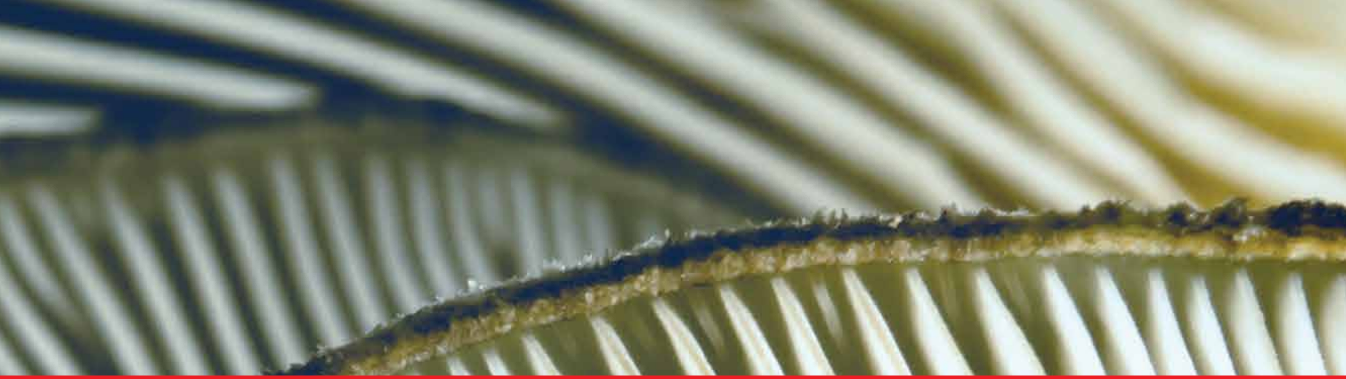

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Health Benefits of Honey and Propolis
Scientific Evidence and Medicinal Uses

Edited by Vagner De Alencar Arnaut de Toledo and Daiani Rodrigues Moreira

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Food Science and Nutrition

Volume 13

Aims and Scope of the Series

The significance of food is undeniable, especially in light of the impending challenge facing humanity: ensuring there will be enough food to meet the basic needs of a population expected to reach approximately 10 billion by 2050. These food-related challenges align with some of the United Nations' sustainable development goals, with a target to achieve them by 2030. One thing is certain: food should be not only nourishing and safe but also tailored to the diverse needs of individuals throughout their lifetimes, all while meeting consumers' sensory expectations. Understanding the diverse chemical composition of food, often referred to as biodiversity, and how these components can contribute to human health by considering factors like bioaccessibility, bioavailability, and bioactivity at the organ level, is crucial for grasping and promoting a healthy diet. Thanks to the continuous evolution of analytical methods and interdisciplinary research, significant strides have been made in the field of food science and nutrition.

Meet the Series Editor

Maria Rosário Bronze has been working in Analytical Chemistry since 1986. Her Ph.D. in 1999 contributed to the study of food products using capillary electrophoresis. The main goal of her research since 1999 has been focused on Analytical Chemistry applied mainly to the analysis of foods and by-products of food industry. She conducted research in collaboration with national and international research groups, at iBET and ITQB Technology Division. From 2017 until 2021 she was head of Food & Health Division at iBET and head of the Food Functionality and Bioactives Laboratory. MR Bronze has been an Associate Professor at the Pharmacy Faculty of Lisbon University and head of the Structural Analysis Laboratory since 2012. As a researcher, MR Bronze is a Senior Scientific Advisor at Food & Health Division at iBET and Head of Food Functionality and Bioactives Laboratory at the same Institute, Collaborator at iMED and Researcher at ITQB NOVA. Her current research is focused on quality and beneficial health effects of food components. Gas and liquid chromatography associated with mass spectrometry are used by MR Bronze in the characterization of samples. Sensory evaluation is also an important area of her research. The main food products studied by her are olive tree products (olive, olive oil, leaves), cereals such as maize, legumes (faba bean, pea, chickpea, lentils) fruits (apple, grapes, opuntia ficus), fruit juices and wine, among others. More recently her interests have also involved biodiversity, bioaccessibility, and bioavailability studies on food products and their components, mainly phytochemicals as phenolic compounds, using different analytical tools such as mass spectrometry. As a senior scientific advisor at Food & Health Division at iBET she is involved in different areas: (i) isolation, characterization and formulation of bioactive and functional compounds or extracts from natural sources and wastes from food and other related industries; (ii) pre-clinical assays to provide support to understand health claims related with the beneficial effects of food nutrients/bioactive components; (iii) establishment of analytical methodologies including mass spectrometry state-of-the-art to fully characterize different matrices, from food products, natural extracts or biological fluids (Food Functionality and Bioactives Laboratory).

Meet the Volume Editors

Vagner de Alencar Arnaut de Toledo completed his Master's degree (1991) and Doctorate (1997) in Animal Production, with an emphasis on Apiculture, at the Faculty of Agrarian and Veterinary Sciences of Paulista State University, Jaboticabal Campus in Brazil and conducted postdoctoral research in Entomology (2006) at the Luiz de Queiroz College of Agriculture - São Paulo University also in Brazil. He is currently a Titular Professor at Maringá State University in Brazil, and he teaches Apiculture in the Animal Science Department, as well as several disciplines in Master's and Doctorate courses in Animal Science. He has coordinated the Bee Research Group (GPBee-UEM) for more than 25 years, solidifying his scientific contributions in the field. He has authored over 80 articles published in specialized scientific journals and has an extensive academic output, including presentations at national and international events, such as posters, oral communications, abstracts, and technical reports. His research expertise focuses on the production and selection of honeybees, with an emphasis on the use of molecular markers, such as MRJP3, in royal jelly production, as well as studies on bee pollination, effects of pesticides on bees, and nutrition focusing on Africanized honeybees. In recent years, several studies in cited areas began with stingless bees.

Daiani Rodrigues Moreira is a Professor at the Maringá State University in Brazil. She earned her Master's degree in Genetics and Breeding in 2015 and completed her Doctorate in the same field in 2022, both at Maringá State University. In 2024, she concluded her postdoctoral studies in Environmental Biotechnology at the same institution, focusing her research on honeybees and stingless bees. Her research covers topics such as nutrition, toxicology, behaviour, royal jelly production, technology and management, genetic improvement, and queen selection. Additionally, she has cell biology, genetics, and animal biotechnology expertise, contributing to an interdisciplinary and innovative approach in her research endeavours.

Contents

Preface

Bee products provided by bees have been explored and utilized since the earliest days of mankind. In this context, honey stands out as one of the oldest and most versatile natural products, recognized for its flavour and nutritional properties and its health benefits, ranging from antimicrobial properties to therapeutic potential in various medical conditions. Propolis has also gained prominence in science and contemporary medicine, with the growing interest in natural and sustainable products.

This book, *Health Benefits of Honey and Propolis – Scientific Evidence and Medicinal Uses*, discusses advancements in using honey and propolis across different countries, exploring the richness of these products in diverse scientific and cultural contexts. Chapter 1 highlights Brazilian honey with geographical indication, emphasizing how its unique floral origin can benefit health. Chapter 2 focuses on the microbiota of honey produced by native stingless bees from the Amazon, uncovering its microbial diversity and antimicrobial activity.

The therapeutic applications of honey are explored in depth in Chapter 3, presenting a systematic review of honey's benefits in treating burn wounds. Chapter 4 examines medicinal honey's ecological and botanical aspects, addressing its production, authenticity, and safety.

Chapters 5 and 6 delve into the health benefits of honey and propolis, offering complementary perspectives on their therapeutic properties. Finally, Chapter 7 discusses using bee products to enhance human health, broadening the range of applications for these natural products.

This book aims to provide an essential source of information, assisting readers in future investigations. It is intended for both early-career and experienced scientists, offering updated and in-depth knowledge to support the development of research projects focusing on the diverse functions and applications of honey and propolis. We hope it will serve as a valuable tool for the scientific community, as a reference for current data and insights to guide future studies and research on these products.

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Section 1

Fundamentals and Origin

Chapter 1

Health Benefits of Brazilian Honeys Are Affected by Floral and Geographical Origin

Douglas Galhardo, Alessandra Fernandes Gonçalves Benites, Daiani Rodrigues Moreira and Vagner de Alencar Arnaut de Toledo

Abstract

Honey has a documented history of use that dates back to biblical times. Honey stands out from other sweeteners, composed primarily of sugars, due to its variety of micronutrients. These, and the sugars, give honey significant therapeutic properties, strengthening the immune system and promoting health. The unique characteristics of each type of honey, including flavor, color, and composition, are influenced by the diversity of nectar collected throughout the year and the species of bee, factors that determine the quality of the product. Thus, Brazil has distinct, well-defined biomes, giving characteristic medicinal properties to the honey produced in each of them, in addition to presenting a flora with a great diversity of plants in each of them. However, there are few studies on Brazilian honey's nutraceutical effects. Such studies can present characteristics of the medicinal properties of each region, ensuring the reliability of the characteristics of honey from a region recognized by the geographical indication, which considers the know-how plus the difference in local flora and fauna, ensuring specific variations between regions and seasonal and environmental influences.

Keywords: Brazilian honey, denomination of origin, floral origin, geographical indication, health-benefiting properties

1. Introduction

Brazil, despite its vast territorial extension and diversity of endemic species [1], has few studies on the quality of produced honey. Honey is the main product marketed by bees, and the Southern region of Brazil accounts for about 40% of the national honey production volume, followed by the Northeast and Southeast regions [2]. In addition to honey, beekeeping offers a variety of commercially valued products, such as wax, bee pollen, propolis, royal jelly, and pollination services. Another growing sector is the production of bee venom and products used in cosmetics, food, and medicines. Moreover, the sale of queens, colonies, swarms, equipment, supplies, and various materials constitutes a relevant market niche.

Honey is a natural, sugary product produced by honeybees, derived from both floral and extrafloral nectarines. The primary sugars found in honey are fructose and glucose, with smaller quantities of other sugars like sucrose, maltose, isomaltose, nigerose, turanose, and maltulose [3]. According to Normative Instruction No. 11, dated October 20, 2000 [4], and the Codex standard for honey, honey is defined as a food product produced by honeybees [5]. It is a viscous and concentrated solution composed mainly of sugars (about 80%) and water (ranging from 15 to 20%).

Given this, it is crucial to understand the various types of honey available across Brazilian territory. Therefore, this study aimed to correlate the floral origin of honey with its geographical location and medicinal properties.

2. Diversity of nectar and its influences on honey

Floral honey can be monofloral, multifloral, and extrafloral honey, which is produced from nectar secretions that do not come directly from flowers but from other parts of plants, such as leaves, buds, and stems [2]. Additionally, honey can be categorized into two classes based on botanical origin flower honey or floral and honeydew honey [6, 7]. The term "honeydew" is used to describe plant secretions and the excretions of insects that feed by sucking the sap from these plants [8, 9]. Example of honeydew-producing organisms include insects and other insects like whiteflies, aphids, and psyllids [2].

Honey is a distinctive and valuable food, renowned for its numerous properties. Its natural sweetness and thick consistency are notable features, as well as its capacity to inhibit microorganism growth, attributed to its low water content and acidic pH [3], hydrogen-peroxide content, minerals and polyphenols, and honeybee enzymes that are present in honey, and they all contribute to the antimicrobial effect of honey [10, 11].

The flavor and color of honey result from a complex combination of sugars, acids, and volatile compounds, varying according to floral origin and the chemical elements present. The composition of honey is influenced by its botanical origin, which can vary based on vegetation, the seasons of the year, and climate [12].

Other constituents of honey that have interference from botanical origin are phenolic compounds, synthesized to protect against biotic and abiotic stress as well as oxidative damage [13]. In addition to phenolic compounds (including flavonoids and phenolic acids), honey has enzymes (such as glucose oxidase and catalase), ascorbic acid, carotenoid-like substances, organic acids, amino acids, and proteins, conferring its antioxidant activity [14]. Baglio [15] reported that the main phenolic acids isolated in honey were caffeic, coumaric, ferulic, ellagic, chlorogenic, and gallic acid also the following flavonoid molecules: quercetin, hesperetin, chrysin, pinocembrin, luteolin, apigenin, myricetin, and kaempferol.

Studies evaluating the effect of honey use on diseases in animals and humans demonstrate anti-inflammatory, antibacterial, antiviral, antifungal, antiviral, and antitumor activities, among other effects [16]. Furthermore, it improves the immune status, providing support for its anticancer activity, with proven effects against breast, colorectal, renal, prostate, cervical, and oral cancer [16]. Kaškonienė and Venskutonis [17] stated that, because phenolic compounds are passed from plants to honey, each honey presents a profile due to its floral origin collected by bees, indicating differences between regions, as well as seasonal and environmental factors. The authors demonstrate that these phenolic compounds are being studied and isolated, which has been providing floral markers for honey of monofloral origin and also from some specific regions. These studies demonstrate the importance of in-depth studies on honey from each Brazilian geographical indication, presenting its medicinal characteristics.

2.1 Geography of production and its influences

The physicochemical composition of honey and its flavor can vary significantly based on the plant of origin, geographic region, beekeeping practices, and environmental and climatic conditions [7, 12]. The diversity of bee plants in Brazil is favored by its vast territorial expanse and varying climatic conditions, allowing for the production of honey from different botanical origins throughout the year [8, 18].

For honey production, documentation is required to prove that the region has become known for its production, along with studies demonstrating the influence of the geographic environment on the qualities of honey. Thus, registration of geographical indications of origin or Protected Designation of Origin can be requested from INPI [19].

Unique biomes, such as the Amazon, Cerrado, Caatinga, Atlantic Forest, and Pantanal, endow honey produced in the country with very diverse characteristics. Depending on the predominant flora in each region, honey can vary in flavor, color, and aroma. For example, honey produced in the Caatinga, from plants like *Cereus jamacaru* and *Myracrodruon urundeuva* Allemão, has a stronger and more pronounced flavor, while honey from the Atlantic Forest, with more humid and tropical flowers, features mild and aromatic characteristics.

Moreover, the intrinsic characteristics of honey, such as local know-how, make Brazilian honey famous for its richness and diversity of flavors that reflect local biodiversity. In this way, each region and its peculiarities can stand out for its unique products or services. Therefore, the term geographical indication is an important tool that associates a product with its geographical origin, recognizing its qualities and traditions, and valuing locally produced products [19]. The geographical indications for honey aim to protect producers and consumers from counterfeiting and highlight the local know-how that adds value to honey in the market [20].

Brazil has five registered geographical indications for floral honey and honeydew honey (**Figure 1**). Honey from the West of Paraná and Pantanal exhibits geographical indications of origin, while honey from Ortigueira, Northern Minas, and Southern Brazilian Highlands holds a Protected Designation of Origin (**Figure 1**) [21].

2.1.1 Honey from the Pantanal

The geographical indication for Pantanal honey has a unique flavor due to its Pantanal origin, with wild fauna and flora [22]. The geographical indication covers 25% of its area in the state of Mato Grosso do Sul and 7% in the state of Mato Grosso. Due to the flooded steppe savanna conditions, the region has few areas for agriculture, making the honey produced in the area even more attractive. The region's history shows that production was mostly extractive, harvesting honey from tree cavities. As knowledge of the benefits and quality of the region's honey increased, technical beekeepers emerged, organizing into associations to ensure environmental quality and honey production in the area [22].

The Pantanal geographical indication area is home to 206 plant species, including 86 herbs, 44 trees, 44 shrubs, and 24 vines [23]. Evaluating honey samples from the

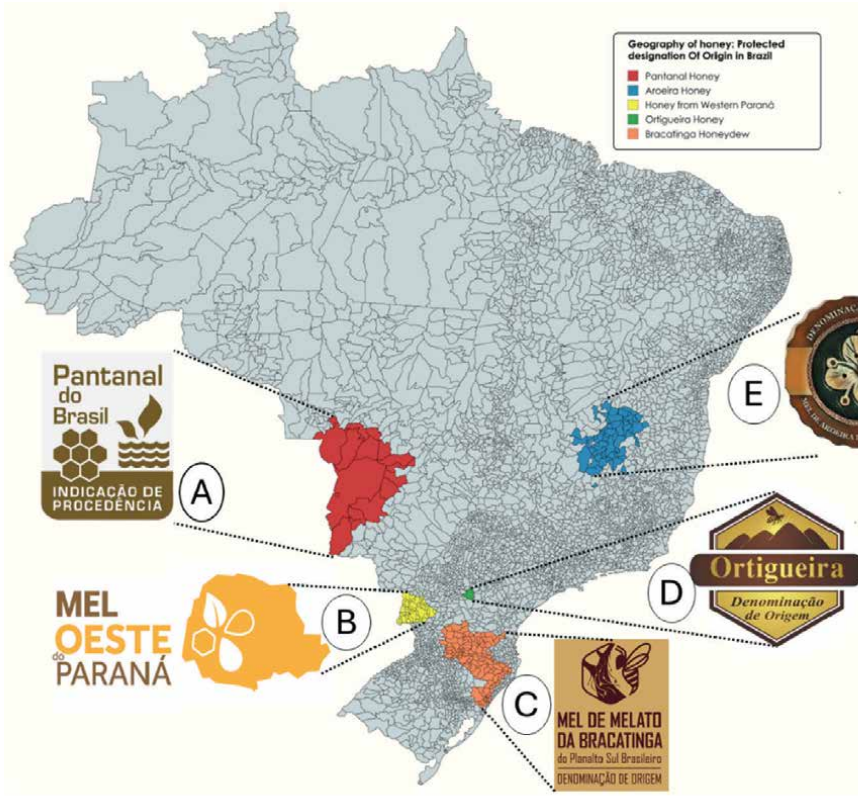

Figure 1.
Honey logos with geographical indications. A: https://igmeldopantanal.com.br/. B: https://coofamel.com.br/. C: https://igmelatodabracatinga.faasc.com.br/. D: APOMEL—Association of Honey Producers from Ortigueira. E: https://meldasgerais.com.br/origem.html.

Pantanal of Mato Grosso identified 63 types of pollen from 55 genera and 40 families, while samples from the state of Mato Grosso do Sul showed 40 pollen types from 32 genera and 24 families [23]. This rich plant diversity significantly contributes to the production of high-quality honey in the region, which, combined with temperature and humidity levels, results in a unique wild honey with a consistent texture, strong and pronounced flavor, and a slight touch of sweetness [24].

Studies evaluating honey from the region present high levels of phenolic compounds and antioxidant activity, giving the honey significant medicinal properties. The authors suggest that these values may be associated with the seasonal flooding typical of the Pantanal biome, which somehow affects the local flora, leading to an increase in the production of these compounds [2]. Despite the great importance of Pantanal honey, there have been few studies on its physical-chemical properties, antimicrobial activity, and studies evaluating its pharmacological effects.

2.1.2 Honey from the West of Paraná

The honey produced in the West of Paraná region has received the geographical indication seal due to its physicochemical qualities and the agro-industrial organization involved in its processing and commercialization [25]. The history of honey characteristics in the West dates back to the colonization period in 1946, when the first settlers arrived in the region, until 1975 when the construction of the ITAIPU binational hydroelectric plant began. This project caused modifications to the entire structure of the region, creating a large flood area for the hydroelectric reservoir. Since then, ITAIPU has promoted the planting of over 44 million seedlings along the Brazilian and Paraguayan banks to ensure the permanent preservation of the lake's margins [26].

Most honey is produced in the reforestation reserves carried out by ITAIPU, presenting similar characteristics, which mostly present the incidence of 69 pollen types and the dominance of its botanical origin coming from *Hovenia dulcis, Mimosa scabrella*, *Mikania*, *Parapiptadenia rigida*, and crops such as *Glycine max* and *Eucalyptus* [27]. Honey from this region displays lighter shades, ranging from white and extra light amber to amber [28, 29]. Thus, honey from the West exhibits beneficial levels of bioactive compounds and antioxidant activity [28, 29]. In addition to presenting good microbiological quality of honey produced in the region [30]. Furthermore, it presents bactericidal and bacteriostatic action against the pathogenic microorganisms *Staphylococcus aureus*, *Escherichia coli,* and *Candida albicans* regardless of the color or concentration of the bioactive compounds [31].

2.1.3 Honey from Ortigueira in Paraná

The Ortigueira region is recognized in Brazil, as a major producer of high-quality honey, attributed to the characteristics of the flora in this territory [32]. APOMEL—Association of Honey Producers from Ortigueira sought the registration of geographical indication (GI) under the category of denomination of origin (DO) for "Ortigueira," referring to the honey produced in this region of Paraná, which was granted by INPI on September 1, 2015. This grant acknowledges that the physico-chemical characteristics of the product result from the botanical conditions of the region, distinguishing it from honey produced in surrounding areas [33].

With the process of obtaining the denomination of origin for Ortigueira honey, counterfeiting attempts to use the label have emerged [33] observed that Ortigueira honey significantly differs from honey produced in neighboring locations in terms of pH, proline, hydroxymethylfurfural, diastatic activity, electrical conductivity, reducing sugars, sucrose, total sugars, free and total acidity, and color. This was further supported by [34], who conducted a metabolic analysis of Ortigueira honey to identify the main compounds responsible for its distinction from honey samples obtained in other cities in Paraná. The analysis identified key sugars, such as isomaltose, sucrose, turanose, and α-glucose, as differentiating factors [34]. These results can be used to ensure the authenticity of the product from the region.

2.1.4 Honey from Aroeira in Northern Minas Gerais

Aroeira honey is valued for its nutritional characteristics and high quality, reflecting the management techniques applied by local beekeepers [35]. Research on the characteristics of honey can aid in its promotion and marketing, increasing its market value.

Honey with geographical indication from Northern Minas originates from the medicinal species *Myracrodruon urundeuva* Allemão and includes the presence of honeydew [36], a species widely recognized in traditional native medicine with therapeutic indications [36]. Based on this, [37] evaluated the biological activity of

M. urundeuva honey and found that it exhibited clinically significant antibacterial activity, highlighting its potential for therapeutic use and contributing to the added value of honey from the region. Similarly [38] observed the inhibitory effect of *M. urundeuva* honey on *Staphylococcus aureus* and enterohaemorrhagic *Escherichia coli*, demonstrating the therapeutic potential of honey.

Additionally, evaluations of the honey show high concentrations of phenolic compounds, confirming its medicinal effects such as antibacterial properties [39], as well as anti-adhesive, antioxidant, and anti-tumor activities [40].

