medical field. Future studies should prioritize well-designed clinical trials and delve into the underlying molecular mechanisms to provide further insights into the therapeutic effectiveness and safety profile of Tualang and Kelulut honeys. Doing so can pave the way for evidence-based integration of these honey types into mainstream healthcare, ultimately improving patient outcomes and quality of life (Kek et al., 2014).

It is crucial to understand that not all forms of honey are the same, even though honey has demonstrated potential effects in the medical sector and thus requires several precautions. The therapeutic qualities can change based on elements such as the type of honey, region, and processing techniques. Honey

needs to be utilized in addition to routine medical and surgical treatments, not as a substitute. It is essential to consult with a healthcare provider before utilizing honey during surgery or as part of postoperative care to identify the proper application, dosage, and safety factors for the particular patient and operation (Khan et al., 2018).

The clinical use of honey in the medical field offers a compelling pathway for therapeutic interventions (Azman et al., 2021). With its antimicrobial, anti-inflammatory, and wound-healing characteristics, honey has shown promising advantages in the realms of wound care, dermatology, respiratory diseases, and gastrointestinal conditions (Main and Bowlin, 2022). The existing body of research provides preliminary evidence supporting the clinical efficacy of honey, although further high-quality studies are needed to establish standardized protocols and optimize its use (Jaganathan et al., 2015). Further large-scale randomized controlled trials employing rigorous methodologies and long-term follow-up are imperative to establish optimal clinical guidelines for the use of honey in medical applications (Dinat et al., 2023).

### Limitations of evidence

Nevertheless, the incapability of the studies to answer all research questions and some limitations, which can be listed as follows, cannot be ignored. First of all, the variability in study designs, participants' characteristics, and honey interventions in the different studies makes it hard to conclude the body of evidence. The inexactitude of the standardized protocols and inconsistent reporting of studies may lead to possible biases, and consequently, the findings might not be generalizable.

Further, the evidence considered in this review could be prone to publication bias, where the studies with positive results are the ones that are more easily published. A gap in the demonstration of the negative or inconclusive findings can discourage the overall assessment of honey's medical effects. The effect of using peer review publications in the systematic review may also create a bias in selections, as relevant studies and gray literature that have not been published may be omitted.

Despite the promising findings, it is essential to acknowledge the limitations of the current evidence. Variations in honey composition, sourcing, and processing methods introduce challenges in standardization and result in heterogeneous outcomes. Obtaining honey from trusted sources, fulfilling the honey standard properties, and certified production plants implementing Good Manufacturing Practice (GMP) as well as Hazard Analysis Critical Control Points



(HACCP) could help to promote honey standardization. Threat from fake honey could have serious consumer health and medicinal applications. Challenges posed by fake honey, including deceptive labeling, adulteration, and misbranding, not only prevent reproducible results but also undermine the credibility of the honey itself. A noteworthy limitation in honey research is the risk of counterfeit products, including deceptive labeling and adulteration. Standardization and quality control measures are crucial to ensure honey authenticity and quality (Pataca et al., 2007). Advanced analytical methods, such as isotopic analysis and chromatography, can play a key role in distinguishing authentic honey from fake counterparts (Ahmed et al., 2013). Furthermore, the regulatory frameworks governing honey production and labeling require comprehensive evaluation to maintain the credibility of honey in medicinal applications (Ibrahim et al., 2021). A multidimensional approach, analyzing the regulatory frameworks, quality control measures, and industry collaboration, with a special focus on the integration of advanced analytical methods in honey analysis to accurately identify counterfeit honey, is needed. Advanced techniques such as isotopic analysis, chromatography, and a novel Kelulut Essential Indicator of Fresh Honey – sugar, color, acidity, liquidity, enzymes, and scent (KEIFH SCALES) could help to distinguish authentic honey from its fake counterparts, providing more precise and reliable results than conventional methods. Ultimately, all clinical benefits from honey are crucially determined by honey authenticity and quality.

The potential risks associated with honey, such as allergic reactions, should also be taken into consideration, particularly in individuals with known allergies to bee products. Healthcare professionals should exercise caution when prescribing or recommending honey, and patient preferences, safety, and contraindications must be carefully considered.