2.1.5 Honeydew from Mimosa scabrella in the southern Brazilian highlands

Brazil hosts a variety of biomes, with the Atlantic Forest standing out. Within this biome, we find the mixed ombrophylous forest, also known as the araucaria forest, which includes a variety of tree species, including Bracatinga (*Mimosa scabrella* Bentham) [2]. *M. scabrella* is a native Brazilian tree predominantly found in the Southern region, encompassing the states of Rio Grande do Sul, Santa Catarina, and Paraná. This species grows at altitudes ranging from 500 to 1200 m, with average annual temperatures between 13 and 23°C [41, 42].

Honeydew produced from plant secretions and excretions of sap-sucking insects is known as *M. scabrella* honeydew. It is economically valued for its antimicrobial, anti-inflammatory, and antioxidant properties [12]. The geographical indication for *M. scabrella* honeydew covers 58,987 km^2 and includes 134 municipalities in Southern Brazil, with 107 in Santa Catarina, 12 in Paraná, and 15 in Rio Grande do Sul [2]. Approximately 80% of *M. scabrella* honeydew production comes from Santa Catarina, with a significant portion being exported [43].

Honeydew production occurs every 2 years due to the life cycle of scale insects. It is primarily produced between December and June, coinciding with a scarcity of nectar and pollen [44]. The *Apis mellifera* produces honey from sugary excretions released by sap-sucking insects such as *Stigmacoccus paranaensis* Foldi. This insect attaches to the *M. scabrella* tree and is found in Southern Brazil, especially on *Ingá*, *Schizolobium parahyba*, and *M. scabrella* trees [45]. After attaching to the trunks of *M. scabrella*, the scale insects begin to feed and release excess sugar in the form of honeydew droplets. Due to its unique characteristics, honeydew has won five awards at the World Beekeeping Award during the Apimondia International Beekeeping Congress [46].

Honeydew is dark and has distinct profiles of amino acids, polyphenols, and sugars compared to floral honey [6, 12]. Additionally, honeydew typically has higher average conductivity values, above 1200 mS/cm, indicating it is rich in minerals, particularly potassium (K) and magnesium (Mg) [12].

Honeydew tends to have a higher pH, greater acidity, higher ash content, darker color, and a larger number of oligosaccharides [47]. It presents a balanced sweetness sensation, resulting from the higher ratio of total sugars to acidity [48]. Unlike floral honey, honeydew contains, in addition to enzymes from bees, enzymes derived from the secretions of the salivary glands and intestines of the scale insects [49]. The physicochemical, sensory, therapeutic characteristics, and bioactive potential of honeydew increase the demand for this product, making it commercially attractive [7, 47]. Honeydew is appreciated and valued for being a nutrient-rich food and having greater antioxidant and antibacterial activity compared to floral honey [50]. The anti-inflammatory activity of honey is attributed to phenolic compounds, the concentration of which depends on the geographical location [51]. Thus, a direct relationship is assumed between the collection region and the anti-inflammatory effect of *M. scabrella* honey.

3. Conclusions

Honey is a product that offers numerous forms of use, where its flavor and color are the result of a combination of compounds that vary according to its floral and geographical origin. The vast floral diversity and the geographical location of Brazilian territory provide a wide variety of honey types with unique characteristics. These types are classified, and through Geographic Indication certification, it is possible to distinguish the honey from different locations, along with the traditional knowledge that enhances the product and highlights honey's medicinal potential. However, additional evaluations need to be conducted to assess the composition of honey in different areas of the country, also analyzing its therapeutic properties.

Conflict of interest

The authors declare no conflict of interest.

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Chapter 2

The Role of Honey Microbiota from Native Stingless Bees of the Amazon: Microbial Diversity and Antimicrobial Activity

Sara R.L. Ferreira, Jéssica L. Araújo, Marly S. Franco and Nilton Muto

Abstract

The honeys produced by stingless bees native to the Amazon (Meliponini) are distinguished by their high moisture and acidity content, along with elevated levels of phenolic acids and flavonoids. They also feature a rich and diverse microbiota, including organisms as *Lactobacillus acidophilus, Bifidobacterium animalis, and Saccharomyces spp.,* setting them apart from honey produced by *Apis mellifera L.* The internal microbiota contributes to natural fermentation processes that enhance honey's acidity and unique properties. These honeys exhibit potent antimicrobial activity, effectively inhibiting the growth of pathogenic bacteria such as *Staphylococcus aureus, Escherichia coli*, and *Pseudomonas aeruginosa.* This antimicrobial efficacy stems from factors like the presence of hydrogen peroxide, low pH levels, low sugar concentration, and specific antibacterial compounds. Consequently, honey holds promise for therapeutic applications, including the development of novel medical and food products. The microbial biodiversity present also suggests potential for discovering new probiotics that could benefit human health.

Keywords: stingless bee honey, microbiota, antimicrobial activity, therapeutic applications, probiotics

1. Introduction

Bees from the Meliponini tribe, commonly known as stingless bees, are a unique group of native bees that have evolved with atrophied defensive stingers, rendering them incapable of stinging. This adaptation distinguishes them from other bees, such as *Apis mellifera* L., which possess functional stingers. Stingless bees are predominantly found in tropical and subtropical regions worldwide, with a significant diversity observed in the Amazon rainforest and other parts of Brazil [1].

Meliponiculture, the practice of breeding and utilizing stingless bees, has been carried out for thousands of years to sustainably produce honey. Indigenous peoples of the Americas, Africa, Asia, and Australia have long recognized the value of stingless bees, not only for their honey production but also for their ecological contributions. Unlike conventional beekeeping with *Apis mellifera* L., meliponiculture involves maintaining and harvesting honey from these small, often complex colonies without the need for protective gear, thanks to the bees' nonaggressive nature. The primary honey-producing bees within the Meliponini tribe belong to several key genera: Scaptotrigona, Tetragonisca, Melipona, and Austroplebeia. Each of these genera exhibits distinct behaviors, ecological roles, and characteristics related to honey production [2, 3]. This sustainable practice not only supports local biodiversity but also preserves traditional knowledge and contributes to the conservation of stingless bee populations worldwide.

Honey produced by native bees (Meliponini) exhibits distinct characteristics compared to that produced by *Apis mellifera* L., including higher moisture content, increased acidity, lower reducing sugar content, and a darker color. The fermentation process, which is more prominent in honey from stingless bees, results in a more acidic honey compared to that of *Apis mellifera*. Additionally, fermentation may contribute to the microbiological stability and therapeutic properties attributed to stingless bee honey [1].

In addition to its distinctive flavor, honey produced by native Amazonian bees contains a variety of substances such as amino acids, phenolic compounds, organic acids, lipids, glucose, minerals, and proteins. It also possesses prebiotics, antioxidants, and anti-allergic properties [4, 5]. These diverse components not only enhance the nutritional value of stingless bee honey but also contribute to its medicinal benefits, making it a valuable resource in traditional and modern healthcare practices.

The rich and diverse microbiota present in stingless bee honey plays a crucial role in its functional and health benefits. Studies indicate that stingless bee honey can serve as a functional and beneficial food for health due to its prebiotic properties. It stimulates the proliferation, viability, and activity of probiotic bacteria such as *Lactobacillus acidophilus* and *Bifidobacterium animalis*, which ferment glucose to produce lactic and acetic acids. These probiotics help balance intestinal microbiota and have the potential to inhibit pathogenic bacteria such as *Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa* [6, 7].

Increasing the population of beneficial bacteria in the colon can be achieved through dietary intake of prebiotic foods like stingless bee honey. This dual action of promoting beneficial bacteria and inhibiting pathogens underscores the therapeutic potential of stingless bee honey in promoting gastrointestinal health and overall well-being [6].

This study aims to explore the microbiota present in stingless bee honey, focusing on microbial diversity and the antimicrobial activity that inhibits the growth of pathogenic bacteria. By delving into the intricate interactions between honey's microbial communities and their health-promoting properties, we can gain a deeper understanding of the potential of stingless bee honey as a functional food and therapeutic agent. This research contributes to harnessing the natural benefits of stingless bee honey for enhancing human health and wellbeing.

2. Native stingless bees

Stingless bees, distinguished by their lack of defensive stingers due to evolutionary atrophy, inhabit a multitude of tropical and subtropical regions globally. These bees are celebrated for their remarkable species diversity, surpassing 550 identified species solely within the Meliponini tribe, a subset of the larger Apidae family. Within Brazil, notably in the expansive Amazon region, these unique bees are locally recognized and referred to as native bees, indigenous bees, or meliponines [1].

The primary genera of stingless bees renowned for honey production encompass Scaptotrigona, Tetragonisca, Melipona, and Austroplebeia. Meliponiculture; the age-old practice of cultivating these bees has been deeply rooted in the Americas for many years. This traditional breeding system serves a dual purpose: not only does it facilitate honey production, but it also plays a pivotal role in conserving these species and fostering the sustainability of their ecosystems through essential pollination services [1, 3].

Native bees play a key and multifaceted role in the intricate web of tropical forest ecosystems, where they are instrumental in pollinating diverse plant species and thereby supporting the ecosystem's vitality and the production of its valuable bio-products. Research conducted by Muto et al. [8] underscored the significant impact of native bees on the productivity of Amazonian fruits, such as açaí (*Euterpe oleracea*). Their findings highlighted the profound link between native bee pollination activities and the enhanced yield of these economically and ecologically important fruits [8].

The production, collection, and storage of pollen, honey, resin, wax, and propolis by native bees are intricately tied to their specific habitats. Recent studies, exemplified by Lopes et al. [9], focusing on the genus Scaptotrigona—a native bee species of the Amazon region—have illuminated the direct influence of collected pollen on its potent therapeutic properties, underscored by its natural habitat. Moreover, research by Silva et al. [10] further substantiates this correlation, isolating bacteria from native bee honey sourced from the floral nectar of açaí (*Scaptotrigona aff. postica*), a species endemic to the Amazon. Their findings suggest these bacteria possess antimicrobial properties capable of inhibiting pathogenic strains, potentially paving the way for novel antimicrobial substances akin to traditional antibacterial antibiotics [9, 10].

Moreover, the medicinal properties of honey produced by native bees are widely recognized and valued in various communities. This distinctive honey is crafted through the meticulous processing of floral nectars, honeydew, and fruit juices, which are matured and stored in cerumen jars, a unique trait not shared by other bee species, influencing its composition. The chemical profile of this honey can vary significantly depending on factors such as colony dynamics, species specificity, seasonal variations, habitat characteristics, and the types of resources collected. Notably, it contains a rich array of bioactive compounds known for their biological activities, including flavonoids, phenolic acids, and enzymes like glucose oxidase and catalase. Furthermore, native bee honey exhibits remarkable microbial diversity, contributing to its unique properties and potential therapeutic benefits [9].

3. Microbial diversity

Microbiological control plays a pivotal role in safeguarding the quality and safety of honey by identifying potential contaminants that could compromise its integrity. Honey, due to its chemical composition and relatively high moisture content, provides an environment conducive to the growth of microorganisms such as bacteria, fungi, and yeasts. While honey possesses inherent antimicrobial properties, including a low pH and natural compounds that typically inhibit microbial growth, it remains susceptible to contamination from various sources. This susceptibility is particularly relevant in the context of stingless bee honey, where higher moisture levels may promote the proliferation of specific bacteria and fungi if not managed effectively.

Thus, rigorous microbiological monitoring is essential to ensure that honey maintains its desired quality, shelf life, and safety for both culinary and medicinal applications [5].

The microbiota present in honey is influenced by a multitude of factors, encompassing local flora composition, bee behavior, and specific beekeeping methodologies. In honey derived from stingless bees native to the Amazon region, the microbiota is notably diverse and abundant, featuring a broad spectrum of bacteria and yeasts. Research highlighted by Domingos *et al*. underscores the potent antimicrobial properties exhibited by Meliponini honey, demonstrating effectiveness against a range of pathogens including *Bacillus cereus, Candida albicans, E. coli, Klebsiella pneumoniae*, *Listeria monocytogenes, P. aeruginosa, Salmonella enterica, Serratia marcescens, S. aureus*, and *Streptococcus pyogenes*. This innate antimicrobial capacity underscores not only the medicinal value of honey but also its essential role in preventing infections, thereby enhancing its therapeutic potential in various applications [11, 12].

Research indicates that honey produced by stingless bees, particularly those native to the Amazon region, harbors a diverse microbiota comprising organisms such as *Lactobacillus spp., Bacillus spp., Acinetobacter junii, Bombella intestini, Corynebacterium lipophiloflavum, Serratia symbiotica, Variovorax paradoxus*, and *Saccharomyces spp.* These microorganisms are known for their ability to produce antimicrobial substances effective against fungi and *Paenibacillus larvae*, as well as their fermentative capabilities [13]. Furthermore, stingless bees establish symbiotic relationships with fungi from various phyla *including Ascomycota, Basidiomycota, Mucoromycotina, and Mortierellomycota*. This rich microflora associated with stingless bees not only contributes to the uniqueness of their honey but also presents potential applications as biological control agents, highlighting the ecological and medicinal significance of these microorganisms [13].

Stingless bees exhibit a complex symbiotic relationship within their hive, involving a diverse array of microorganisms including bacteria, viruses, yeasts, and filamentous fungi. This symbiosis plays a crucial role in shaping the microbiota within their hives, which in turn influences the process of honey formation and enhances its biochemical characteristics. The presence of these microorganisms is instrumental as they contribute to the production of enzymes, organic acids, and facilitate sugar fermentation processes [14, 15]. This intricate symbiotic system not only supports the bees' nutritional needs but also underscores the ecological importance of these interactions in maintaining hive health and honey quality.

Furthermore, fungi and bacteria are recognized for their capacity to synthesize metabolites endowed with potent antimicrobial properties. Research conducted by Santos et al. [14] has identified several bacterial genera including *Bacillus, Lactobacillus, Micrococcus, Pseudomonas, Providencia, Serratia*, and *Vagococcus*, which produce bioactive compounds effective in suppressing the growth of various bacterial species. Moreover, fungi such as Cladosporium, Aspergillus, and Penicillium have been found to secrete antimicrobial molecules that can significantly reduce bacterial populations by inhibiting specific bacterial strains [15]. This microbial ability to produce antimicrobial metabolites underscores their potential role in ecological dynamics and highlights their application in various fields including medicine and biotechnology.

These beneficial bacteria play a pivotal role in the natural fermentation process of honey, a phenomenon that significantly enhances its unique properties. The fermentation facilitated by these bacteria yields a spectrum of compounds that may confer various health benefits, including the inhibition of pathogens and the promotion of a balanced and healthy microbiome [16]. This microbial activity not only enriches the biochemical profile of honey but also underscores its potential therapeutic value, highlighting the intricate interplay between microbial ecology and the beneficial properties of natural products like honey.

In addition to lactic acid bacteria, yeasts also play a significant role in shaping the composition of honey. These microorganisms take an active part in the fermentation processes, exerting an influence on the nutritional quality of the final product [16]. The composition of honey can vary greatly depending on environmental factors and the botanical sources visited by the bees. This variability contributes to the diversity of properties and flavors observed in different types of honey [11].

The microbial diversity found in honey not only contributes to its antimicrobial and therapeutic attributes but also plays a fundamental role in its natural preservation. Certain microorganisms within honey can effectively protect it against spoilage by competing with potential contaminants and inhibiting their growth. This natural microbial protection mechanism helps extend the shelf life of honey, ensuring its quality and safety over time. Thus, the intricate microbial community within honey underscores its multifaceted role as a nutritious food product with potential health benefits and as a naturally preserved culinary ingredient [16].

4. Antimicrobial and antioxidant activities

Honey produced by native Amazonian bees is distinguished by its antimicrobial potency, a trait that can be attributed to a variety of factors. Firstly, the enzymatic production of hydrogen peroxide within the honey serves as a potent antimicrobial agent, actively combating pathogenic bacteria. This natural mechanism contributes significantly to the honey's ability to inhibit microbial growth and promote wound healing. Additionally, the naturally acidic pH of honey creates an unfavorable environment for bacteria, further enhancing its antimicrobial properties. These combined attributes highlight honey from native Amazonian bees as a highly effective and natural antimicrobial agent, making it a valuable resource in both traditional medicine and modern healthcare practices [10].

The phenolic compounds found in the honeys of stingless bees contribute significantly to the antimicrobial and antioxidant properties. These bioactive compounds, which are secondary metabolites produced through bacterial fermentation processes, possess a diverse chemical composition [17]. The chemical profile and concentration of these phenolic compounds are directly influenced by the floral sources from which the honeys are derived, which can vary with the seasons [18]. Phenolic compounds are well-known for their antioxidant and antimicrobial properties and are classified into different categories, such as flavonoids and phenolic acids [19]. These classifications reflect the wide range of beneficial effects these compounds have on health, emphasizing their importance in the therapeutic potential of stingless bee honey.

In honeys originating from the Amazon, it is common to find phenolic acids such as gallic acid, coumaric acid, and vanillic acid, as well as flavonoids such as naringenin [2, 17, 20–22]. The antimicrobial activity of these compounds can be attributed to their ability to cause damage to the bacterial cell membrane [23], leading to protein denaturation [24]. Consequently, these compounds enhance the therapeutic activities of honey by acting as both antioxidants and antimicrobials. This dual function underscores the significant health benefits of Amazonian stingless bee honey.

Honey also contains small amounts of antioxidant enzymes, such as catalase and peroxidase, which complement the antioxidant activity of phenolic compounds.

These enzymes help protect the body's cells against oxidative stress, thereby promoting cellular health and preventing premature aging and degenerative diseases [25]. By neutralizing harmful free radicals, these enzymes play a crucial role in maintaining the overall well-being of the body, enhancing the therapeutic potential of honey.

As an antimicrobial factor, there are also proteins with this capability, known as antimicrobial peptides (AMPs). A notable example is meliponin, an antimicrobial peptide isolated from various species of stingless bees [26]. Meliponin has demonstrated significant activity against a wide range of bacterial pathogens, including *S. aureus* and *E. coli* [26, 27]. In addition to meliponin, other AMPs such as defensins and abaecins have been identified and characterized in different species of Meliponini [22]. These AMPs contribute to the robust antimicrobial properties of stingless bee honey, further enhancing its potential as a natural therapeutic agent.

The action of AMPs generally involves interacting with the cell membranes of microorganisms, causing destabilization and eventual lysis of these cells. This mechanism is particularly effective against gram-positive and gram-negative bacteria, as well as pathogenic fungi [27]. The physical and chemical properties of AMPs, such as their positive charge and amphipathic structure, enable these molecules to bind to and permeabilize microbial membranes, leading to cell death [28]. This ability to disrupt microbial cell membranes underscores the potent antimicrobial properties of AMPs and their potential role in the defense mechanisms of stingless bees.

The AMPs found in insects are classified into four distinct families: alpha-helical peptides (such as cecropin), cysteine-rich peptides (such as defensin and drosomycin), proline-rich peptides (such as apidaecin, drosocin and lebosin), and glycine-rich peptides (such as atacin). These AMPs show activity against fungi, bacteria, and parasites and have potential applications in agriculture and medicine. Cecropin, the first antimicrobial peptide purified from insects, was isolated from the hemolymph of *Hyalophora cecropia* in 1980, and since then, more than 200 insect AMPs have been identified. Antimicrobial peptides can be used in the development of new antibacterial drugs, and cecropins, in particular, have the potential to be used in the coating of biomaterials to prevent infections associated with these biomaterials [29, 30].

Besides AMPs, other components of the stingless bee immune system, such as enzymes and signaling peptides, also contribute to their antimicrobial defense [28]. The interaction between these various molecules results in an efficient and multifaceted immune response. This collaborative defense mechanism ensures a robust protection against a wide range of pathogens, highlighting the complexity and effectiveness of the stingless bee immune system.

The therapeutic use of stingless bee honey began to be considered due to studies reporting its antimicrobial activity. Stingless bee honey has demonstrated activity against various pathogens, including *B. cereus, C. albicans, Citrobacter freundii, Enterobacter cloacae, E. coli, K. pneumoniae, L. monocytogenes, P. aeruginosa, Salmonella enterica, Serratia marcescens, Shigella sonnei, S. aureus, Streptococcus pyogenes, and Yersinia enterocolitica* [11]. These findings highlight the potential of stingless bee honey as a natural antimicrobial agent in therapeutic applications.

The combination of antimicrobial and antioxidant properties makes stingless bee honey a natural and effective option for promoting health. Ongoing studies continue to explore new applications and aim to better understand the mechanisms behind these beneficial properties. This research reinforces the importance of preserving native bees and their ecosystems, as they play a crucial role in producing honey with significant therapeutic potential [19, 25].

5. Health implications and therapeutic applications

Exploring the honey microbiota and its inherent antimicrobial properties expands the therapeutic potential and also provides information to address the pressing issue of antibiotic resistance. Honey from stingless bees has a celebrated history in traditional medicine, revered for its multifaceted healing properties in diverse cultures. Historically, it has been used to treat a wide spectrum of ailments, including digestive disorders, eye diseases, respiratory infections, fatigue, wound healing, stimulation of childbirth, as well as skin ulcers and bruises [11].

Its efficacy in wound care is extensively documented in ancient medicinal texts from civilizations such as Egypt, Greece, and India, where honey was esteemed for its capacity to reduce infections, soothe burns, alleviate pain, and manage malodor [31]. This rich historical use underscores honey's enduring role as a therapeutic agent with broad-ranging applications in both traditional and modern medical practices. Moreover, as scientific understanding of honey's microbiota grows, so too does its potential to offer alternative treatments in the face of antibiotic-resistant pathogens, highlighting its relevance in contemporary healthcare approaches.

Honey produced by Meliponini bees is renowned in folk medicine for its health benefits, attributed to its pharmacological properties primarily derived from phenolic compounds. This variety of honey is utilized in folk medicine for treating various ailments and is also incorporated into diets for its natural compounds, which possess anti-inflammatory and antioxidant effects that promote health benefits [32].

Honey produced by native Amazonian bees represents a promising avenue for the development of novel medical, cosmetic, and food products. The phenolic compounds found in this honey, derived from diverse plant sources, exhibit variability influenced by factors such as the origin of nectar, bee species, harvesting season, and local climate conditions. These compounds encompass a spectrum of bioactive substances, including phenolic acids and flavonoids, which, coupled with the honey's distinctive physicochemical properties, classify Meliponini honey as a potent antioxidant capable of scavenging free radicals. This antioxidant potential positions it favorably for various applications, such as integration into hydrogels for wound treatment. Studies have demonstrated that hydrogel dressings incorporating honey can significantly enhance healing outcomes, achieving an impressive 85% healing rate compared to 50% observed with traditional gauze dressings [33]. This underscores the honey's versatility and therapeutic efficacy, highlighting its potential to innovate within medical and skincare fields while leveraging its natural bioactive profile for beneficial health outcomes.

In addition to its well-established antioxidant attributes, honey sourced from stingless bees is increasingly valued for its potent anti-inflammatory effects. Recent research has identified several key compounds within this honey, including p-coumaric acid, salicylic acid, aromadendrin, and taxifolin, which are known for their anti-inflammatory properties. These bioactive components have demonstrated efficacy in mitigating inflammation in various contexts, including experimental models of liver inflammation induced by substances such as paracetamol [33]. This dual action of antioxidant and anti-inflammatory properties highlights the therapeutic potential of stingless bee honey and places it as a promising natural remedy for treating inflammatory diseases and promoting health.

The microbial diversity observed in honeys derived from stingless bees underlines their ecological importance and indicates their potential for the discovery of new probiotics that could significantly benefit human health. In a remarkable *in vitro* study conducted by de Melo et al. [6], it was found that the phenolic acids present in broths containing stingless bee honey exhibit a bioactivity that stimulates the growth and vitality of probiotic bacteria such as *Lactobacillus acidophilus and Bifidobacterium animalis*. These probiotics are known for their ability to metabolize sugars such as glucose and fructose through fermentation, producing beneficial metabolites like lactic acid and acetic acid. Lactic acid, in particular, aids in preventing spoilage and the growth of pathogenic microorganisms during fermentation [34].

This interaction between stingless bee honey and probiotic bacteria suggests a synergistic relationship that could potentially improve digestive health [6]. The results of these studies highlight the nutritional and therapeutic potential of stingless bee honey and open the way to exploring its applications in functional foods and dietary supplements aimed at improving intestinal health and immune function. Thus, the microbial biodiversity present in stingless bee honey presents interesting avenues for future research into the development of innovative probiotic therapies and health-promoting products.

6. Conclusion

Research on the microbiota of honey produced by native stingless bees in the Amazon region reveals a diverse array of microorganisms with notable antimicrobial and therapeutic potential. The microbial diversity found in these honeys is noteworthy for its capacity to inhibit pathogen growth, as well as for its antioxidant and anti-inflammatory properties. These findings are paving the way for the development of new medicinal and food products that capitalize on the distinctive qualities of these honeys to enhance human health. Furthermore, a deeper understanding of the interplay between stingless bees and their beneficial microorganisms underscores the critical importance of preserving these species and their natural habitats. Such conservation efforts are necessary not only for sustaining biodiversity but also for promoting sustainability in the Amazon region. By safeguarding stingless bees and their ecosystems, researchers and conservationists contribute to the health of local communities and the broader global environment.

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Conflict of interest

The authors declare no conflicts of interest.

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Section 2

Standardization and Quality Control

Chapter 3

A Systematic Review of Honey's Benefits for Burn Wound Treatment

Ferhat Ozturk, Andrea Karyme Lozano, Christina Ndayisenga and Ayse Celik Yilmaz

Abstract

Burn wound management has traditionally relied on established treatments, yet emerging evidence underscores honey as a potent and versatile therapeutic agent. This systematic review evaluates the scientific evidence supporting honey's use in treating burn wounds, highlighting its efficacy and benefits compared to conventional therapies. The review encompasses both clinical trials and animal studies published between January 1, 2013, and June 30, 2024. A comprehensive search of MEDLINE, EMBASE, CINAHL, and ScienceDirect databases was conducted, resulting in the inclusion of 38 eligible studies. The analysis focuses on randomized controlled trials and full-text research articles that investigated honey's role in burn wound care. Key attributes of honey, including its antimicrobial, anti-inflammatory, antioxidant, and tissue regeneration properties, are examined. The review discusses various types of honey, their composition, and their specific impacts on wound healing, including faster recovery times, reduced infection rates, and improved scar formation outcomes. Additionally, this review highlights the synergy between honey and other adjunctive treatments, such as ascorbic acid. The findings affirm that honey offers significant advantages in burn wound management, supporting its continued use and integration into modern wound care protocols. This chapter provides a comprehensive overview of honey's role in enhancing burn wound healing, reinforcing its value as both a traditional remedy and a scientifically validated treatment option.

Keywords: honey, burn wound treatment, systematic review, clinical trials, animal studies

1. Introduction

The treatment of burn wounds has long been a challenge for medical professionals, with traditional remedies often playing a role. As the search for effective therapies continues, researchers are increasingly interested in exploring the potential of honey and honey-containing dressings. These products offer the promise of accelerating wound healing, preventing infection, reducing scarring, and minimizing toxic or side effects. Honey, a centuries-old antimicrobial agent, has garnered significant attention due to its multifaceted properties [1]. Since the early twentieth century, scientific investigations have revealed the complex composition and functional qualities of honey, confirming its potential as a biological wound dressing [2, 3]. Unlike conventional therapeutic agents, honey possesses multiple bioactivities that synergistically promote healing [4].

Honey is a natural product produced by bees of the Apis genus. These bees collect nectar from flower blooms or secretions from other insects, which they enzymatically process into honey. Honey is a highly saturated sugar solution with significant nutritional value and a sweet, delicious taste. Its composition includes primarily sugars, but also smaller amounts of amino acids, proteins, enzymes, organic acids, flavonoids, phenolic acids, vitamins, minerals, volatile substances, and polyphenols [1, 5–8]. Bees from different regions, climates, and ecosystems worldwide produce various types of honey, each with unique pharmacological activities, potency, and content. Factors such as geography, season, processing, storage, and bee species influence these characteristics [9–11]. While honey is often used in chronic wound care, it has potential for broader medical applications.

Honey's bioactivity potential and medicinal uses are diverse, which are summarized in **Figure 1**. These include:

Antimicrobial: Honey's antibacterial properties are due to its acidity, high flavonoid, phenolic acid, and hydrogen peroxide content, and osmotic effects from its high sugar concentration [12, 13]. These characteristics make medical-grade honey effective in wound healing and treating respiratory, gastrointestinal, and dermatological infections [14, 15].

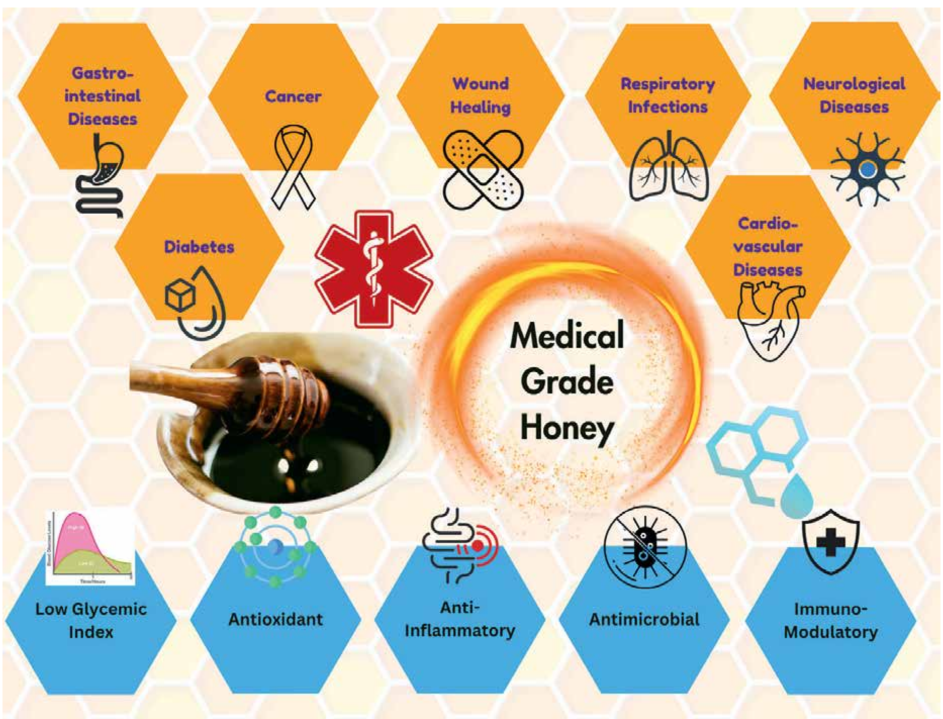

Figure 1.
Bioactivity potential and medicinal uses of medical-grade honey.

Antioxidant: Honey's strong antioxidant properties are derived from its phenolic acids, flavonoids, and tannins, which help protect cells from oxidative damage caused by reactive oxygen species (ROS) [11, 16, 17]. Antioxidants in honey are crucial for the prevention and treatment of cardiovascular, neurological, and gastrointestinal diseases, as well as cancer [18, 19].

Anti-inflammatory: Chronic inflammation is associated with various disorders, including allergies, metabolic syndromes, cardiovascular dysfunctions, cancer, and autoimmune diseases [20–22]. Honey has demonstrated both pro- and anti-inflammatory activities by stimulating the production of inflammatory mediators and downregulating inflammatory transcription factors or suppressing proinflammatory cytokines [23–25]. This dual role makes honey a valuable therapeutic agent in managing inflammatory conditions.

Immunomodulatory: Honey has been shown to modulate the immune system by inducing immunostimulatory responses in both in vitro and in vivo studies. As a result, medical-grade honey can boost immune responses, both preventatively and therapeutically, which offers significant potential for treating cancer and infectious diseases [1, 26, 27].

Low-Glycemic Index: Honey contains a high percentage of carbohydrates (76%), including glucose, fructose, maltose, turanose, sucrose, and trehalose in varying proportions [8, 28]. Honeys with a high fructose-to-glucose ratio (>1.2) have been found to have a low glycemic index and promote a high satiety response. Therefore, these honeys are used in the treatment of patients with type-2 diabetes [29–31].

2. Honey as a medicine

2.1 Historical and current use

The medical use of bees and bee products has fascinated humans since ancient times, with honey a prominent example. Historically, honey has served as both a food and a medicine across various cultures and geographies. Evidence of honey's medicinal use dates back to ancient Egyptian and Greek civilizations and traditional Chinese, Indian, and Islamic medicine. Ancient records, such as Sumerian clay tablets (c. 6200 BC), Egyptian papyrus (c. 1900–1250 BC), the approximately 5000-year-old Veda (Hindu holy book), the Quran, the Talmud, the Bible, and writings of Hippocrates (c. 460–357 BC), confirm honey's historical role in medicine [1]. Hippocrates recommended honey-based mixtures for managing diseases like fever, pain, and wounds. Prehistoric Egyptians viewed bees as blessed and utilized honey in medicinal applications such as wound dressings. Judeo-Christian and Islamic traditions considered honey a divine gift, with Islamic texts like the Quran and Hadith praising honey's medicinal properties. The Chinese also incorporated honey into their traditional treatments, as documented in Li Shizhen's sixteenth-century medical text, 'Compendium of Materia Medica' [32]. Egyptians believed that honey and other substances like aloe vera and animal fat protected wounds from evil spirits [33].

For centuries, honey has been widely utilized across Europe, the Middle East, Asia, and eventually the Americas, reflecting its availability and importance in traditional folk medicine across diverse cultures. Despite its longstanding use, honey only began to gain the attention of modern medicine in the late twentieth century. Since the 2000s, scientific clinical studies have validated honey's medicinal properties, solidifying its place in contemporary clinical practice.

Initially recognized for its effectiveness in wound care, honey's therapeutic potential extends far beyond this application. Its use has expanded into various medical disciplines, including the treatment of upper respiratory tract infections, dental diseases, mucositis, ophthalmic conditions, gastrointestinal diseases, and diabetes management [34–36]. Additionally, honey has been explored for alleviating side effects of cancer treatments and other non-conventional medical applications, showcasing its versatility as a natural remedy.

2.2 Wound healing and honey

Wound healing is a complex process involving numerous interconnected pathophysiological and immunological mediators aimed at restoring the cellular integrity of damaged tissue. Various approaches are employed to treat both acute and chronic wounds. While many of these methods are effective, poorly healing and chronic wounds continue to pose a significant global health challenge. These hard-to-heal wounds may arise due to persistent infections, excessive inflammatory cytokines, proteases, and oxidants, all of which can severely impact patients' quality of life [25, 37]. In recent years, the challenge of wound healing has intensified due to the emergence of multidrug-resistant bacteria, which can disrupt the wound repair process. With the limitations of existing treatments and the growing issue of antibiotic resistance, there is an urgent need for innovative therapies that can effectively eliminate infections and promote healing. Honey has gained attention as a promising treatment option in this context [38, 39].

Honey in wound healing is not a new concept; it has been used for treating wounds since ancient times. With advancements in technology and scientific research, the underlying mechanisms of honey's antibacterial and healing properties are being progressively uncovered. Today, honey has regained attention in wound care, likely due to the rise in antibiotic-resistant microbial pathogens. Honey has been shown to possess antimicrobial properties, stimulate immune responses or modulate inflammation, facilitate autolytic debridement, promote the growth of wound tissues to speed up recovery, and aid in the healing of dormant wounds, all while exhibiting significant anti-inflammatory effects [40]. Due to its antimicrobial, antioxidant, and anti-inflammatory activities, honey has been used in treating various types of wounds, such as burns and ulcers [41]. Although large, unbiased randomized clinical trials are still needed to establish definitive scientific conclusions, the growing body of literature in recent years supports honey's efficacy in promoting healing across a range of skin wounds [13, 42].

2.3 Medical grade honeys

Honey provides numerous health benefits as evidenced from its historical and current use in medicine; however, standardized criteria should be met to ensure the quality, safety, efficacy, and therapeutic potential of honey. Honey can become contaminated with harmful substances when plants in honey harvesting areas are treated with herbicides or pesticides or when the honeybees are exposed to industrial pollutants like heavy metals, antibiotics, or environmental toxins [16, 43]. Furthermore, bacterial contamination, such as the presence of *Clostridium* endospores, poses significant risks. Using honey directly from beekeepers or supermarkets is not advised, as these kinds of honey may not be extensively tested for safety and efficacy. Honey from a beekeeper may potentially be contaminated with environmental pollutants and harmful plant derivatives, while honey in the supermarket may be processed with heat and filtration, thus have lower biological activity potential. It could even be unsafe for wound healing, as its safety and toxicity cannot be assured, and improper sterilization techniques may render it ineffective. Honey used for medical purposes must be free from chemical contamination, such as pesticides, herbicides, or heavy metals. Therefore, there are standard preparation methods for medical-grade honey to ensure its safety and effectiveness for therapeutic uses [44].

Medical grade honey (MGH) is recognized as a treatment for various conditions such as wound care, digestive health, skin conditions, etc. MGH undergoes a meticulous sterilization process, employing methods like gamma radiation or ozonation, and is sourced from organic origins (untreated bees and unpolluted environments). This is done to minimize contaminants, debris, or harmful microorganisms that could be found in the honey and ensure its therapeutic efficacy. Unlike the honey found in supermarkets, medical-grade honey is specially formulated and processed for medical purposes [45–48]. It is registered and meets national requirements (these vary depending on each country's regulations) to receive medical product labeling. The criteria of medical grade honey also require it to have proven biological activity. The storage and production of the honey is regulated to ensure the quality of medical-grade honey. Currently, in clinical practice, various commercial honey-based wound care products, including gels, ointments, and dressings, have received approval from the US Food and Drug Administration (FDA) and are classified as medical devices. Many of these products contain medical-grade Manuka honey, one of the most extensively researched honey varieties globally and the first to attain medical-grade status [49]. As of 2024, **Table 1** shows the medical-grade honey products available in the wound market that have been certified by either the Food and Drug Administration (FDA) or Conformite Europeenne (CE), certifying that a product has met EU health, safety, and environmental requirements.

While the definition of MGH is not universally established, Hermanns et al. [44] provide valuable criteria that MGH should meet:

- *Organic purity*: Must be sourced from organic origins, free from toxic substances such as pesticides, herbicides, and heavy metals.

- *Sterilization*: Must undergo gamma-irradiation to eliminate harmful microorganisms, ensuring it is free from pathogenic contaminants.

- *Physicochemical standards*: Must meet specific criteria, including appropriate pH, viscosity, and sugar content, necessary for medical therapies.

- *Regulatory compliance*: Must adhere to strict production and storage standards, complying with all relevant legal, safety, and regulatory requirements.

- *Biological activity*: Must demonstrate a substantially higher level of biological activity compared to regular honey, particularly in terms of antimicrobial, antioxidant, anti-inflammatory, and wound-healing properties.

- *Medical efficacy*: Must be suitable for use in wound treatment and other medical applications, proving its effectiveness through standardized procedures and certifications.

Product name	Manufacturer	Honey type	MGH content	Sterilization method	Certification	Supplements
Activon	Advancis	Manuka	100%	Gamma irradiation	FDA & CE	—
L-Mesitran	Triticum	Organic	40 and 48%	Gamma irradiation	FDA & CE	Vitamins C and E, zinc oxide, essential oils
Manuka Fill	Links Medical Products Inc.	Manuka	100%	Gamma irradiation	FDA & CE	—
Medihoney	Derma Sciences	Manuka	80%	Gamma irradiation	FDA & CE	—
Melladerm Plus	SanoMed Manufacturing	Polyfloral	45%	Ozonation	CE	Vitamins C and E, glucose oxidase
Principelle IF	Principelle	Dark buckwheat	n.a.	Gamma irradiation	CE	Minerals, trace elements, oxides
Revamil	Bfactory Health Products	Polyfloral	100%	Gamma irradiation	CE	—
Surgihoney	Matoke Holdings	Any honey	100%	Heated	CE	Glucose oxidase
Therahoney	Medline	Manuka	100%	Gamma irradiation	FDA	—
Vivamel	Tosama	Chestnut	100%	Gamma irradiation	CE	—
Meletus	Melipharm	Mix of monoflorals	100%	Gamma irradiation	CE	—
ManukaDress–T	MedicarePlus Int	Manuka	100%	Gamma Irradiation	FDA	—
Melloxy	SanoSkin	Multi-flower	40%	Ozonation	ARTG	Olive Oil
Therahoney	MedLine	Manuka	100%	Gamma Irradiation	FDA	—
APIS	SweetBio	Manuka	40%	Gamma Irradiation	FDA	Collagen
BeeCure	SanMelix	Buckwheat		Gamma Irradiation	FDA-pending	MGO

FDA: Food and Drug Administration of the US.
CE: Conformite Europeenne.
ARTG: Australian Register of Therapeutic Goods.

Table 1.
Medical-grade honey (MGH) wound care products (2024).

3. Burn wounds

3.1 Burn degrees

A burn is an acute injury resulting from exposure of the skin or subcutaneous tissues to heat, cold, electricity, chemicals, or radiation. Burns pose a significant global health issue, affecting individuals across all age groups, though they are more prevalent among children and the elderly. These injuries can severely damage the skin and impact multiple organs and systems [50]. Research into the pathophysiology of burns has identified three distinct wound areas: coagulation, stasis, and hyperemia. The coagulation area represents the tissue destroyed at the time of injury. Surrounding this is the stasis area, where inflammation begins, and perfusion is compromised. Beyond the stasis area is the hyperemia zone, where microvascular perfusion remains intact. Within the first 48 hours following the injury, the stasis area progresses to necrosis, leading to increased wound depth and expansion [51].

Burns can suppress the immune system, cause excessive fluid loss, lead to sepsis, and result in multiple organ failure. They are classified by depth into first-degree, second-degree, third-degree, and fourth-degree burns, depending on the extent of skin damage [52].

First-degree burns affect only the epidermis, causing mild edema, hyperemia, and pain. The capillary refill and basement membrane remain intact, and no bullae form. These burns are typically caused by sun exposure or brief contact with flames and heal within 7–10 days without scarring. Protection from drying and cracking with topical ointments is usually recommended [50, 51].

Second-degree burns are categorized as superficial and deep. Superficial second-degree burns damage the entire epidermis and the upper dermis, presenting with bullae filled with plasma and fluid rich in vitamin A. These burns are painful due to exposed nerve endings and generally heal in about 14 days with minimal scarring. Second-degree burns extend to the deeper dermis, affecting capillaries, hair follicles, and sweat glands. Although nerve endings are destroyed, resulting in less pain and a sensation of pressure, healing can take up to three weeks and may require an eschar excision and grafting. Infection can exacerbate the condition, potentially progressing to a third-degree burn [50, 51].

Third-degree burns involve full-thickness damage to the epidermis and dermis, often leading to a painless area with no capillary circulation. Healing is prolonged and may necessitate eschar excision and skin grafting [51].

Fourth-degree burns penetrate all skin layers, including subcutaneous fat, muscles, bones, and tendons, resulting in a charred appearance. These severe injuries may require amputation of the affected extremities. Treatment decisions are based on the burn's depth, extent, the patient's overall health, and age [51].

3.2 Current treatments

First aid measures are crucial for the initial management of burn injuries. After ensuring the patient's safety, the affected area should be immediately cooled with cold water. It is essential to remove any burnt clothing and replace it with clean linens to minimize the risk of wound contamination and to help maintain body temperature. Following the acute treatment phase, burn care is divided into four main components: resuscitation, burn dressing, intensive/supportive care, and rehabilitation. Effective wound care is a fundamental aspect of burn management [52, 53].

Prophylactic systemic antibiotics are not typically used in the treatment of acute burns. Instead, topical antimicrobials remain the cornerstone of non-surgical burn care. These topical agents come in various forms, including creams, ointments, liquids, and impregnated dressings. Silver-based dressings are commonly utilized due to their broad-spectrum antimicrobial activity and minimal resistance from microorganisms. However, the literature on the superiority of one dressing type over another is inconsistent, and there is no definitive consensus. Burn units often select dressings based on availability, personnel preference, and historical experience. Regardless of the dressing used, some degree of antimicrobial activity is generally desired [54].

Burn wound care methods include:

- Active hydrogels [55]
- Honey-based dressings [4, 48]
- Chitin-based dressings [56, 57]
- Negative pressure wound therapy (NPWT) [58]
- Larval debridement therapy (using Lucilia sericata larvae) [59]
- Use of fish skin [60]
- Regenerative medicine [55]
- Tissue engineering products [56].

Major breakthroughs in burn care emerged in the twentieth century, particularly in the management of fluid loss, resuscitation, and the hypermetabolic response to burns. Advances were also made in infection control, the development of topical antimicrobials, and early excision of burned tissue. Techniques such as wound closure using autologous or allogeneic skin grafts, keratinocyte culture, and the introduction of artificial skin substitutes further revolutionized treatment. Prompt implementation of these strategies after a thermal injury can be life-saving, while also reducing hospital stays and accelerating recovery times [61].

Extensive scientific findings prove that honey may offer significant advantages over currently used therapeutic agents in wound and burn healing processes [3, 4, 25]. Increasing numbers of studies worldwide reveal new findings regarding the therapeutic effects and biochemical composition of honey in wound healing. In this section, clinical and experimental studies investigating the effects of honey on burn wound healing over the last decade are systematically reviewed, and their results are discussed.