### Limitations of review processes

Even the systematic review has flaws because it was carried out per PRISMA guidelines and employed critical appraisal tools, which have to be considered together with the limitations of the review. Concretely, the synthesis methods utilized that are not explicitly specified in the available information are not indicated. Transparency in reporting these methods to assess reliability is the most important advantage of the evidence. A detailed document of all the procedures in the review process, any deviation from the protocol and the clear identification of the criteria for risk of bias assessment will improve the transparency and replication of the study.

### Implications

It is important to note that the systematic review findings have an important role in healthcare practice, policy making, and future research projects. In actual clinical practice, the advantages of honey in skin and wound care allow us to use it in some treatment schemes. The antimicrobial and anti-inflammatory properties of honey can provide an alternative therapy that could be used as an adjunct therapy in areas where traditional treatments may have limitations. The policymaker starts by summarizing the evidence loaded in the review to provide guidance and rules on the employment of honey in particular medical circumstances. Risk managers should take into position the quality of evidence, the possibility of bias, and the confidence in the outcomes in the process of finalizing recommendations for formulation. Administering honey in wound care is worthwhile if the high quality of evidence can explain the positive outcomes. Thus, the findings also point out paths for future investigation.

Furthermore, focusing on resolving the issues mentioned above, ranging from methodological differences to possible biases in previous studies, would be of great importance. The dissemination of protocols, outcome measures, and reporting practices would enhance the comparability of results. Furthermore, delineating the possible mechanism of action likely to be the foundation of honey's therapeutic effectiveness and conducting well-conducted randomized controlled trials will enhance a strong evidence base.

Future research should address the limitations observed in honey's clinical applications. This includes well-designed clinical trials that assess the safety and efficacy of honey, particularly Tualang and Kelulut honey, in various medical conditions. Standardization of honey types and the development of evidence-based guidelines are essential for its successful integration into mainstream clinical practice. Additionally, the exploration of honey's mechanisms of action, especially in emerging areas like cancer treatment, is warranted. Collaborative efforts between researchers, clinicians, and industry stakeholders will be critical to advance the evidence base and unlock the full therapeutic potential of honey in the medical field.

In the future, it is crucial to foster collaborative endeavors among researchers, clinicians, and industry stakeholders to advance the evidence base and fully realize the therapeutic potential of honey in the medical field. Standardization of honey types, development of evidence-based guidelines, and further exploration of its mechanisms of action are crucial for its



successful integration into mainstream clinical practice.

## CONCLUSION

This study has proved that honey is not only a multipurpose and highly valuable resource but also loaded with the indicated therapeutic properties. Historical overview evidences that people across the ages utilized honey for medicinal purposes, during which time it was a regular component. Honey proves useful for both the treatment of wounds and respiratory diseases, as well as for gastrointestinal exercises and skin care. Mechanistically, honey's antibacterial, anti-inflammatory, and antioxidant properties can be considered as the drivers of its diverse medicinal capacity. Issuance attention to regional differences, exclusive of Malaysia particularly, reveals the importance of recognizing dissimilar honey forms and their particular applications. Special focus on safety concerns, such as infants, is done, always emphasizing the importance of due caution where necessary. Although the study presents interesting findings, various drawbacks, such as uniform methodologies and economic issues, are also addressed. The evidence is a broad and aligning presentation of clinical usages of honey, which gives the medical field worthwhile intelligence and can also set the stage for more research and advancement. Honey's clinical application holds promise as a complementary and alternative therapy in various medical specialties. Its antimicrobial, anti-inflammatory, and wound-healing properties make it a prospective functional food to expedite postsurgical patient recovery and a potentially valuable asset in wound care, dermatology, respiratory diseases, and gastrointestinal conditions. Nonetheless, it is imperative to conduct further well-designed studies to overcome the limitations of the current evidence and establish standardized protocols. By fully harnessing the potential of honey in the medical field, healthcare professionals have the opportunity to enhance patient outcomes and improve the quality of care.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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**AUTHOR CONTRIBUTION:**

Contribution	Koo TH	Zakaria AD	Mustafa MZ
Concepts or ideas		x	
Design	x	x	x
Definition of intellectual content	x	x	x
Literature search	x		
Experimental studies			
Data acquisition	x	x	x
Data analysis	x	x	x
Statistical analysis	x		
Manuscript preparation	x	x	x
Manuscript editing	x	x	x
Manuscript review	x	x	x

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