4. Systematic review methodology

4.1 Databases

This systematic review conducted a literature review to determine keywords and subject headings. Analysis and eligibility criteria were defined and documented by Systematic Reviews and Meta-Analyses for Preferred Reporting Items (PRISMA). A systematic search was conducted in MEDLINE, EMBASE, CINAHL, and ScienceDirect databases, covering articles published between January 1, 2013 and June 30, 2024. MeSH (Medical Subjects Headings) content was used for keywords. Boolean connectors: and, or, not were used to limit the scanning. Keywords; It was determined as "honey", "honey dressing", "burn", "burn injury", "burn wound" and "burn care".

4.2 Selection/exclusion criteria

The published studies underwent a rigorous systematic review based on their originality, the interventions implemented, the comparisons made, and the overall study design. All articles included in the study addressed the use of honey on burn wounds. The study exclusively incorporated randomized controlled trials and research articles available in full text and published in English. Exclusions were made for, reviews, qualitative studies, conference abstracts, and studies either lacking complete texts or presented in languages other than English.

Three reviewers independently assessed the abstracts to determine their eligibility for inclusion in the review. They meticulously examined details such as the year of the study, its design, the number of participants, and the experimental method involved in each selected study. Moreover, they documented the kind of honey employed, the outcomes reported, and any limitations identified within each study. Further, in their thorough examination, studies were disqualified and removed from consideration if they were found to be duplicates, utilized incorrect methodologies, or breached ethical guidelines. The evaluators employed the PICOS Checklist for Systematic Reviews to appraise the quality and validity of the studies gathered for the review (**Table 2**) [62].

The primary search identified 954 studies from online databases and 18 through manual searching (**Figure 2**). After title screening, 82 articles were retrieved for full-text assessment. Forty-three articles, including reviews, systemic reviews, and congress proceedings, were excluded from the systematic review. The remaining 38 publications were included in the systematic review. The included publications were published between 2013 and 2024; 30 articles were designed as experimental animal model studies, five were designed as prospective clinical studies, one was designed as retrospective studies, and two were designed as case series. The studies were generally

PICOS	Inclusion criteria	Exclusion criteria
Population	Population Adult and pediatric patients with superficial, partial thickness, full-thickness burns, second-degree burn wounds or third-degree burn wounds or animal burn wound model	Other types of wounds
Intervention	Honey dressing	N/A
Comparison	SSD (cream dressing), aleo vera, milk, herbal ointment, vaseline	Other treatment modalities (early excision and grafting etc.)
Outcome Measures	Complete wound healing time, reduction in wound size, pain relief, antimicrobial activity	N/A
Study Design	Randomized controlled trials, case reports, retrospective studies, prospective clinical studies, animal studies	Observational studies, congress proceedings, reviews, abstracts, or quality improvement projects

Table 2.
Evaluation criteria based on the PICOS checklist.

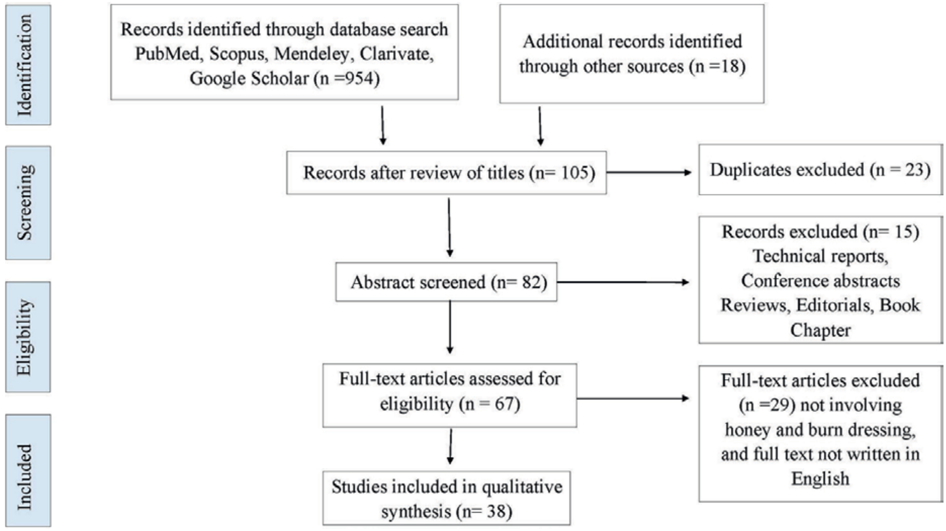

Figure 2.
PRISM follow diagram.

experimental, involving honey being applied to burn wounds and compared with other treatments. Apart from medical honey, studies examined the composition of natural kinds of honey and their effects on burn wounds [13, 63, 64].

Figure 3.
Global distribution of clinical and animal studies on honey's therapeutic effects in burn wound healing (2013–2024).

In addition to evaluating the clinical and experimental studies, it is essential to consider the geographical distribution of research on honey's effects on burn wound healing. A visual representation of the number of clinical and animal studies across different countries highlights significant regional concentrations (**Figure 3**).

The majority of these studies are concentrated in the Middle East and South Asia, regions with a long history of traditional honey use in medicine. This geographical pattern reflects both cultural practices and emerging scientific interest in honey's therapeutic potential [65]. By mapping these studies, we gain insight into the global research trends and identify areas where further investigation may be needed to fully understand honey's role in burn wound healing.

5. Clinical trials and animal studies

Honey has demonstrated significant therapeutic potential in burn wound healing, with various studies highlighting its effectiveness in increasing collagen density and stimulating tissue regeneration both in clinical trials and animal studies as summarized in **Tables 3** and **4**, respectively.

The 2016 clinical trial by Christina Duncan and colleagues compared the healing times and sterility of burns treated with silver sulfadiazine versus medical-grade honey. The study found that participants receiving active Leptospermum honey (ALH) gels experienced significantly faster healing, with an average duration of 8.1 days, compared to the typical 1 to 2 weeks for partial-thickness facial burns treated with silver sulfadiazine [67]. Moreover, wounds treated with honey achieved sterility

No	First author, year	Study design/ setting	Location	Population	Intervention and comparison
1	Choudhary et al., 2016 [66]	Clinical Trial	India	Adult only (200)	Unidentified honey dressing, and SSD dressing were applied to burn wounds in the groups. Hematological evaluation was performed.
2	Duncan et al., 2016 [67]	Case series	United States	Adults and children (7)	Manuka honey, SSD and bacitracin were applied to the burn wounds of the patients. Wound healing time, infection rates and pain-relieving effects were compared.
3	Liche et al., 2018 [14]	Clinical Trial	Nigeria	Adults and children (64)	The study investigated the effects of silver sulfadiazine and Actilite® honey on bacterial colonization and wound healing in children with partial superficial burns. Microbiological swabs were collected on days 0, 3, 7, and 10, while wound healing was evaluated over the same period.

No	First author, year	Study design/ setting	Location	Population	Intervention and comparison
4	Mohammadzamani et al., 2020 [68]	Clinical Trial	Iran	Adults (35)	The antibacterial effects of cinnamaldehyde, carvacrol, and honey, both individually and in combination, were evaluated. These were compared to imipenem, used as the control, through the broth dilution method.
5	Moniruzzaman et al., 2022 [69]	Clinical Trial	Bangladesh	Pediatric patients (70)	The patients in Group-1 (n = 35) relied on honey as medication, while patients in Group-2 (n = 35) relied on 1% SSD.
6	Taoufik et al., 2022 [70]	Retrospective Study	Bangladesh	Pediatric patients (57)	Data of children involving superficial thermal burns on less than 40 percent of the body surface were collected from hospital records. These children were treated with pure, unprocessed, undiluted honey obtained from hives after the wounds had first been cleaned with normal saline.
7	Ahangar et al., 2023 [71]	Randomized Clinical Trial	Iran	Adults (80)	Patients with deep second-degree and third-degree burns less than 40% of total body surface area were included and were randomly divided into two groups of honey (n = 40) and stapler (n = 40).
8	Boekema et al., 2024 [73]	Case series	Netherlands	Adults and children (6)	This study investigated the antimicrobial effects and possible cytotoxicity of L-Mesitran Soft (MGH-gel) and its individual components, Medihoney, Flammazine (silver sulphadiazine), and silver nitrate (AgNO3).

Table 3.
Clinical studies examining the effectiveness of honey on burn wounds.

within 7 days, whereas those treated with silver sulfadiazine did not. Patients also preferred the ALH gel for its wound coverage, protective properties, rapid healing, and natural composition.

In a 2024 study titled "Comparing the Antibacterial and Healing Properties of Medical-Grade Honey and Silver-Based Wound Care Products in Burns," Boekema and colleagues examined the antimicrobial and healing effects of honey, particularly focusing on L-Mesitran Soft [73]. This study, conducted in the Netherlands using an ex vivo model of Pseudomonas aeruginosa-infected burns, compared various

No	First author, year	Location	Population	Intervention and comparison
1	Jastrzębska-Stojko et al., 2013 [73]	Poland	White Pigs (2)	The study involved a histopathological and biochemical examination of scar formation processes in experimentally induced burn wounds in white pigs. The treatment used 1% and 3% Sepropol balms, which contained standardized extracts of propolis and honey.
2	Nakajima et al., 2013 [74]	Japan	Mice (126)	In the study, Japanese acacia honey and manuka honey Silversulfadiazine (SSD) were applied to burn wounds and their effectiveness was compared.
3	Schencke et al., 2013 [75]	Chile	Guinea Pigs (15)	Ulmo honey with ascorbic acid were applied to burn wounds and their effectiveness was compared.
4	Rad et al., 2014 [76]	Egypt	Rats (64)	Honey-impregnated placental membrane and SSD-impregnated placental membrane were applied to burn wounds. The number of polymorphonuclear (PMN) leukocytes, vascular channels, and fibroblasts between the two groups were examined.
5	Alaa Moustafa and Atiba, 2015 [77]	Nigeria	Dogs (5)	A mixture of honey, beeswax, and olive oil (MHBO), and silver sulfadiazine (SSD) was applied in second-degree burns. The effects of the different products used on the percentage of wound healing, the time required for complete wound healing, and the degree of inflammation and exudate were studied.
6	Meteoglu et al., 2015 [78]	Turkey	Rats (35)	Saline dressing, honey dressing, SSD, and, honey dressing + sherbet were applied to burn wounds in the groups. Microscopic analysis of the wound healing was performed through monitoring the skin epithelialization, granulation, reovascularization, inflammation, and fibroblast maturation via immunohisto-chemical methods.
7	Saremi et al., 2016 [79]	Iran	Mice (16)	In the study, subjects were divided into honey + nano-zinc, nano-albumin + honey, honey + nano-albumin + nano-zinc, and no treatment groups.
8	Farzadinia et al., 2016	Iran	Rats (21)	Honey, milk, and Aloe vera (HMA) ointment were performed on experimentally induced second-degree burns.
9	El-Kased et al., 2017 [72]	Egypt	Mice (40)	Honey-chitosan hydrogel applied to burn wounds. After application, tissue pH, swelling, wound healing and antimicrobial activity were evaluated.
10	Sogebi et al., 2017	Nigeria	Dogs (1)	Wound management using pure honey dressing, with initial treatment including debridement, chlorhexidine cleansing, and topical application of Dermazin® cream. Supportive therapies included Enrofloxacin, Multivitamins, Vitamin B complex, and Vitamin C.

No	First author, year	Location	Population	Intervention and comparison
11	Baakdah et al., 2017 [80]	Malaysia	Rats (21)	Tualang honey and prednisolone were applied to burn wounds. Serum interleukins, leukocyte counts, and pain behavior were compared between the groups.
12	Vaghardoost et al., 2018 [81]	Iran	Rats (40)	A mixture (sesame oil, camphor, and honey) and Vaseline were applied to second-degree burn wounds. The results of epithelialization, neovascularization and wound contraction speed were compared between the groups.
13	Yari et al., 2018 [82]	Iran	Mice (32)	Nano zinc, honey, and aloe vera were applied to third-degree burn wounds. The results of healing rates, infection control, and tissue regeneration were compared between the groups.
14	Schencke et al., 2018 [83]	India	Guinea Pigs (15)	Ulmo honey and ascorbic acid were applied to burn wounds. The results of stereological polymorphonuclear leukocyte, morpho quantitative characteristics, collagen levels were compared between the groups.
15	Dawane et al., 2018 [84]	India	Wistar Rats (54)	Ointment base, honey, sandalwood paste, calendula ointment, honey and sandalwood paste, honey and calendula ointment, honey and sandalwood and calendula, cooling with tap water and SSD were applied to burn wounds. The parameters observed were epithelization period and percentage of wound contraction.
16	Mirzaei et al., 2018 [85]	Iran	Wistar Rats (15)	Alginate-based honey hydrogel was applied to burn wounds. The effects of the dressings used in terms of wound healing and reducing infection were examined.
17	Yadav et al., 2018 [86]	India	Sprague-Dawley Rats (48)	Medicinal honey, photo-biomodulation (PBM), and combination of medicinal honey and PBM were applied to full-thickness burn wounds. Histopathological examinations were performed on tissue samples taken from the wounds and biomarkers indicating healing were analyzed.
18	Febriyenti et al., 2019 [87]	Indonesia	Sprague-Dawley Rats (24)	Rats were assigned to four groups: treatment groups (receiving honey gel or film), a negative control, and a positive control (treated with the marketed product "B"). The study assessed parameters including the percentage of wound closure and tensile strength.
19	Rathinamoorthy et al., 2019 [88]	India	Wistar Rats (9)	Honey loaded Chitosan Bioactive wound dressing and commercial dress were applied to partial thickness burn wounds. The wound healing efficacy was analyzed using wound contraction percentage and histopathology results.

No	First author, year	Location	Population	Intervention and comparison
20	Nikahval et al., 2020 [89]	Iran	Rats (16)	They are combined with ovine acellular peritoneal matrix, honey, and ovine fetal skin extract applied to infected burn wounds. The control group was dressed with physiologic saline.
21	Hosseini et al., 2020 [90]	Iran	Rabbits (10)	Rabbits with induced burns were treated with different dressings: honey dressing for the first group, milk dressing for the second group, a honey-milk combination dressing for the third group, and a 5% sulfadiazine dressing for the fourth group. The wound healing rates and histological findings were then compared among these groups.
22	Bulut et al., 2021 [64]	Turkey	SpragueDawley Rats (40)	The effects of four different honey types on burn wound healing in an animal model and silver sulfadiazine as the standard treatment compared.
23	Yolanda et al., 2021 [91]	Indonesia	Rats (28)	The impact of topical treatments—honey, Aloe vera gel, and MEBO (Moist Exposed Burn Ointment)—on collagen density during the healing of second-degree burns in rats was evaluated and compared.
24	Khaleghverdi et al., 2021 [92]	Iran	Wistar Rats (12)	The effectiveness of a mixed herbal ointment—comprising Myrtus, honey, Aloe vera, and Pseudomonas phage—on the healing of second-degree burn wounds in rats infected with Pseudomonas aeruginosa was evaluated and compared.
25	Anis et al., 2022 [93]	Egypt	Rabbits (10)	The efficacy of a natural composite (honey and essential oils) was evaluated and compared with MEBO® (0.25% β-sitosterol) and DERMAZIN® (1% SSD) creams for the treatment of thermally induced skin burns in rabbits.
26	Kulyar et al., 2022 [94]	Ecuador	Rabbits (24)	Natural honey and medical grade honey (Manuka), were applied to burn wounds, and their effectiveness was evaluated.
27	Baakdah et al., 2023 [80]	Saudi Arabia	Wistar Rats (60)	The rats were divided into six groups, and a different dressing was applied to the wounds in each group: Group 1 (burns + nigella sativa honey), Group 2 (burns+moringa honey), Group 3 (burns+sidr honey), Group 4 (burns+ pumpkin honey), Group 5 (burns+vaseline), and Group 6 (Negative control).
28	Akaba et al., 2023 [63]	Cameroun	Wistar Rats (36)	The effects of three different honey types on burn wound healing in an animal model and Brulex® (Zinc Oxide) as the standard treatment compared.

No	First author, year	Location	Population	Intervention and comparison
29	Muñoz et al., 2023 [13]	Chile	Guinea pigs (20)	Three different Ulmo honeys and hydrogel were applied to burn wounds. The properties of honey and their antibacterial effects on wounds were compared.
30	Kadi et al., 2024 [95]	Saudi Arabia	Wistar Rats (60)	Nigella sativa honey, moringa honey, sidr honey, pumpkin honey and vaseline were applied to second-degree burn wounds. Wound healing, infection and fibroblast levels were evaluated.

Table 4.
Studies examining the effectiveness of honey in animal burn wound model.

No	Studies	Intervention (implementation) and key results
1	A pilot study of the efficacy of active leptospermum honey for the treatment of partial-thickness facial burns (Duncan et al., 2016) [67]	All patients cleansed their wounds daily with soap and water, then applied Leptospermum honey. Physicians independently assessed healing through wound photography and daily tests for exudate presence. Wound cultures were used to evaluate bacterial growth on days 1 and 7. The healing time was consistent with or better than expected outcomes with standard treatment. Additionally, wound cultures showed no abnormal bacterial growth, despite the absence of antibiotic treatment.
2	Pediatric first-degree burn management with honey and 1% silver sulfadiazine (Ag-SD): comparison and contrast (Moniruzzaman et al., 2022) [69]	In the study, Group-1 (n = 35) received honey as their treatment, whereas Group-2 (n = 35) was treated with 1% SSD. Patients treated with honey experienced better clinical outcomes for managing superficial partial-thickness burns. Additionally, honey dressings enhanced overall patient compliance and significantly reduced dressing costs, which is a critical factor in burn wound management.
3	Comparing the antibacterial and healing properties of medical-grade honey and silver-based wound products in burns (Boekema et al., 2024) [73]	This study examined the antimicrobial effects and potential cytotoxicity of L-Mesitran Soft (MGH-gel) in comparison to its individual components: Medihoney, Flammazine (silver sulfadiazine), and silver nitrate ($AgNO_3$). The results revealed that MGH demonstrated similar antimicrobial efficacy against Pseudomonas aeruginosa as Flammazine and $AgNO_3$, while surpassing Manuka honey.
4	The effect of honey-impregnated human placenta membrane on burn wound healing in rat (Rad et al., 2014) [76]	Honey-impregnated placental membrane and SSD-impregnated placental membrane were applied to burn wounds. The number of polymorphonuclear (PMN) leukocytes, vascular channels, and fibroblasts between the two groups were examined. The honey-impregnated placenta membrane was an ideal tissue for temporary wound coverage and repair surface injuries after partial thickness burns.
5	Biological activity of propolis-honey balm in the treatment of experimentally evoked burn wounds (Jastrzębska-Stojko et al., 2013) [96]	The study involved a histopathological and biochemical analysis of scar formation in burn wounds experimentally induced in white pigs, treated with 1% and 3% Sepropol balms containing standardized extracts of propolis and honey. Scar formation in wounds treated with Sepropol began significantly earlier compared to the control group. Additionally, wounds treated with Sepropol showed a statistically significant increase in hydroxyproline levels, which corresponds to a higher collagen content, compared to the control group.

Table 5.
Selected clinical trials and animal studies among the burn treatments using honey.

treatments, including Flammazine (silver sulfadiazine), 1% silver nitrate, Medihoney, L-Mesitran Soft, raw honey, Vitamin C&E, and a mix without honey. L-Mesitran Soft showed antimicrobial and epidermal regeneration effects similar to silver-based products, and it outperformed Medihoney. This suggests that supplemented medical-grade honey could be a viable alternative to silver-based dressings.

Medical-grade honeys are primarily used in animal studies to identify their potential to be considered for clinical practices (**Table 5**).

A 2015 animal study highlighted honey's anti-inflammatory properties, which contribute to tissue regeneration by reducing scar formation and enhancing overall wound healing [76]. This study showed that honey-treated wounds had fewer polymorphonuclear (PMN) leukocytes and more fibroblasts and granulation tissue compared to non-honey-treated groups.

Jastrzębska-Stojko [96] further supported the combined benefits of honey and other natural products, emphasizing the potential for honey-based therapies to be effectively incorporated into clinical practice for improved wound care [96]. Another clinical study comparing burn treatments for pediatric first-degree burns found that honey resulted in less exudation and sloughing, and accelerated epithelialization compared to 1% silver sulfadiazine [69].

In conclusion, these studies provide strong evidence supporting honey's superior clinical outcomes for treating superficial partial-thickness burns and its potential as a valuable component in wound healing regimens.

6. Conclusion

In conclusion, this systematic review of honey's benefits for burn wound treatment underscores its significant therapeutic potential, particularly when using medical-grade honey. The evidence highlights honey's ability to enhance wound healing, reduce infection rates, and minimize scarring, thanks to its antimicrobial, antioxidant, and anti-inflammatory properties. However, the review also reveals a critical gap in the understanding of the specific properties of the various honeys used in animal and clinical trials. This lack of detailed information underscores the need for standardization in the preparation and application of honey for medical purposes. Ensuring that honey is processed to meet stringent medical-grade standards is crucial for optimizing its efficacy and safety in burn wound care. Thus, future research should focus on standardized protocols and comprehensive characterization of honey types to fully realize its benefits in burn wound treatment.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 4

Medical Grade of Honey: Ecology of Production, Botanical Origin, Authenticity and Safety

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Abstract

Providing medicinal honey involves a unique process based on scientific regulations and guidelines. Little attention has been paid to the integrative and comprehensive criteria for medical grade honey (MGH) production and evaluation. Because of the high importance of this valuable natural product and its use as a medicinal supplement, treatment aid, and even a therapeutic agent, the guidelines and criteria for identifying and authenticating medical grade honey (MGH) must be reviewed and analyzed. Medicinal grade honey is achieved through a continuous chain from the location of colony establishment to the production process to storage and screening. Any disruption in this chain will disrupt the entire process. Furthermore, numerous geographical zones lack the ability to produce medicinal honey. Accordingly, the production of natural honey for medicinal use requires harsh conditions so as to guarantee the health of consumers. Medical grade honey covers a limited range of naturally produced honey in the world.

Keywords: bee products, medical grade, ecology, authenticity, botanical origin

1. Introduction

The US Food and Drug Administration (FDA) has distinguished between food and drug classes, requiring medicine to obtain pre-market approval as well as efficiency and safety reports. Medical foods, however, are not controlled as drug supplies under the Federal Food Drug and Cosmetic Act but should be regulated under the food rules. Food classes comprise conventional foods, medical foods, dietary supplements, and foods for special dietary uses (FSDUs) [1]. Food is a combination of chemicals or nutrients that support diverse functions in the body (e.g., energy, growth, and protection against diseases). The nutritive element (primary metabolites) covers macronutrients (e.g., proteins, lipids, and carbohydrates) and micronutrients (e.g., minerals, vitamins, and water). Additionally, secondary metabolites cover bioactive or phytochemical components that have significant effects on human health as well as disease control (hypertensive, cardiovascular, inflammatory, and cancer diseases) and are classified as functional components [2].

Some prominent human disorders can be managed by medical foods, including Alzheimer's disease, diabetes, inherited metabolic disorders, gastrointestinal disorders, and cancer. Such foods can also aid in targeted nutrition, improved compliance, and reduced side effects [3].

A medical food is one formulated specifically for physician-supervised administration and dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation [4].

The Codex standard for the labeling of and claims for Foods for Special Medical Purposes defines foods for special medical purposes as those specially processed or formulated and dispensed for the dietary management of patients; they may be used only under medical supervision [5].

The American Society for Parenteral and Enteral Nutrition (ASPEN) has developed special standards for medical foods used for hospitalized patients, which are classified as either oral nutrition (ON) or enteral nutrition (EN-gastrointestinal tract via a tube, catheter, or stomach) foods. Accordingly, foods are designated as medical grade (MG) based on specific special considerations, guidelines, and regulations.

Because of its nutritional and medicinal properties, honey is known as a functional food product that guarantees biological functions are balanced [6]. Clinical studies have confirmed the health benefits of honey resulting from its bioactive compounds [7].

Natural honey has been used as a therapeutic agent in treating human diseases since ancient times [8]. The earliest references emphasizing the use of honey include clay tablets from Sumerian (6200 BC), Egyptian papyri (1900–1250 BC), Veda documents (5000 years ago), the Holy Quran, the Talmud, and the Bible as well as other sacred texts from different countries [9]. Honey has also been used as a remedial agent for infections and wounds for over 5000 years. Hippocrates (460–357 BC) and Aristotle (384–322 BC) both used natural honey as an effective remedy for treating wounds. Dioscorides, known as the father of pharmacognosy, used natural honey to treat sunburn, ulcers, inflammation of the throat and tonsils, and coughs. He introduced the yellow honey of Attica (Greece) as the best honey. In his medical manuscripts, the famous Iranian physician Abu Ali Sina mentioned honey being used medicinally for wound repair, to strengthen the stomach and cardiovascular system, to treat skin diseases, as an antidote, and for relief from insect bites [8].

Medicinal honey is organic, free of contaminants or toxic substances, gamma sterilized under standardized conditions, and free of dangerous microorganisms. It can be used safely in medical therapies, must adhere to strict production and storage standards as well as legal and safety regulations, and must comply with the physicochemical criteria that are important for the use of honey as a wound-care product [10–12].

Prominent papers have reported MGH being applied for wound management as well antibacterial effects [10, 13–17].

Providing medicinal honey involves production ecology, harvesting and storage, authentication, grading, and clinical trials. Accordingly, from production to supply is a unique process based on scientific regulations and guidelines that will be discussed in this manuscript. Little attention has been paid to the integrative and comprehensive criteria for MGH production and evaluation. Because of the high importance of this valuable natural product and its use as a medicinal supplement, treatment aid, and even a therapeutic agent, it is vital that the guidelines and criteria for identifying and authenticating MGH be reviewed and analyzed. The current study aims to provide an overview of production criteria and authentication as well as the determination of plant origin and health and classification of medicinal-grade honey.

2. Methods

Searches of the online databases of Wiley, Oxford, Springer, PubMed, Google Scholar, and Science Direct were conducted using diverse mixtures of the terms: medical grade, authenticity, botanical origin, honey ecology, and therapeutic effects. Abstracts of identified articles were carefully assessed, key data were identified, and analyses were extracted from the main texts. Our review firstly provides an introduction to authenticity and grading standards and guidelines; then we analyze medical grade honey using an integrated and multidisciplinary approach.

3. Authentication and grading

CODEX Alimentarius [18] states that honey is a natural sweet substance produced by honey bees from the nectar of plants, secretions of living parts of plants, or the excretions of plant-sucking insects on the living parts of plants which bees collect, transform by combining with specific substances of their own, deposit, dehydrate, store, and leave in the honeycomb to ripen and mature. Natural honey must strictly adhere to the mentioned definition; any violation constitutes fraud in honey and causes its nutritional and medicinal properties to be reduced or destroyed.

Honey for consumption must comply with international food standards. Higher quality standards are necessary for MGH [19]. Accordingly, determining the medical grade of honey is a complex procedure that includes authenticity assessment, determination of the botanical origin, and confirmation of the health factors. One of the most important achievements of honey quality control is grading, which effects fair pricing, increases consumer confidence, and improves community health while also increasing demand and reducing or removing fake honey from the economic cycle.

Identifying and authenticating natural honey require the integrity of diverse methods, including physico-chemistry, phyto-chemistry, melissopalynology, microbiology, and organoleptic analyses. The first criterion for determining MGH is the evaluation of the honey's authenticity. The United States composed the first standards for honey which include extracted honey [20] and comb honey grading [21]. CODEX [18] and ISO [22] have published international standards for the quality control of honey. The Republic of China (Taiwan), China, Europe, Japan, Korea, ANZ, and Iran [23] have developed honey standards at the national level.

MGH must meet a wide range of physicochemical, phytochemical, melissopalynological, and microbiological (INSO.org) component standards to ensure the level of quality established by the European Union [24].

4. Physicochemical factors

Physicochemical factors mainly comprise sugar content (sucrose and fructose/glucose), pH, proline, moisture percentage, diastase activity, free acidity, hydroxymethylfurfural (HMF) content, ash content, and electrical conductivity (EC) [25, 26]. The first step in evaluating MGH is to determine whether the honey complies with the basic physicochemical standards (primary authenticity). Honeys with better physicochemical characteristics are more suitable choices for further screening. On the basis of Codex Standard [18], the main quality factors include diastase activity, ≥8 Schade unit, hydroxylmethylfurfural (HMF) content, ≤40 mg/kg (or ≤80 mg/kg in honey from tropical climates), ≤20 g/100 g free acidity, ≤50 mequiv/kg), and a pH ranging from 3.4 to 6.1 (averaging about 3.9). The honey's freshness and quality are also strongly affected by storage conditions, and the quantity of hydroxymethylfurfural (HMF) and diastase activity are strangely correlated with the freshness and quality of honey [27].

The enzyme activity of honey is mainly connected to the concentration of the nectar flow as well as the composition of the nectar. Enzyme content can be significantly reduced by processing and warming; elongated storage times also affect the authenticity and quality [28]. Some natural honeys, however, originate from rich nectar (e.g., citrus and acacia) that have low levels of natural enzyme activity [29]. The α- and β-amylase (diastase) number (diastase activity) indicate honey's freshness. Natural honey also contains the active enzymes α-glucosidase (invertase), glucose oxidase, catalase, acid phosphatases, proteases, and esterases [30].

Honey's freshness and quality are closely related to its effective medicinal compounds. Polyphenols, minerals, vitamins, and fragrance are all significantly higher in medical grade honey than in food grade honeys. Both pH and EC are chemical indicators of the mineral and acid contents of honey. They are also the most valuable markers that differentiate between blossom and honeydew honeys which have diverse therapeutic effects [31]. EC value depends on the acid and ash content of honey; higher values represent higher conductivity [32]. The free acidity (acid content) of honey is useful for evaluating fermentation in honey. Microbial modifications affect total acidity over the permissible range. EC and pH are also valuable markers for differentiating between nectar and honeydew honey. Higher levels of minerals in honey indicate greater EC values [33].

The mineral components of honey are correlated with its botanical origin, color [34], geographical origin, environmental factors [35], honey comb age [36], and length of storage [37]. Lighter honeys have lower levels of minerals than darker ones.

Component	General requirement	Exceptions
Fructose and glucose content	Blossom honey: _60 g/100 g Honeydew honey: _45 g/100 g	
Sucrose content	5 g/100 g	False acacia, Alfalfa, Firewood Banksia, French honeysuckle, Red gum, Leatherwood, citrus spp.: _10 g/100 g, Lavender, Borage: _15 g/100 g
Moisture content	18%	Calluna, Erica (_23%)
Water-insoluble content	_0.1 g/100 g	Pressed honey: _0.5 g/100 g
Electrical conductivity	Blossom honey: _0.8 mS/cm Honeydew Honey: _0.8 mS/cm	Strawberry tree, Bell heather, Eucalyptus, Lime tree, Tea tree, Ling heather, Manuka or jelly bush
Free acid	50 milli-equivalents acid/1000 g	
Diastase activity	8 (Schade scale)	Honey with natural low enzyme content (e.g., citrus honey) and HMF content _15 mg/kg: _3 (Schade scale)
HMF	40 mg/kg	Fresh and unheated honey: _15 mg/kg Honeys of tropical origin: _80 mg/kg

Table 1.
Criteria for guaranteeing honey quality [41].

A significant correlation has also been reported between metal content and both total phenolic and antioxidant activities of honey [38]. Moreover, the Maillard reaction (MR), a non-enzymic reaction between free amino acids and sugars, occurs during prolonged heating and storage. In addition, decreased diastasis activity indicates an increased level of HMF; however, increased temperatures have been reported in honey stored for lengthy periods [39].

HMF is another bio-indicator of honey safety which occurs through the dehydration of hexose in honey under acidic conditions. It depends mainly on the chemical structure of honey (e.g., pH, sugar, total acidity processing, and storage temperature). Accordingly, the maximum acceptable level of HMF is 40 mg/kg in both blossom and honeydew honey [40]. The amount of proline decreases with increases in the artificial sugar compounds added to honey. Moreover, it decreases when honey is heat-treated (**Table 1**).

5. Palynological factors

Pollen assessment (melissopalynology) is significant in the grading, authenticating, and quality control of honey [42]. Melissopalynology was first explained and proposed by the International Commission for Bee Botany (ICBB), then updated by Louveaux [43]. Analysis efficiently aids in determining the geographical and botanical origin of honey [44]. Melissopalynology also provides valuable data on honey extraction and filtration, fermentation [45], some types of adulteration [46], and contamination with mineral dust, soot, or starch grains [43]. This method is also key to determining monofloral honey [47]. Honeys derived from different botanical and geographical origins are remarkably distinct in phytochemical and biological characters that significantly affect their phytochemical components as well as their medical and therapeutic features. The International Commission for Bee Research (ICBR) recommends a pollen count higher than 1200 grains per honey sample to achieve percentages of plant taxa with an accuracy of about 1%. However, it recommends a count of 500–1000 pollen grains per honey sample. The Louveaux method [43] is the most well-known method in melissopalynology and requires a lot of expertise and experience. This method divides pollen frequency into the following four classes: Predominant pollen (more than 45% of total pollen count), secondary pollen (between 16 and 45%), important minor pollen (between 3 and 15%), and minor pollen (below 3%). Some exceptions (e.g., Medicago, Citrus and Ziziphus) should be considered in evaluations [48].

Melissopalynology is a vital tool for developing both regulatory standards and certification for honey. It also provides key data for determining poisonous pollen or other adulterations [49] as well as allergenic pollens. Some pollen grains transferred into the honeycomb by the honey bee can cause allergic responses in humans. Honey pollen proteins are one of the main causes of allergic reactions to honey [50]. Honey bees collect nectar from diverse flowers, some of which, such as *Rhododendron* spp. (Ericaceae), *Lasiosiphon* sp. (Thymelaceae), and *Serjania lethalis* (Sapinaceae), are very toxic. Notably, the pollen of *Euphorbia geniculata* is highly poisonous for bees, yet honey contaminated with this pollen does not affect human health [48].

DNA metabarcoding is an efficient method for tracking honey bees and determining their geographical and botanical origins. It also has some advantages over melissopalynology, as it does not require knowledge or systematic experience and, therefore, can easily be used to analyze a honey's botanical and geographical origin [51].

6. Phytochemical and biochemical factors (functional components)

To date, about 300 different types of honey have been documented and connected mainly to botanical origins. These various types show variations in biological activity, phytochemical constituents (e.g., volatile compounds and carbohydrates), and organoleptic properties (color, taste, and smell), and thus induce diverse therapeutic effects [52]. The chemical and biological features of honey depend mainly on the botanical and geographical origins of nectar. Seasonal and environmental features have a great impact on honey properties [53]. According to CODEX [18], natural honey is produced by honey bees from the nectar of plants and honeydew. The main chemical constituents (e.g., polyphenols, carbohydrates, and amino acids) originate from plant species. These phytochemical components are affected by ecological factors and geographical origin [54]. The high diversity of the mentioned constituents makes botanical origin the most variable marker for the authentication and quality control of honey. The main phytochemical markers include carbohydrates, amino acids, polyphenols, and aromatics. Minerals and vitamins, however, are classified as subsidiary evidence to authentication [55].

Carbohydrates comprise the main chemical constituent of nectar and include sucrose, glucose, and fructose, which range from 7% to 70% w/w and are a result of adaptation to pollinators [56] and phylogenetic structure [57]. Additionally, other monosaccharides (e.g., mannose, arabinose, and xylose), disaccharides (maltose and melibiose) or, more rarely, oligosaccharides (raffinose, melezitose, stachyose) show less frequency in nectar. Nectar sugars show significant variations, both within and between species, which severely affect the sugar profiles and medicinal properties of honey. It has been reported that carbohydrate profiles can be effective markers for differentiation in some monofloral honeys [58]. Some authors, however, believe that the sugar profile alone is not enough to identify the botanical and geographical origins of honeys. Accordingly, the quantitative spectra of sugars can assist the quality control and grading of honey [59]. The total or ratio of sugars (glucose and fructose) show higher efficiency than other evaluated sugars of honey. The main disaccharides in blossom honeys are sucrose, maltose, trehalose, and turanose. Honeydew honeys show higher levels of oligosaccharides than blossom honeys, especially trisaccharides (e.g., melezitose and raffinose) which have not been reported in blossom honey. Higher levels of erlose and isomaltose have also been found in honeydew honeys. Moreover, blossom honey contains higher levels of glucose and sucrose [60].

Prebiotics are known as non-digestible food elements that usefully improve the activity of some bacteria in the colon of the host. They are usually polysaccharides or oligosaccharides. Other known prebiotics comprise malto-oligosaccharides, especially isomaltose, cellobiose, panose, maltotriose, melezitose, raffinose, maltose, turanose, and maltotriose. Additionally, prebiotic agents of honey include nulobiose, kestose, nystose, isomaltose, and faffinose [61]. Kestose, inulobiose, and nystose have been reported in Malaysian [62], raffinose in Italian [63], and isomaltose and melezitose in New Zealand [61] honeys. Moreover, erlose and raffinose have been reported in honeydew honey [64].

Low levels of proteins have also been found in honey samples, but they have displayed low efficiency in authenticating honey. Honey proteins are derived mostly from the pollen and nectar of plants [65] but originate mainly from the enzymatic process honey bees use to break down pollen and nectar [66]. Short or bioactive peptides in foods are composed of a small number of amino acids and are mostly produced by the enzymatic hydrolysis of large proteins from animal and plant origins. *Acacia* and *sidr* honey have the mentioned peptides [67]. Potent antioxidant peptides originating from honey can improve the tolerance of eukaryotic cells against oxidative stress [68]. The results of a new study on honey [69] affirmed the role of the peptides created by honey bees as antibacterial agents in honey.

The enzyme activity of honey, related mainly to α-glucosidase (invertase), α- and β-amylase (diastase), glucose oxidase, catalase, acid phosphatase, proteases, and esterases [70], depend on the strength of the nectar flow. Moreover, enzyme content in honey, considered as a bio-indicator of processing, depends on heating as well as the storage properties [28].

Diastase shows great variations among the studied honey based on the floral and geographical origin. Nectar flow, foraging patterns of the honey bee, and pH are other factors affecting diastase activity, which decreases in old and heated honey. Similarly, invertase activity depends mainly on floral origin. Glucose oxidase is inactive under the low pH of honey. Gluconic acid and H_2O_2 is generally made through honey ripening. Nevertheless, it represents a very slow action in ripe honey. Diluting honey improves glucose oxidase activity. The proteases derived from pollen, nectar, and cephalic gland secretions of the honey bee are recognized as protolithic agents in honey. They mainly improve the bee's immune system reaction against parasites [71].

The H_2O_2 produced from glucose oxidase activity motivates photolytic activity in honey enzymes, which leads to the digestion of dead tissues and improves the development of blood vessels to promote the delivery of oxygen, nutrients, and fibroblasts for tissue regeneration. A total of 26 free amino acids have been reported in honey [72] derived from nectar, pollen, and bees [73]. In addition, storage changes and reduces honey's amino acids. Pollen is a main source of amino acids in honey, so different honeys can be distinguished by their botanical and/or geographical origin [74]. Moreover, the variability of the amino acid content in honey depends mainly on the floral sources and production time [75]. The existence of some amino acids (e.g., cysteine, tryptophan, and arginine) is recognized as a diagnostic character of certain honey types [76]. Proline is the main amino acid of honey originating from the honey bee and is a main factor in the authentication and ripening of honey [44]; however, it varies according to the botanical and geographical origin of the honey [47]. In addition, the total profile of amino acids is effective in distinguishing between various types of honey. Nevertheless, neither a solitary amino acid nor a collection of them plays any prominent role in differentiating some kinds of honey. Additionally, the quantitative profile of some amino acids can be effective in determining honeys originating from different geographical regions. The enantiomeric ratio of amino acids is reported to be an indicator of processing methods, storage conditions, and age [54]. Thermal treatment or heating (e.g., up to 90°C) reduces the protein and amino acid contents of some honeys (e.g., Tualang, Gelam, and Acacia) [77].

Some glycoproteins (e.g., the MRJP family) of honey display antibacterial properties [78]. Some glycoproteins and glycopeptides are considered immunomodulatory agents in some natural honeys (e.g., Sidr and Acacia) [33]. Moreover, some honey peptides display antigiardial activity [79], and arabinogalactan proteins in honey help regulate the inflammatory process. Honey enzymes are main agents in metabolic processes, freshness, and some antimicrobial features of natural honey. The invertase content is significantly higher in honeydew honey than blossom honey. Protease is known to improve immune reactions as well as biological defenses against pathogens [71]. Acid phosphatase is a bio-indicator of fermentation in honey [80].

Low fatty acids contents (e.g., palmitic acid, oleic acid, lignoceric, linoleic acid, stearic acid) in honey have been reported to have no significant clinical effects on consumers [81].

It has been proved that the antioxidant activity of honey is mainly dependent upon its botanical origin [82]. Polyphenol compounds, flavonoids, carotenoid derivatives, catalase, peroxides, glucose oxidase enzymes, ascorbic acid, organic acids, Maillard reaction products, amino acids, and proteins show antioxidant activity in honey [83].

The phenolic acids (chlorogenic, coumaric, ellagic, caffeic, and ferulic acid), flavonoids (pinosembrine myceticine, quercetin, galangin, hesperetin chrysin, and kaempferol), carotenoids, ascorbic acid, catalase, peroxidase, and Maillard reaction products are the main biological and phytochemical constituents responsible for the antioxidant activity of honey [84]. Polyphenols have high potential for use in key formulations of nutrition- and health-oriented bee products. The antioxidant, anti-inflammatory, antimicrobial, pro-oxidant, antihypertensive, anticancer, and antiatherosclerotic effects of honey are related mainly to honey polyphenols (e.g., quercetin, apigenin, myricetin, and luteolin).

The antibacterial features of honey result from its high osmolarity, hydrogen peroxide, low pH, glucose oxidase secreted by the hypopharyngeal of the honey bee as well as the catalase activity resulting from flower pollen and nectar, and propolis and its phenolic derivatives. The antioxidant activity in honey is known as an indicator of the strength of the antibacterial, anti-inflammatory, anti-allergenic, anticoagulant, and anticancer features [85], especially those effective on breast, cervical, and prostate cancers and osteosarcoma [86]. The direct and indirect therapeutic activities of honey against COVID-19 are related mainly to its phenolic component contents [87]. The polyphenols have a significant relationship with the color of the honey; darker honey has a higher polyphenol content, and as a result, more antioxidant power. Blossom and honeydew honeys vary significantly in chemical and biological characteristics, which causes prominent variations in their antimicrobial, anti-inflammatory, and antioxidant properties. Therefore, it is necessary to distinguish between these honeys for medical uses.

Honey also has volatile components that belong to the following seven classes: aldehydes, ketones, acids, alcohols, esters, hydrocarbons, and cyclic compounds. These volatile compounds reflect the botanical and geographical origins of honey, as confirmed by several studies [88]. They display anti-inflammatory, wound healing, antioxidant, pain relieving, antitumor, antibacterial, anticancer, antihyperglycemic, and hypotensive properties; however, some of them, such as furan derivatives and acetone, exhibit low toxic effects. In addition, a wide range of volatile compounds has been used as phyto-markers for differentiating between honeydew and blossom honey [89].

There are some aromatic and non-aromatic organic acids in honey resulting from aerobic and anaerobic fermentation [90]. Organic acids exhibit variations based on the botanical and geographical origins of the honey [91]. Non-aromatic acids are responsible for the antibacterial and antioxidant activities of honey (They accelerate the action of other antioxidants) [92], the phyto-indicator of honey fermentation, the treatment of Varroa infestation [93], and honey authenticity. They also aid in the determination of the botanical and geographical origins of honey [94].

Honey contains fat-soluble and water-soluble vitamins that are useful for the physiological health of the body. These, too, vary on the basis of the botanical and geographical origins of the honey [95] and are present in minute volumes, and thus have low biological effects (e.g., antioxidant and metabolic) on human health [27]. Although consuming more honey than the usual dosage can compensate for this deficiency, this, itself, can create complications in the metabolism of the body. Furthermore, honey vitamins are subsidiary markers of honey authenticity. Heating and storage reduce the nutritional value of honey vitamins [59].

7. Safety and health factors

Honey is an important bio-indicator of ecological conditions, such as environmental pollution (heavy metals, toxins). In modern beekeeping, contamination can occur directly because of veterinary actions or indirectly because of the bee itself through collecting nectar, pollen, or consuming contaminated water [96]. Honey must be free of measurable levels of pesticides, herbicides, antibiotics, and heavy metals that show toxicity even at low levels (arsenic, lead, and cadmium). In addition, the amounts of iron and zinc should not exceed permissible levels for foods. Many chemical contaminations, including residual toxins, heavy metals, antibiotics, and radioactive elements, have been reported in honey [97]. Accordingly, medical grade honey must be free of these polluting chemicals. CODEX [18] has described the prominent criteria for evaluating residue, pesticides, veterinary drugs, and heavy metals.

Gathering honey under organic conditions is not sufficient to guarantee the absence of all possible contaminants. A wide range of bacteria, yeasts, and molds have been reported in honey [98] which may affect its safety as well as other features [99]. Scientific evidence has shown the microorganism contamination of honey originating from three sources: One, pollen, digestive tracts of honey bees, air, soil, dust and nectar; two, animals including insects, rodents, etc. that penetrate the hives during honey maturation; and three, human activities (e.g., harvesting and equipment) [100].

Clostridium botulinum is a known bacterium in the environment whose endospore content in honey varies from 5% to 64% [101]. Clostridium spores cause botulism and can cause fatal poisoning in infants [102]. In addition, several documents have reported cases of anaphylactic shock in humans, especially infants, after the consumption of raw honey caused by these contaminants.

Diverse fungi varieties are reported to grow in honey, despite the unsuitable conditions for mycotoxin making, and they can cause different infections. The prominent microorganisms reported in honey comprise the following yeasts (e.g., *Debaryomyces hansenii*, *Zygosaccharomyces rouxii*, *Zygosaccharomyces mellis*, *Aureobasidium pullulans*, and *Cryptococcus uzbekistanensis*) and bacteria (e.g., *Bacillus cereus*, *Clostridium perfringes*, *Bacillus*, *Bacteridium*, *Streptococcus*, *Achromobacter*, *Citrobacter*, *Enterobacter*, *Erwinia*, *Escherichia coli*, *Flavobacterium*, *Klebsiella*, *Proteus*, and *Pseudomonas*, *Enterobacteriaceae*, *Penicillium* spp., *Torulopsis* spp., *Aspergillus* spp., *Actinomyces*, *Bacteroides*, *Clostridium*, *Enterobacter*, *Enterococcus*, *Escherichia*, *Klebsiella*, *Lactobacillus*, *Proteus*, *Pseudomonas*, *Staphylococcus*, and *Streptococcus*) [103]. *Gluconobacter oxydans*, *Lactobacillus kunkeei, Pseudomonas* spp., and *Bacillus* spp. have been reported in honey and can act as probiotics. *Saccharomyces, Rhodotorula*, *Debaryomyces*, *Hansenula*, *Lipomyces*, *Oosporidium*, *Pichiu*, *Torulopsis*, *Trichosporon*, *Nematospora*, and *Schizosaccharomyces* are the main extracted yeasts that can be used in foods. These biological contaminations are inactive in honey; however, they represent new side effects when moved into a living host through consumption [11].

The same applies to antibiotic treatment of bee colonies, as in the long run, trace amounts can contribute to the global burden of antibiotic resistance. To produce MGH, raw honey should at least meet organic food standards and be free of detectable amounts of pollutants. Preferably, it should be certified as organic. A worldwide collection of standards, guidelines, and codes of practice has been collated by the Revised Codex Alimentarius Commission (CAC) to create uniform international food standards. Residual pollutions are known as an important factor in genetic mutations as well as cellular degradation [104]. The chemical pollutant of honey is related mainly to soil formation and floral origin that penetrate plants, are passed to the nectar, and finally enter the honey through the honey bees [105]. The negative results of chemical pollutants cover a wide range of both acute and chronic disease, leading to coma or even death. A wide range of pesticides (e.g., insecticides, bactericides, herbicides, organic acids, and fungicides) used in agriculture lead to the contamination of bee products [106]. Several studies have reported all macro-elements (Fe, Cu, and Zn) and, to a lesser extent, micro-elements (Cd, Pb, Ag, Si, Br, and Co) as present in honey [107]. Heavy metals as well as toxic trace elements have been reported in honey found in close proximity to industrial areas. Additionally, the water, soil, and air of contaminated urban and agricultural zones are agents that aggregate these toxic elements in honey [106]. Accordingly, the amount of these compounds in honey should always be monitored so as to identify products with these compounds in minimum amounts or amounts within the standard range.

Studies have shown that HMF and its derivatives have organotoxic, enzyme-inhibitory, mutagenic, genotoxic, carcinogenic, and DNA-damaging effects [108]. HMF is known as the main intermediate product resulting from two reactions: the acid-catalyzed degradation of hexose and the 3-deoxyosone in the Maillard reaction. The occurrence of simple carbohydrates (glucose and fructose), several acids, and minerals can increase HMF production in honey. Additionally, storing honey in metal containers enhances HMF levels. Moreover, HMF is produced from oligosaccharides and polysaccharides that can produce hexoses (e.g., fructose, sucrose, and glucose) in the hydrolysis reaction. Long-term storage [109], heating, and certain physicochemical properties of honey (e.g., pH, free acids, total acidity, lactones, and mineral content) are critical to increasing HMF levels. Additionally, increasing the humidity, length of heating [110], and density of metallic ions in honey (e.g., Mn, Mg, Ze, and Fe(II)) exhibit a high correlation with HMF formation. In low pH or acidic conditions, HMF can form at low temperatures and in high water content. A high fructose-to-glucose ratio can also accelerate HMF production. Additionally, the concentrations of metallic ions (e.g., Mg, Zn, and Fe(II)) affect HMF production positively during storage.

CODEX [18], European Commission (EC) regulations [24], DIN [111], and ISO [112] have presented the most important guidelines and standards for honey health.

8. Clinical trials

Clinical trials produce valuable data on the safety, dosage, and efficacy of drugs. They aim to guarantee the scientific validity of research results. Pharmacological studies on bee products have improved in recent years, with both *in vitro* and *in vivo* studies proving the therapeutic effects in humans [113]. Accordingly, multiple drugs and supplements have been developed from bee products throughout the world. Several studies have recommended that the use of MGH be evaluated in clinical studies [114]. To date, several clinical studies have investigated MGH [115]. Honey's greatest potential lies in its antimicrobial effects, as it prevents a wide spectra of bacterial taxa (anaerobic, aerobic, gram-negative bacteria, and gram-positive). MGH is an alternative to antibiotics for wound treatment. Honey has also been successfully used to cure a wide range of mucositis [116], herpes simplex labialis [117], and surgical and chronic wounds [118]. It also inhibits a wide range of yeasts and fungi as well as some viruses. Based on concentration, honey exhibits bacteriostatic or bactericidal effects [119]. The antibacterial features of honey are related to its physical and chemical factors, namely high-pressure osmosis, the presence of hydrogen peroxide (H_2O_2), high acidity (low pH), and antioxidants, all of which reduce the growth of the mentioned microorganisms. The presence of diverse phytochemical components in honey, such as polyphenols, also prevents bacterial activity [120]. Some specific phytochemical components (e.g., MGO in Manauka honey) exhibit specific activities against microbial organisms. The acidity of honey is a well-known trait of its antibacterial effectiveness resulting from the existence of certain key organic acids (e.g., gluconic acid). Nevertheless, this factor is not effective against bacteria alone, especially when diluted in foods or biological fluids of the body. H_2O_2 is produced enzymatically, and enzyme activity increases when honey is diluted. Additionally, a linear connection exists between the H_2O_2 content and the antibacterial potency of honey [121]; however, H_2O_2 concentrations vary among honey from different botanical and geographical origins. Nevertheless, some honey samples present high antibacterial activity while producing low amounts of H_2O_2 and vice versa [122].

The functional structure of MGH in wound healing is highly correlated with the presence of hydrogen peroxide, high osmolality, acidic pH, non-peroxide elements, nitric oxide, and phenols. Honey also improves autolytic debridement, promotes regeneration of wound tissues, and stimulates anti-inflammatory activities, thus accelerating wound healing. In addition, honey reduces the occurrence of extreme scar formation [123].

MGH improves the defense of the heart system by improving lipid metabolism, weakening cell apoptosis through its antioxidant features and antiaging activities, blood pressure variation, recovery of the pulsation of the heart, and reducing heart attack risk [124]. Additionally, the anticancer mechanisms of MGH include modulation of insulin signaling and estrogenic activity, facilitation of the antitumor effects of anticancer drugs, control of cancer-related complications, free radical scavenging effects, fixing wounds and chronic ulcers, anti-proliferative activity, immunomodulatory activity, anti-inflammatory effects, antioxidant activity, antimicrobial effects, anti-mutagenic activity, the induction of apoptosis and angiogenesis, and P53 regulation [125].

Various pre-clinical and clinical studies have confirmed the protective activities of MGH against metabolic syndrome. MGH decreases blood sugar levels, thus preventing weight gain. It also increases the metabolism of lipids by decreasing total triglycerides (TG), cholesterol (TC), and low-density lipoprotein (LDL) and improving high-density lipoprotein (HDL), thereby reducing the risk factors of atherogenesis. Furthermore, it improves the sensitivity of insulin to maintain stable blood glucose levels and protect the pancreas from high motivation-caused insulin resistance. Additionally, the antioxidative activities of MGH help decrease oxidative stress. Finally, MGH protects the vasculature system from endothelial disorders and tissue rebuilding [126]. The antioxidant features of honey display hepatoprotective and cardioprotective effects [127].

MGH also exhibits hypolipidemic, anti-obesity, antihypertensive, and antidiabetic effects resulting from its low glycemic index (GI), thereby limiting overweight, improving fat storage, and enhancing insulin sensitivities. Honey also reduces glucose levels in blood, increases the metabolism of lipids, and thus prevents atherogenesis, limits oxidative stress, and defends against endothelial dysfunction. Accordingly, MGH is an effective agent against metabolic syndrome [126].

MGH exhibits neurological (antinociceptive, anticonvulsant, anxiolytic, antidepressant) effects and improves memory capacity [128]. Additionally, oral consumption of MGH is known to prevent cisplatin nephrotoxicity caused by a reduction in oxidative stress, leading to the suppression of inflammation [129].

MGH has exhibited a significant effect on non-alcoholic steatohepatitis (NASH), hepatotoxicity, liver fibrosis, cirrhosis, liver disease, and liver injury. In addition, honey displays significant effects against liver cancer cells [130]. It also plays an important role in supporting and improving sports performance, bone health, and immune function when combined with a suitable sports plan. MGH is also effective against immune disorders and human immunodeficiency virus, and it is an effective therapeutic agent for respiratory tract diseases, wound healing, gastroenteritis, and several illnesses in children and infants [131].

MGH is effective against gastrointestinal disorders, such as gastroesophageal reflux, malabsorption, dyspepsia, gastritis, gastric ulcer, gastroenteritis, IBS, constipation, hemorrhoids, anal fissures, IBD, and pancreas diseases. It is also effective against periodontal diseases, pharyngitis (sore throat), cough, and hiccups. MGH exhibits high potential in boosting the immune system, being an anti-inflammatory agent, and in healing chronic ulcers to prevent the cancer. In addition, it is effective in cancer therapy [132]. MGH is used as a supplementary treatment in the management of chemotherapy-associated oral mucositis in pediatric patients. It is also effective in preventing disease progression in cancer patients [125].

MGH is effective against several conditions in women. For example, it decreases the initial pains of dysmenorrhea, improves cesarean section and episiotomy wounds, controls the quantity/period of menstrual bleeding as well as the space between two menstrual cycles, treats headache, nausea, vomiting, and menstruation pain, and aids in labor development. It is also effective in treating candida, a vaginal disease in women [133].

MGH exhibits high antioxidant activity resulting mainly from the phenolic compounds related to free radical scavenging, hydrogen-donation, singlet oxygen quenching and/or metal ion chelation. Those honeys with a higher level of polyphenols display higher antioxidant activity; however, a wide range of compounds, including catalase, glucose oxidase, peroxidase, ascorbic acid, α-tocopherol, carotenoids, amino acids, proteins, organic acids, Maillard reaction products, and other minor components have less effect on this activity [134].

MGH has antinociceptive, anxiolytic, anticonvulsant, and antidepressant properties. It also enhances the oxidative status of the brain and exhibits neuroprotective and nootropic effects. It decreases microglia-induced neuro-inflammation resulting from ischemia-reperfusion injury or immunogenic neurotoxins, reduces neuroinflammation in the hippocampus, and improves memory [135].

Currently, the number of approved products under the name of medicinal honey and with specific trade names in the world is very limited. The US Food and Drug Administration (FDA) has approved some products originating from MGH, especially those formulated on Manuka honey, including dressings, pastes, ointments, and gels [136]. The main known MGH types are described below.

Manuka honey is made in Australia and New Zealand by bees that pollinate the native *Leptospermum scoparium* (Myrtaceae), also known as a tea tree. Methylglyoxal (MGO) and dihydroxyacetone (DHA) are the main phyto-chemical components found in the nectar of *Leptospermum scoparium.* The higher the concentration of MGO is, the higher the antibacterial effect classified by grades named the Unique Manuka Factor (UMF™) will be. Manuka is used mainly for wound and burn healing, but its other therapeutic uses include treatments for skin conditions (e.g., eczema and dermatitis), cough or sore throat, and digestive disorders.

Tualang (TH) is a monofloral forest honey produced by the *Apis dorsata* (rock bee) that builds its hive among the branches of the Tualang tree (*Kompassia excelsa*), distributed mainly in tropical rain forests. Tualang honey has bactericidal and bacteriostatic activity and is rich in antioxidant components that exhibit a high potential for preventing cancer [132].

Gelam, another monofloral honey produced by wild *Apis dorsata* (rock bee), originates from *Melaleuca cajupati* Powell. (Myrtaceae), known as the "Gelam tree." Gelam honey is mainly used in therapies to treat cholera, vaginal infection, thrush, acne, verruca, warts, cold sores, nits, athlete's foot, and insect bites and to aid wound healing [137].

Kelulut is a forest honey produced in Indonesia by the wild kelulut bee (*Trigona* sp.) that contains high levels of antioxidant components. This honey has a sweet and sour taste and is used by indigenous people to treat canker sores [138].

Kanuka honey is derived from the Kanuka tree (*Kunzea ericoides* (A.Rich.) Joy Thomps) from Myrtaceae that grows in New Zealand. It exhibits significant antibacterial, anti-inflammatory, and antioxidant activity [139], which is effective in wound management.

Revamil honey (RS) is made under controlled conditions in greenhouses and exhibits high antibacterial effects [140]. RS has also shown anti-bactericidal activity against antibiotic-resistant gram-positive and gram-negative bacteria.

Ulmo honey originates from the Ulmo tree (*Ucryphia cordifolia*) and is produced in Chile. It is equal to Manuk UMF25+ in terms of its antibacterial power [141].

9. Discussion

Honey can be classified as either a medical food (MF) or medical grade (MG). It contains nutritive components (primary metabolites, proteins, lipids, carbohydrates, and micronutrients such as minerals, vitamins, and water) as well as secondary metabolites (e.g., bioactive or phytochemical components). The ratio between these two components determines the medicinal or food value of honey. Medical grade honey contains effective medicinal compounds (including pharmacological effects). The primary step to determining the medical grade of honey is to evaluate the authenticity of natural honey based on set standards. The second step is to evaluate the levels of its functional components. A supplementary step can be clinical trials to screen the honey's therapeutic effects. The evaluation of honey factors and their compliance with set standards will aid in guaranteeing the primary conditions for the quality and therapeutic potential of medicinal grade honey. The biological and phytochemical components of honey are mainly dependent on botanical origins and ecological factors. Storage and processing also affect the medical constituents of honey (e.g., polyphenols and volatiles) [92]. The Apimondia Working Group on International Organic Standards for bee products has provided guidelines on the following for the production of organic products: The usage of young and productive queens, providing honey bees suitable pollen and nectar resources and access to clean water, feeding bees in necessary situations, arrangement order in the establishment of hives, implementing measures to reduce stress to the honey bees, feeding or removing sufficient honey and pollen resources for the dearth period, protective measures against bee diseases, appropriate use of medicines, healthy management of bee products, and locating proper establishments for honey bees. Successful beekeeping is strongly dependent upon the existence of a sufficient number of good quality forage resources (e.g., nectar and pollen) [142]. One of the most vital actions of the beekeeper is selecting the number of hives to be located in a particular habitat so as to achieve the highest efficiency in foraging performance [143]. Key factors in producing the top grades of honey (such as medical grade) are the ecological conditions governing the establishment of honey bee colonies. These factors in habitats include vegetation types, density as well as frequency spectra of valuable plant taxa for the honey bee, non-fragmented habitats, distance from permanent water sources, distance from roads, distance from power lines and antennas, altitudinal variations, geomorphologic diversity, and organic crop surface [144]. Therefore, the use of chemically synthesized allopathic products in organic apiculture (the basis of medicinal honey production) is forbidden. In addition, apiaries must be at least 3 km away from sources of industrial pollution [145]. Some experts [146], however, believe that the settlement zone of the bee colony should be up to 10 km away from contaminated areas. Evaluating the ideal number of bee colonies is vital to reducing the competition and ensuring the high quality of honey [147]. Imbalances in the standard establishment of colonies can reduce the quantity and quality of production [148]. To counteract this, beekeepers move colonies from one habitat to another so as to provide food for the colony and increase the quantity and quality of the honey. Additionally, the migration rate of the colonies depends on the density and quality of vegetation in the habitats [149].

Because of the diversity in possible honey sources resulting from a wide range of plant taxa, each honey is unique. Plant nectars are the main sources for the production of honey. Quantitatively and of course to a greater extent qualitatively, nectar profiles display a lot of variety. The qualitative diversity of chemical components is often related to the species, genus, and family of the nectar-producing plants; however, quantitative diversity is often related to the ecological and geographical conditions of the honey production. Monofloral honeys (obtained from the nectar of specific plant species) are the main sources of bioactive compounds [150] and display a prominent potential for therapeutic features [84]. Thus, they are known as a higher class of medical honeys [47]. Several valid studies have confirmed that monofloral honeys have different bioactive compositions for medicinal uses [84, 151, 152]. Monofloral honeys are also main sources of antioxidant activities. They contain a wide range of phytochemical components with functional properties (e.g., phenolic acids, flavonoids, and minerals) and thus exhibit a marvelous potential for medical uses [84]. There are significant differences in the effective medicinal compounds of blossom honey and honeydew. Accordingly, differentiating between the mentioned kinds of honey is necessary to control the quality and grading of honey. The therapeutic effects of several monofloral honeys, such as Citrus [153], Ziziphus [154], Thymus [155], Teucrium [156], and Astragalus [157], have been confirmed in clinical trials.

The glycemic index (GI) indicates how rapidly different foods affect blood glucose levels as well as the relative increase in blood glucose level 2 hours after consuming a particular food. Its values range from 0 to 100 (pure glucose). Glycemic load (GL) is calculated on the basis of the highest dose of honey consumption per drink and can range between 50 and 80 g. Honey can have a glycemic index of between 32 and 87, depending on its botanical and geographical origins and fructose content [158]. Monofloral honeys exhibit diverse ranges of fructose content and fructose/glucose. Accordingly, honey containing the lowest level is the most appropriate choice for diabetic patients. A study in Turkey identified Citrus and Thyme honeys as having a low GI and Lime, Chestnut, and Pine honeys as having a medium GI [159].

Additionally, Citrus and Pod Locust with low GI values and Christ Thorn, Mixed Floral, and Thistle honeys with medium GIs have been reported in Jordan. Honey can be polluted by environmental factors as well as by beekeeping activities. The main chemical contaminants of honey include pesticides, antibiotics, and heavy metals, all of which are harmful to human health. These chemical components biomagnify and bio-accumulate, leading to high concentrations in the body over time. The negative effects of these compounds in sick people are extremely dangerous. Accordingly, MGH should have the lowest amounts of these pollutants so as not to impose secondary pressures on the patient.

Because of their chemical and physical characteristics, microorganisms have a strong ability to spread in honey. Therefore, reducing or even eliminating pollutants is very important to obtaining MGH. Honey absorbs bacterial spores and keeps them for a long time. The harmful effects of these biological contaminants, especially *C. botulinum* spores that are acquired through honey consumption cannot be ignored. Numerous reports have indicated the negative effects of these bacteria. Because honey can become biologically contaminated, sterilization seems to be necessary, especially MGH to be used for wound healing [160]. Up to now, several sterilization methods have been reported, for example, pasteurization, refrigeration, freezing, and most especially gamma radiation for MGH [19, 161]. Moreover, membrane processing completely separates yeast cells from honey [162]. Ultrasound, infrared heat, and microwave processing are other unconventional ways to sterilize honey [163]. The bubbling ozone gas placed in an ozone-resistant container displays high efficacy in destroying endospores in honey. While bacteria are destroyed by sterilization, their endotoxins can penetrate the honey and eventually have negative effects on consumer health. There is a positive correlation between released endotoxins and the amount of endospores. Accordingly, screening for low levels of microorganisms in honey is a necessary step in MGH selection. The maximum limit is suggested to be 10 CFU/g honey for fungi and molds and 10 CFU/g honey for bacteria [10]. Bacteria are destroyed by sterilization; however, some endotoxins (e.g., LPS) can penetrate honey and lead to inflammatory pyrogenic reactions. Higher endospore counts release a higher number of toxins. Accordingly, a honey with fewer microorganisms (maximum limits of 10 CFU/g honey for bacteria and 10 CFU/g honey for fungi and molds) is the better choice [10]. It has been reported that low-dose gamma irradiation (e.g., 2.5 KGy and 5 KGy) is not effective in honey sterilization. Larbi et al. [100] revealed that 20 KGy gamma radiation is suitable for destroying bacteria and maintaining the nutritional-medicinal values of honey. Furthermore, gamma irradiation ranging from 20 KGy to 30 KGy at a temperature of 25°C had no significant negative effect on the physicochemical features of honey. Using gamma irradiation (25 KGy) has not been shown to have significant effects on reducing the antibacterial effects of honey [19, 120]. Gamma radiation, however, has been found to reduce all values of HMF [160] and to effect a minor reduction in pH after irradiation at 40 KGy. Gamma irradiation for the sterilization of honey has been reported to be a safe method for eliminating microorganisms and bacterial spores in honey for use in pediatric patients and in wound healing.

The medical grade of honey can be improved by several complementary natural products (e.g., medicinal plants and mineral elements). Numerous studies have shown that honey, in combination with other natural products such as medicinal plants, has stronger therapeutic effects. Some examples include honey and cinnamon for breast cancer [164] and honey and ginger against *Escherichia coli*. The mixture of honey and cider vinegar improves the detoxification of the liver to enhance overall health and aids in weight loss. Additionally, garlic, cinnamon, Zataria multiflora, cardamom, and basil [82] have been shown to improve the therapeutic properties of honey. Moreover, honey and royal jelly combined exhibit a synergic effect [165]. In addition, medicinal honey increases the effectiveness of medicines [8].

Some known MGH products have additional elements, such as hypoallergenic lanolin (CAS 8006-54-0) and PEG 4000 (CAS 25322-68-3). PEG (CAS 57-55-6), polypropylene glycol, lanolin, polyethylene, omega 3, and vitamins E, A, and D have been known to improve the quality of MGH treatment in wound healing [10].

Honey is recognized as an allergenic food that induces different levels of allergenic reactions varying from mild (e.g., cough, etc.) to severe (e.g., anaphylaxis). The allergenic factors of honey include gland secretions and wax from the honey bee, flower nectar, and pollen proteins. Sensitization to honey allergens and allergenic reactions from honey should be considered when using honey in treatments [166].

Medicinal grade honey is achieved through a continuous chain from the location of colony establishment to the production process to storage and screening. A disruption in any part of this chain will cause problems in the entire process. Furthermore, numerous geographical zones lack the ability to produce medicinal honey. Accordingly, harsh conditions are considered in the production of natural honey for medicinal use so as to guarantee the health of consumers. Medical grade honey covers a limited range of naturally produced honey in the world. It must be categorized on the basis of effective chemical components; some classes are suitable for oral consumption, while others must only be used externally, especially for wound treatment. Medical food products have become an important assistant in hospitals and nursing homes, promoting the recovery of patients.

Several produced honeys originating from various botanical and geographical regions in the world have a high potential for becoming medicinal grade honeys. This requires several steps: Sampling of all ecological regions producing each type of honey, and comprehensive analysis including physicochemistry, phytochemistry, microbiology, melissopalynology, safety, and health. Finally, clinical trials must be conducted to evaluate the therapeutic effects of selected honeys. Accordingly, such comprehensive characterization (authenticity, grading, and clinical trials) provides valid and referable documentation for the use of a honey as an MGH.

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Chapter 5

Therapeutic Properties of Honey and Propolis

Fatiha Abdellah

Abstract

Honey and propolis are both bee products that have been used for centuries for their medicinal properties. Honey is a natural substance produced by bees from the nectar of flowers. Honey has been shown to have a number of health benefits such as anti-inflammatory effect, immune boosting property, and antimicrobial activity, which is attributed to both physical factors: acidity and osmolarity, and chemical factors: hydrogen peroxide, volatiles, and polyphenols. This can help to promote wound healing and preventing infections. Propolis, also known as bee glue, is a resinous substance that bees collect from trees. It is used to seal cracks in the hive and to protect the bees from bacteria and viruses. Propolis contains a number of bioactive compounds that are thought to be responsible for its health benefits. These include flavonoids, phenolic acids, and esters. Propolis has been established to have multiple beneficial health effects. It has antibacterial and antifungal activities; this may be helpful in treating wounds, infections, and some skin conditions. Propolis is also characterized by its anti-inflammatory effect. In conclusion, honey and propolis have the potential to be used as natural remidies for various disorders.

Keywords: honey, Propolis, health benefits, natural remidies, disorders

1. Introduction

In current times, the search for natural and alternative therapeutic agents is becoming more and more popular [1]. Natural bee products, particularly propolis and honey, are often regarded as excellent sources of bioactive compounds with significant biological potential [2]. The goods' healing properties of these products are associated with their bioactive composition and the plant source from which they originate [3]. Honey bee products have received a lot of attention in both traditional and modern medicine [4]. Honey and propolis have been revered for centuries for their potential health benefits [5]. These natural products are packed with antioxidants, vitamins, minerals, and other bioactive compounds that contribute to their therapeutic properties. Honey is a complex mixture of sugars, enzymes, and water, with its composition varying based on the floral source. Beyond its delightful taste, honey offers a range of potential health benefits [6]. Propolis, often referred to as bee glue, is a resinous substance collected by bees from trees and plants. It has a sticky texture and is used by bees to seal and protect their hive. Propolis boasts a wide array of potential health benefits [7]. Several studies reported that the bioactive compounds of honeybee products had therapeutic and medicinal properties and improve the human health. Honey and propolis contain bioactive substances that have been shown to exhibit many health benefits, including anti-inflammatory, anti-microbial, antioxidant, anti-cancer, anti-ulcer, immunomodulatory, neuromodulatory, and metabolic syndrome prevention effects [8]. These properties make honey and propolis useful for treating and preventing a variety of chronic illnesses, including diabetes, cancer, and inflammatory disorders. In this context, the focus of this chapter will be on the biological effects and the health benifits of honey and propolis.

2. Honey

Honey is a healthy and natural food produced by honeybees from plant nectar, plant secretions, or plant-sucking insect excretions on plant surfaces [9].

2.1 Chemical composition of honey

Honey is composed mainly of sugars such as glucose, fructose, maltose, and sucrose and water. Other trace amounts of proteins, organic acids, amino acids, vitamins, flavonoids, and acetylcholine are also present (**Table 1**) [10]. In addition to phenols, minerals, and enzymes, honey also includes trace levels of bioactive substances such as proline, carotenoid, total flavonoid content, salicylic acid, naringin, and taxifolin (**Table 2**) [14].

Substance	Content (%)	
Water	17,2	
Sugars	Levulose (d-fructose)	38.19
	Dextrose(dglucose)	31.28
	Sucrose (saccharose)	1.31
	Maltose and other reducing disaccharides	7.31
	Higher sugars	1.50
	Total sugars	79.59
Acids	(gluconic, citric, malic, succinic, formic, ect); total acids calculated as gluconic acid:	0.57
Proteins	(amino acids: glutamic acid, alanine, arginine, glycine, leucine, isoleucine, aspartic acid, valine, histidine and lycine):	0.26
Ashes	(minerals: potassium, sodium, magnesium, calcium, phosphorus, iron, manganese, copper, etc):	0.17
Minor component	Mainly comprising pigments; aromatic substances; sugar; alcohols; tannins; enzymes; diastases including amylase, peroxidase, succindehydrogenase, phosphatase, and invertases; and vitamins including thiamine, riboflavin, nicotinic acid, vitamin K, folic acid, biotin, pyridoxine, and pantothenic acid:	2.21

Table 1.
Chemical composition of honey.

Bioactive compound	Amount	Reference
Carotenoid content	0.6–6.2 mg/kg	[11]
Proline level	4.6 mg/kg	[12]
Total phenolic content	1.3–126 mg (GAE)/100 g	[11]
Total flavonoid content	1.9–4.2 mg (QE)/100 g	[12]
Salicylic acid	8.2–94.8 μg/100 g	[13]
Naringin	4–32 μg/100 g	[13]
Taxifolin	12–1920 μg/100 g	[13]

GAE: gallic acid equivalent; QE: quercetin equivalent.

Table 2.
Bioactive components of honey.

2.2 Health benefits of honey

Honey has been used for thousands of years for its medicinal properties. Its unique composition, rich in natural sugars, vitamins, minerals, and enzymes, gives it numerous therapeutic virtues and health benefits [15].

2.2.1 Antibacterial activity

Honey has been shown to have antibacterial properties against a wide range of bacterial species, including aerobes and anaerobes, Gram positives, and Gram negatives (**Table 3**) [16]. Honey has an important antibacterial effect against methicillin-resistant *Staphylococcus aureus* (*MRSA*) and several *Pseudomonas* strains, which are commonly associated with burns and wound infections [14]. The antibacterial properties of honey are mainly attributed to many factors including its low water content, high viscosity, acidity osmolality, glucose oxidase enzyme, hydrogen peroxide content, and non-peroxide components, especially the presence of methylgyoxal (MGO) and phenolic compouds [17].

2.2.2 Antifungal activity

Since ancient times, honey has been used as a natural remedy for many ailments, including fungal infections. Honey has been used as an alternative to treat severe fungal infections in place of other therapies due to its inherent antifungal characteristics [18]. The antifungal effect of honey has been shown in several studies. Abdellah et al. [19] found that *Daucus carota* honey had an antifungal effect against *Candida albicans*.

The result of a study done by Vică et al. [6] revealed that Romanian honey exhibited an antifungal effect against six fungal strains: *Aspergillus* niger, *Aspergillus flavus, Candida albicans, Penicillium chrysogenum, Rhizopus stolonifer*, and *Fusarium oxysporum*.

A recent study conducted by Dang et al. [20] has reported that vetnameen honey has antifungal properties against *C. albicans* ATCC 10231.

Haines et al. [21] demonstrated that many Western Australian honeys and manuka honey exert antifungal activity *in vitro* against species of clinically important yeast including: *Candida albicans, Candida parapsilosis, Nakaseomyces glabratus, Pichia kudriavzevii, Saccharomyces cerevisiae*, and *Trichosporon asahii*.

Bacterial Species	Disease caused
Bacillus anthracis	Anthrax
Corynebacterium diphtheriae	Diphtheria
Escherichia coli	Diarrhea, septicaemia, urinary infections, wound infections
Haemophilus influenzae	Ear infections, meningitus, respiratory infections, sinusitis
Klebsiella pneumoniae	Pneumonia
Mycobacterium tuberculosis	Tuberculosis
Proteus spp.	Septicaemia, urinary infections
Pseudomonas aeruginosa	Urinary infections, wound infections
Salmonella spp.	Diarrhea
Salmonella choleraesuis	Septicaemia
Salmonella typhi	Typhoid
Salmonella typhimurium	Wound infections
Serrata marcescens	Septicaemia, wound infections
Shigella spp.	Dysentery
Staphylococcus aureus	Abscesses, boils, carbuncles, impetigo, wound infections
Streptococcus faecalis	Urinary infections
Streptococcus mutans	Dental carries
Streptococcus pneumoniae	Ear infections, meningitis, pneumonia, sinusitis
Streptococcus pyogenes	Ear infections, impetigo, puerperal fever, rheumatic fever, scarlet fever, sore throat, wound infections

Table 3.
List of bacterial species sensitive to honey and the illnesses they can cause [16].

Honey's antifungal properties are attributed to a variety of factors. Honey's low water content generates a strong osmotic pressure that can impact the fungal cell wall; its low pH restricts the growth of fungus; and its high viscosity prevents infection. Moreover, glucose oxidase breaks down glucose to form hydrogen peroxide (H_2O_2), which is the primary antifungal agent in honey [22].

2.2.3 Antiviral properties of honey

Honey has been used as a remedy for many viral illnesses since ancient times. It is a crucial treatment for respiratory pathogens, such as viruses that induce coughing. Honey has been shown in numerous studies to have an antiviral effect against a wide spectrum of viruses [23].

According to a study done by Watanabe et al. [24], honey especially Manuka honey has a strong inhibitory effect against the influenza virus, suggesting that it may have therapeutic benefits.

The result of a recent study conducted by Kalediene et al. [25] reported that honey extract "Camelyn" had an antiviral effect against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The inhibitory effect of honey against herpes simplex virus type 1 has been demonstrated by Ghapanchi et al. [26].

The antiviral activity of honey is due to several factors including:

Hydrogen peroxide (H_2O_2) is one of the key compouds in honey that is supposedly responsible for its antiviral properties.

Acidity: Low pH of honey makes it difficult for viruses to proliferate.

Excessive sugar content: The high sugar content of honey can produce a drying atmosphere that inhibits the virus's growth [17].

Aascorbic acid (vitamin C) has been shown to have antiviral immune responses, especially against the influenza virus [27].

One of the most important mechanisms underlying the honey's antiviral activity and its main compounds is interrupting the proteins required for viral attachment and penetration into host cells [28].

2.2.4 Antioxidant effect

Several studies have revealed that oxidative damage is the principal cause of the majority of chronic diseases, including cancer, heart disease, and neurological degeneration [29]. Honey is widely recognized as a natural antioxidant. It has also been demonstrated that honey's medicinal potential is always correlated with its ability to neutralize reactive oxygen species and its antioxidant activity. The components that give honey its redox characteristics include probably flavonoids, vitamins (vitamin C, vitamin E), enzymes (catalase, peroxidase), and phenolic acids, in addition to trace amounts of minerals, like copper and iron [30]. The antioxidant activity of honey could also be attributed to the synergistic effects of these minor compounds [31]. The antioxidant properties of honey have been demonstrated by numerous studies.

Al zahrani et al. [32] indicated that three varieties of honey from different botanical and geographical (Manuka honey from New Zealand, acacia honey from Germany, and wild carrot honey from Algeria) have strong antioxidant activities, evaluated by three different tests: ferric-reducing antioxidant power (FRAP Assay), DPPH radical-scavenging activity, and ABTS assay.

The result of a study done by Dżugan et al. [33] reported that honey had antioxidant activity evaluated by reducing power (FRAP test) and DPPH test.

Abdellah et al. [34] demonstrated that two varieties of honey from Algerian steppe (*Euphorbia cheiradenia* and *Noaea mucronata*) have an important reducing power and free radical-scavenging activity against the 1,1-diphenyl-2-picrylhydrazyl (DPPH).

2.2.5 Anti-inflammatory properties

It is commonly known that a number of diseases including autoimmune and cardiovascular disorders are correlated with systemic inflammation [35]. Honey has anti-inflammatory properties that can help reduce pain and swelling associated with various affections. The anti-inflammatory characteristics of honey may be due to its phenolic and flavonoid constituents and enzymes. These compounds can help to scavenge free radicals, which are molecules that can damage cells and contribute to inflammation. In addition, sugar and non-sugar components are recognized to have immunomodulatory impacts [36]. The anti-inflammatory effect of honey has been studied by scientific research. The result of *in vivo* study done by Stavropoulou et al. [37] reported that the administration of Greek honey samples to LPS-stimulated mice revealed a potent anti-inflammatory activity by suppressing the TNFα serum levels and the expression of TNFα and iNOS in the liver. Honey was shown to have anti-inflammatory properties by reducing the activities of cyclooxygenase-1 and cyclooxygenase-2. Moreover, consuming diluted natural honey has led to decreases in the plasma concentrations of prostaglandins in normal individuals, including PGE2 (prostaglandin E2), PGF2α (prostaglandin F2a), and thromboxane B2 [38].

According to the result of a study done by Safi et al. [39], the expression of TNF-α, IL-1β, and IL-6 was significantly reduced in the cells pre-treated with Gelam malysian honey and quercetin. This was followed by a decrease in the expression of phosphorylated IRS-1, JNK, and IKK-β.

Many studies have demonstrated that honey considerably lowers serum pro-inflammatory markers, including TNF-α and IL-6, in various cancer types [40–42].

There are various modes of action that could account for honey's anti-inflammatory properties such as suppression of the classical complement system, suppression of the production of ROS, inhibition of leukocyte infiltration, inhibition of the expression of inducible NO synthase and COX-2, and lastly, inhibition of the matrix metalloproteinase 9 (MMP-9) [43].

2.2.6 Honey for wound healing

Wound infection is an essential factor that delays or inhibits wound healing. It has a harmful effect on patients and can intensify suffering; it halts the process of healing, contributing to prolonged hospital stays, along with higher treatment expenses [44]. Honey has been used for centuries as a natural remedy for wound healing. Recent research has begun to shed light on the scientific basis for this traditional practice. Honey has a high sugar content and low pH, which creates an environment that is inhospitable to bacteria. This can help to prevent wounds from becoming infected. Several studies have reported the use of honey in the treatment of infections and wounds. **Table 4** lists numerous studies that demonstrate the effective use of honey in wound healing [57].

The wound healing properties of honey is associated with its physical characteristics, which include its hypertonicity, lower pH, and complex chemical composition. Hydrogen peroxide (H_2O_2) is an essential and a powerful antibacterial and wound-healing agent found in honey. The physical characteristics of honey form a barrier of defense and through osmosis produce a moist environment for wound healing that is not adherent to the underlying tissues of the wound [57]. Honey accelerates the healing process of wounds by stimulating regenerative tissue growth and epithelization [44].

2.2.7 Anti-ulcer effects

A gastric ulcer is a lesion that affects the muscularis mucosa as well as the entire gastrointestinal mucosa [58]. Serious complication and side effects such bleeding, perforation, or obstruction of the stomach outlet occur in about 25% of people with this illness [59]. Currently, treating stomach ulcers is challenging because of

Origin of Honey	Type of Lesion	Effects of Honey	References
Iran	Surgical incision on rabbits	Less edema, fewer polymorphonuclear and mononuclear cell infiltrations, less necrosis, better wound contraction, improved epithelialization, and lower glycosaminoglycan and proteoglycan concentrations	[45]
India	Wounds created on buffalo calves	Promotes granulation and scar formation; complete healing of full-thickness wounds occurred faster with honey than with nitrofurazone or sterilized petrolatum	[46]
Egypt	Infected diabetic foot wounds	Fast healing and significant decrease of bacterial load.	[47]
Turkey	Split-thickness skin graft donor site	Wounds show faster epithelialization time and a low sense of pain than paraffin gauzes and saline-soaked gauzes	[48]
United Arab Emirates	Injured skin or conjunctiva in mice or rat	Accelerates wound healing and eradicates infection	[49]
Yemen	Postoperative wound	Eradicates bacterial infection, accelerates wound healing, and minimizes scar formation	[50]
Thailand	Postoperative wound disruption	Complete wound healing within 2 weeks	[51]
Nigeria	Wounds and ulcers	Debrides wounds rapidly, replacing sloughs with granulation tissue, promotes rapid epithelialization, and absorption ofedema	[52]
Mexico	Fournier's gangrene	Accelerates wound healing	[53]
Ireland	Nonhealing ulcers	Manuka honey decreases wound pH and causes a reduction in wound size	[54]
France	Wounds	Accelerates wound healing	[55]
Germany	Resistant wound infection in seven patients	Complete wound healing	[56]

Table 4.
Wound healing effects of honey.

the limited effectiveness and side effects of medications available in the market. Consequently, it is important to find safer, more potent antiulcer treatments with fewer adverse effects rather than artificial medications derived from natural sources. Honey is a natural product that has long been known to provide therapeutic benefits [60, 61]. Treatment of digestive disorders with honey has a long history. Honey has the potential to reduce stomach ulcers and enhance digestion. It has been reported that honey is used to prevent and treat rotavirus- and/or bacteria-induced gastritis, duodenitis, and stomach ulcers [60, 61]. It inhibited microorganisms' adhesion to the intestinal epithelium, which is the first stage of the development of bacterial infection [62]. Honey has antibacterial effect against *Helicobacter pylori*, which is the common cause of stomach ulcers as demonstrated by numerous studies. Ndip et al. [63] reported that honey at 10% concentration inhibited the growth of *H. pylori* isolates. Another study done by Cviljević et al. [64] indicated that chestnut honey has an inhibitory effect against *Helicobacter pylori*. Harakeh et al. [65] revealed that Saudi honey significantly reduced the ulcer indices and essentially protected the glandular mucosa from lesions. The result of *in vivo* study conducted by Djebli et al. [66] revealed a significant gastro-protective effect of Saharian (Sidr) honey against HCl/Ethanol-induced stomach ulcer. Honey has been found to contain phenolic compouds, specifically flavonoids, which are responsible for its anti-ulcerous properties. Flavonoids increase the mucosal content of prostaglandins, which enhances the protective effect on the gastric mucosa, thus preventing ulceration. The antigastric ulcer of honey can also be attributed to its antibacterial, anti-inflammatory, and antioxidant effects in addition to its ability to reduce the gastric juice's acidity [67].

2.2.8 Prebiotic effect

Prebiotics are defined as "non-digestible food ingredients that selectively stimulate the growth and/or activity of one or a limited number of beneficial bacteria in the colon, thereby improving host health and having a beneficial effect on the host" [68]. Honey also has prebiotic properties, which means it can promote the growth of beneficial bacteria in the gut. Several studies demonstrate that honey stimulates the development of probiotics *Bifidobacterium* and *Lactobacillus* species, including *B. longum, B. adolescentis, B. breve, B. bifidum, and B. infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus reuteri,* and *Lactobacillus rhamnosus* [69–71]. Other research has demonstrated that honey not only promotes the growth of probiotic cultures but also improves the metabolism of bacterial strains from the human gut.

Honey's prebiotic properties are primarily attributed to its oligosaccharide content. These complex sugars act as a selective food source for beneficial gut bacteria, promoting their growth and activity and helping them to outcompete harmful microorganisms, as well as antimicrobial compounds, which have synergistic effects with the probiotics against several pathogens [72]. Some phenolic compounds in honey may also indirectly support gut health by influencing the gut microbiota. The prebiotic content of honey can vary depending on factors like floral source, geographical origin, and processing methods. **Table 5** outlines the various kinds of honey that are sources of prebiotics and their effects on probiotics that are often present in the human digestive system.

2.2.9 Anticancer

In the modern world, cancer is a major cause of death and significant health burden [79]. Cancer treatments with the conventional methods have reported serious side effects. Furthermore, the hunt for chemopreventive and chemotherapeutic drugs derived from food or natural items has attracted more attention [80]. Scientists were therefore drawn to less harmful treatments and innovative technics; one of the most often used natural products whose potential to prevent cancer is being studied is honey. Certain polyphenols found in honey, including kaempferol, pinocembrin, pinobanksin, apigenin, chrysin, galangin, quercetin, acacetin, and caffeic acid phenyl ester, have grown to become viable pharmaceutical medicines used in cancer treatment [81]. The anticancer effects of honey have been demonstrated by many scientific research.

Probiotic	Prebiotic sources	Key findings	References
Lactobacillus acidophilus	Honey	Honey enhanced the coaggregation of *E. coli* with *L. acidophilus* NCDC 291 more than with *L. acidophilus* NCDC 13. • Both strains showed a higher capability of autoaggregation and hydrophobicity and reduced autolytic activity with inulin compared to honey.	[73]
Lactobacillus acidophilus, Bifidobacterium bifidum	Sesame honey (*Sesamum indicum*)	Sesame honey (5%) exhibited selective and significant growth-supporting properties of the probiotics.	[74]
Lactobacillus acidophilus, Lactobacillus rhamnosus	Chestnut honey	Chestnut honey has positively impacted probiotic bacteria by increasing growth and modulating probiotic properties such as auto-aggregation and surface hydrophobia	[75]
Bifidobacterium bifidum and Lactobacilli	Clover honey (Unprocessed and sterilized)	Increased B. bifidum colony counts were observed in all honey-supplied groups (Group A-5 g, B-10 g, and C-15 g honey), with group B showing a significant rise in comparison with the control.	[76]
Bifidobacteria	Buckwheat honey	Buckwheat honey assists in propagating native Bifidobacteria and prohibits the growth of the pathogenic bacterium in the gut system.	[77]
Limosilactobacillus reuteri	Manuka honey (Drapac DrKiwi AMF5, AMF10, AMF15 and AMF20)	High sugar and oligosaccharides contributed to higher probiotic cell biomass of AMF20, but no obvious pattern in biomass with a decrease in AMF concentration.	[78]

Table 5.
Prebiotic effects of honey.

The result of a study done by Kaya and Yıldırım [82] revealed that honey extracts have an anticancer effect and inhibit the proliferation of human prostate cancer cells (PC-3).

Jaganathan and Mandal [83] revealed that honey had an antiproliferative effect in colon cancer cells.

Another study done by Swellam et al. [84] showed that bee honey has anticancer effects against bladder cancer in mice both *in vitro* and *in vivo*.

2.2.9.1 Potential anticancer mechanisms of honey

The anticancer properties of honey have been attributed to a number of processes (**Figure 1**) including:

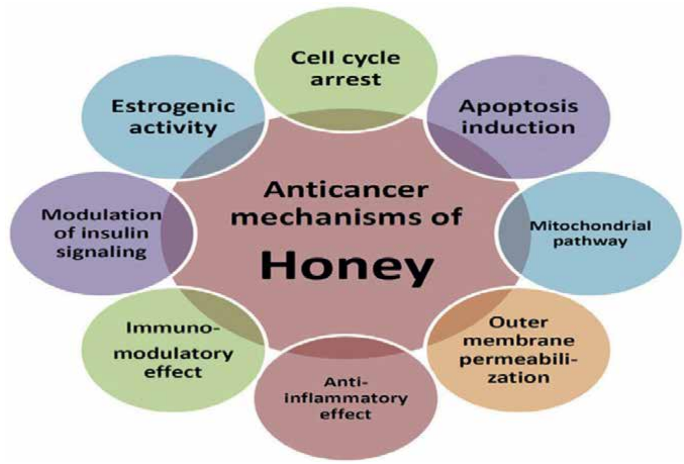

Figure 1.
Potential anticancer mechanisms of honey.

2.2.9.2 Antioxidant properties

Honey is rich in antioxidants, such as flavonoids and phenolic compounds, which help neutralize harmful free radicals. These free radicals contribute to oxidative stress, linked to cancer development [85].

2.2.9.3 Anti-inflammatory effects

Chronic inflammation is associated with cancer. Some components in honey have anti-inflammatory properties, potentially helping to reduce inflammation [86].

2.2.9.4 Anti-proliferative effects

Honey may inhibit the growth and proliferation of cancer cells. Studies have shown that certain types of honey can induce cell death (apoptosis) in cancer cells [87].

2.2.9.5 Modulation of oxidative stress

Honey can help regulate the balance between antioxidants and oxidants in the body. This balance is crucial for preventing oxidative damage, a factor in cancer development [88].

2.2.9.6 Immune system modulation

Some components in honey may stimulate the immune system, enhancing its ability to fight cancer cells [89].

3. Propolis

Propolis is a resinous substance produced by bees (*Apis mellifera*) from tree exudates, mainly resins of leaf buds mixed with beeswax and glandular bee secretions.

Honeybees use propolis to seal and protect their hives. Propolis aids in preserving the internal temperature of the hive at about 35°C [90, 91].

3.1 Chemical composition of propolis

Propolis has a very complicated chemical composition. A typical raw propolis sample is composed of 50% resin (a polyphenolic fraction made up of flavonoids and related phenolic acids), 30% bee wax (a wax and fatty acid mixture), 10% volatile essential and aromatic oils, 5% bee pollen (a protein and free amino acid mixture), and 5% other materials (organics and minerals). Propolis can contain.

other substances such as vitamins (vitamin B1, B2, B6, C, and E; nicotinic acid; and folic acid), minerals (calcium, magnesium, iron, copper, zinc, manganese, nickel, cobalt, vanadium, and strotium), sugars (fructofuranose, α-D, glucopyranose, β-glucopyranose), enzymes (adenosine triphosphatase, glucose 6-phosphatase, succinate dehydrogenase), aldehydes, ketones, alcohols, and steroids [92]. The chemical composition of propolis is highly variable and depends on several factors inluding: the season, location, local flora, kind of tree, and plant species chosen for collecting, as well as the climate [93].

3.2 Health benefits of propolis

Propolis has been used for centuries for its potential health benefits; it has demonstrated a wide range of therapeutic properties such as antimicrobial, antiaoxidant, anti-inflamatory activities (**Figure 2**), primarily due to its complex chemical composition, rich in flavonoids, phenolic acids, terpenoids, and other bioactive compounds (**Figure 3**) [94].

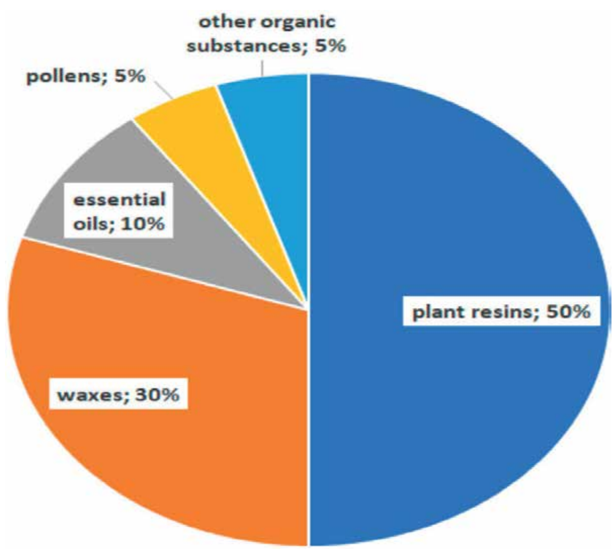

Figure 2.
Chemical composition of propolis.

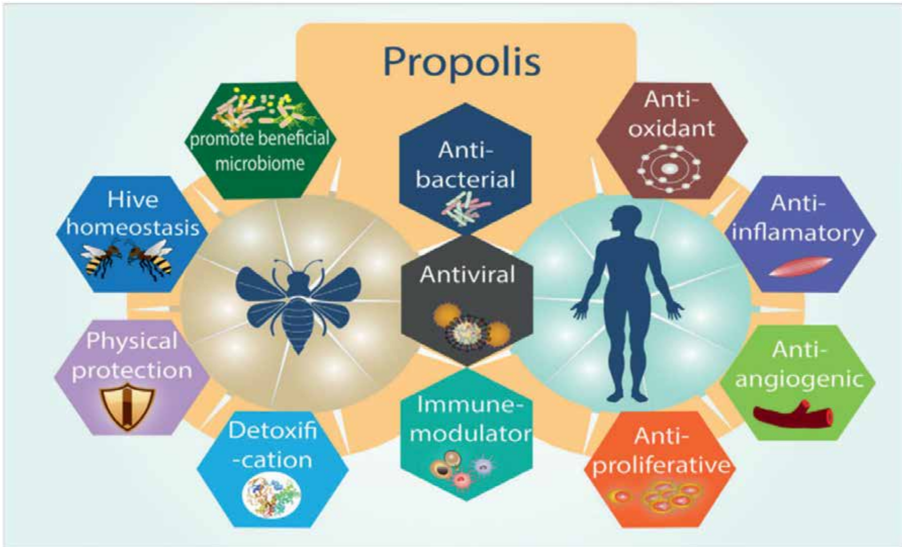

Figure 3.
The use of propolis in both human and bee health.

3.2.1 Antimicrobial effects of propolis

Propolis has demonstrated antimicrobial activity against a wide range of microorganisms, including both Gram-positive and Gram-negative bacteria, fungi, and viruses.

The result of a study done by Nichitoi et al. [95] revealed that the Romanian propolis extracts demonstrated antibacterial and antifungal activity against the following microbial strains: *Escherichia coli* (K12-MG1655), *Bacillus subtilis spizizenii nakamura* (ATCC 6633), and yeast, *Candida albicans* (ATCC 10,231).

Polish propolis has shown an inhibitory effects against different bacterial species, including both Gram positive and Gram negative such as *S. aureus, Staphylococcus epidermidis, Bacillus subtilis, Micrococcus luteus, Bacillus megaterium, Bacillus brevis, Enterococcus faecalis* and *E. coli, Enterobacter cloacae, K. pneumoniae, P. aeruginosa, Pseudomonas syringae, Proteus mirabilis,* and *Citrobacter freundii* 96 [96–98].

Propolis's ethanolic extract totally inhibited the growth of a number of bacteria, including the methicillin-resistant strains of *Staphylococcus aureus* and the reference strain of Mycobacterium TB (H37RV) [99].

Propolis extracts from different regions of Poland also showed an antifungal effect against several fungal species including: *Candida albicans, Candida tropicalis, Candida glabrata, Trichoderma viride, Aspergillus niger, Penicillium chrysogenum, S. cerevisiae, Aspergillus versicolor, Paecilomyces variotii, Penicillium funiculosum, Penicillium cyclopium, and Aureobasidium pullulans* [96, 97, 100].

Propolis has also been shown in the literature to have antiviral properties against a variety of viral strains, including the herpes simplex virus (HSV-1), the influenza virus, the HIV-1, and the SARS-CoV-2 [101, 102].

Refaat et al. [103] reported that propolis administered in a liposomal encapsulation neutralized SARS-CoV-2 *in vitro* just as well as remdesivir.

The antimicrobial activity of propolis is due to its complex chemical composition, which includes: *flavonoids*, phenolic acids, and *terpenoids*. The antimicrobial properties

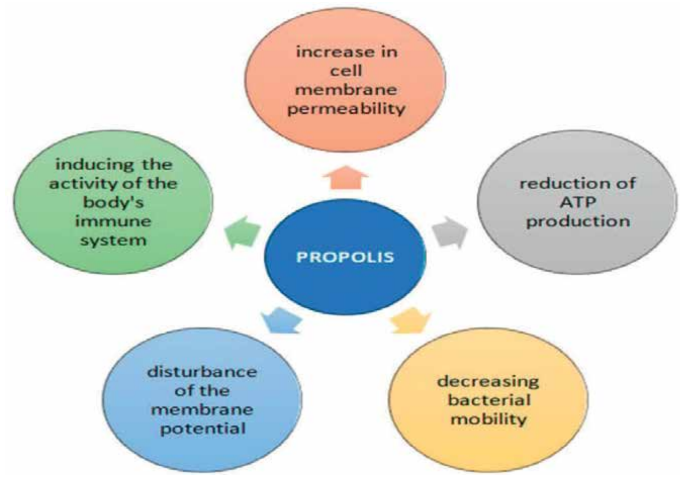

Figure 4.
Mechanisms of the antimicrobial activity of propolis.

of propolis have been attributed to a number of processes such as disruption of membrane potential, reduction of ATP production, increasing of cell membrane permeability, and induction of the activity of the body's immune system (**Figure 4**) [104].

3.2.2 Antioxidant activities of propolis

Propolis is rich in polyphenols, particularly phenolic acids and flavonoids, and possesses significant antioxidant activity, as demonstrated by several scientific studies.

Nichitoi et al. [95] reported that Romanian propolis extracts had antioxidant properties by scavenging the long-lived free radicals 2,2′-azino-bis (3-ethylbenzothiazoline-6 sulfonic acid) diammonium salt (ABTS) and 1-diphenyl-2-picryl-hydrazyl (DPPH).

In vitro assays have demonstrated that the production of superoxide and hydroxyl radicals was completely inhibited by water extract of 50 mg/mL of propolis [105].

A human study done by Diniz et al. [106] indicated that standardized propolis extract reduced biomarkers of oxidative stress cell damage in healthy humans, with increased antioxidant enzymatic capacity, especially of superoxide dismutase (SOD).

The result of a study conducted by Kocot et al. [107] revealed that Brazilian green propolis had strong antioxidant property refered to its content of 3,5-dicaffeoylquinic acid, 3,4,5-tricaffeoylquinic acid, artepillin C, and 4,5-dicaffeoylquinic acid.

It was demonstrated by Kumazawa et al. [108] that the antioxidant activity of propolis correlated with its content of total phenolics compound and flavonoids.

3.2.3 Anti-inflammatory effects

Propolis has been ued for centuries in traditional medicine for its potential health benifits. One of its most studied properties is its anti-inflammatory effect.

According to Machado et al. [109], the administration of propolis extracts (5 mg/kg) orally to mice for 6 days enhanced the anti-inflammatory cytokine production and decreased the pro-inflammatory cytokine inhibition in treated mice.

Xool-Tamayo et al. [110] demonstrated that Mayan propolis had strong anti-inflammatory properties and reduced the expression of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and increased the anti-inflammatory cytokines (IL-10 and IL-4).

Xu et al. [111] reported that Brazilian green propolis extract had an anti-inflammatory effect by decreasing inflammatory cytokine levels.

The anti-inflammatory properties of propolis are primarily attributed to its complex composition, rich in various bioactive compouds. The key factors contributing to its anti-inflammatory effects are: favonoids (caffeic acid phenethyl ester (CAPE), Chrysin and galangin), phenolic acid (caffeic acid, ferulic acid), and terpenoids, which conctribute to the anti iflammatory activity by modulating the immune reponse.

It has been demonstrated that quercetin, naringenin, and caffeic acid phenethyl ester (CAPE) derived from propolis inhibit prostaglandin and leukotriene synthesis in zymosan-induced acute peritoneal inflammation both *in vivo* and *ex vivo* [112].

Propolis terpenoids inhibit the production of inflammatory mediators including interleukin (IL)-1b and IL-10 and inducible nitric oxide synthase (iNOS) [113].

The specific anti-inflammatory effects of propolis can vary depending on its geographic origin, as the composition of propolis can differ based on the plant sources available to bees in different regions.

3.2.4 Propolis's anti-cancer properties

Propolis has long been utilized for its antibacterial and anti-inflammatory properties in traditional medicine. Its potential as an anti-cancer agent has been explored in scientific studies in recent years. Scientific researchers have investigated the potential anti-cancer effects of propolis on various types of cancer.

The cytotoxic efficacy of Brazilian green propolis is demonstrated against AGP-01 gastric cancer cells. P-coumaric acid and artepillin C are two of the main substances that contribute to these activities [114].

Doi et al. [115] demonstrated that propolis significantly reduced tumor size and aggressiveness of colorectal cancers induced by 1,2-dimethylhydrazine (DMH) injection.

It has also been demonstrated that ethanolic propolis extract induces DNA damage in colon cancer cell lines, leading to apoptotic cell death [97].

Propolis contains a diverse array of compounds, including flavonoids, phenolic acids, terpenoids, and vitamins, each with its own potential anticancer properties. The synergistic effects of these compounds are believed to enhance their anticancer efficacy.

Propolis may exert anticancer effects through several mechanisms:

Inhibition of cancer cell growth: Propolis has shown the ability to slow down or stop the growth of cancer cells [116].

Induction of apoptosis: This process, also known as programmed cell death, is essential for eliminating damaged or abnormal cells, including cancer cells. Research has shown that propolis is a mediator of both extrinsic and intrinsic apoptotic cancer cell death [117, 118].

Antioxidant properties: Propolis contains antioxidants that can help protect cells from damage caused by free radicals, which are linked to cancer development.

Anti-inflammatory effects: Chronic inflammation is associated with an increased risk of cancer. Propolis' anti-inflammatory properties may help reduce this risk [115].

Inhibition of angiogenesis: This process involves the formation of new blood vessels, which tumors need to grow. Propolis may interfere with angiogenesis [119, 120].

Boosting immune response: Propolis can stimulate the immune system, enhancing its ability to fight cancer cells.

3.2.5 Antidiabetic properties of propolis

The prevalence of type 2 diabetes has increased in developed countries. Discovering natural remedies is essential for the treatment and prevention of this illness [121].

Numerous studies have shown that propolis has antidiabitic properties and can reduce blood sugar levels in both human and animal models.

The result of a study done by Zakerkish et al. [122] revealed that the administration of 1000 mg of Iranian propolis daily for 3 months could increase insulin sensitivity in type 2 diabetes patients.

El-Sharkawy et al. [123] reported that propolis supplementation at a dose of 400 mg/day for 6 months decreased fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c) levels in type 2 diabetes patients.

Propolis extracts had shown antidiabetic properties in a model of type 1 diabetes in rats induced by streptozotocin [124].

According to a study done by Kang et al. [125], propolis may be a promising antidiabetic drug for the treatment of insulin-insensitive diabetes.

The key components responsible for the antidiabetic effects of propolis are phenolic compounds including: caffeic acid phenethyl ester (CAPE), chrysin, quercetin, and flavonoids.

3.2.5.1 Mechanisms of action of antidiabetic effects of propolis

Propolis exerts its anticancer effect through several mechanisms including:

Antioxidant activity: Propolis neutralizes harmful free radicals, reducing oxidative stress associated with diabetes complications [126].

Anti-inflammatory effects: By inhibiting inflammatory markers, propolis helps to manage the chronic inflammation often linked to diabetes [121].

Insulin sensitization: Some components in propolis can enhance the body's response to insulin, improving glucose uptake by cells [122].

Glucose metabolism regulation: Propolis may influence enzymes involved in glucose metabolism, helping to maintain blood sugar levels.

Pancreatic protection: Some studies suggest that propolis might protect pancreatic beta cells, which produce insulin [127].

3.2.6 Oral health

Propolis is widely used in oral health. Its anticaries, antimicrobial, and anti-inflamatory properties make it an ideal product in helping to maintain oral health. It has been shown to be effective in treating caries, supragingval plaque, gingivitis, and periodontitis. Propolis is also effective as a cavity, intracanal, root canal, and dental pulp medicament (**Figure 5**).

Tanasiewicz et al. [128] demonstrated the therapeutic efficacy of toothpaste and gel containing 3% ethanolic extract of propolis in a group of patients at higher risk of developing gingivitis from dental plaque.

Propolis has been demonstrated to have antibacterial properties against germs that cause periodontal disease [129–131].

It has been reported that propolis reduces halitosis [132, 133]. Propolis has been shown to have bactericidal effect against several bacteria that cause dental caries *in vitro* and in animal models [134, 135].

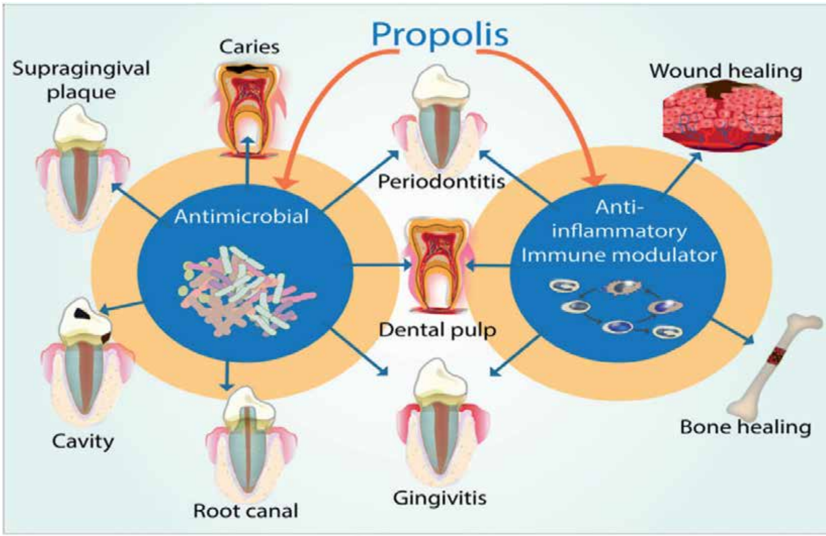

Figure 5.
The potential uses of propolis in dentistry.

The result of a study carried out by Ikeno et al. [136] revealed that propolis had inhibited the growth of *Streptococcus sobrinus, S. mutans*, and *Streptococcus cricetus*.

Human clinical trials have demonstrated the efficacy of propolis in lowering and/or suppressing the growth of *S. mutans* and other caries-causing bacteria [137].

It has been demonstrated by Kuo et al. [138] that caffeic acid phenethyl ester (CAPE), a component of propolis, has strong anticancer properties and cause apoptosis in TW2.6 human oral cancer cells by lowering the levels of proteins linked to carcinogenesis.

The oral health beneficial properties of propolis has been attributed to its phenolics and flavonoid contents, in addition to other fatty acids such as oleic, palmitic, linoleic, and stearic acid [139].

4. Conclusion

The possible health benefits of honey and propolis were the main focus of the current chapter. These bee products are incredibly rich in bioactive compounds like enzymes, phenolic acid, terpenes, flavonoids, and polyphenols, which have biological roles in improving health and preventing certain diseases. Propolis and honey both have important nutritional and functional qualities, making them effective in different ways. In addition, their accessibility and absence of serious side effects render them a promising natural healthcare choice that may help control and treat several chronic disorders. Therefore, these bee products have the potential to become powerful apitherapeutic agents. However, certain safety measures must be implemented in cases of allergies associated with honey and propolis, as well as in determining the appropriate dosage for ingestion. Hence, more research is required to better understand the mechanisms of action of these bee products' pharmacological activity as well as the suitable amounts that have the potential to provide positive health effects.

Conflict of interest

The author confirms that this chapter's content has no conflict of interest.

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Chapter 6

Nature's Remedies: Unlocking the Therapeutic Potential of Honey and Propolis

Shah Alam, Muhammad Asif Aziz, Muhammad Waqar and Aafaq Rasheed

Abstract

Honeybees are important for pollination and produce products including honey, propolis, royal jelly, pollen, beeswax, and bee venom. Honey is a sweet liquid substance prepared by honeybees, which collects nectar and pollen from different flowers, and propolis is a glue substance collected by bees from different plant parts. In this review aimed to provide comprehensive studies on honey and propolis composition, bioactive compounds contained. as well as the bioactive components that are present. The purpose of this paper is to provide an overview of the biological potential of honey and propolis for human health. This includes their capacity to suppress bacteria, improve wound healing, and impact specific disorders. Furthermore, it is important to emphasize the benefits of honey and propolis for various health conditions, including allergies, oral problems, dermatological issues, and gastrointestinal disorders, as well as their antimicrobial, anti-inflammatory, immunomodulatory, antioxidant, anti-tumor, and cardiovascular properties. However, we have not fully elucidated the mechanisms of action of propolis and honey on all the previously listed activities. To gain a fuller understanding of its mechanics and the potential uses of this phenomenon, additional research is required.

Keywords: honeybee, honey, propolis, biological activity, health benefits

1. Introduction

The honeybee is a social insect, a mainly important pollinator of different plants, including crops, vegetables, and fruit trees [1, 2], additionally, produce honey and many other products such as propolis, beeswax, royal jelly, pollen, and bee venom [3], recently, utilization of bee products by humans for nutritional and medicinal purpose all around world [4].

Recent research is increasingly focused on the health benefits and pharmacological properties of bee products, driving the development of nutraceuticals and functional foods derived from these sources. Functional foods are designed to enhance physiological or psychological health beyond basic nutrition, offering significant health maintenance, improved well-being, and reduced risk of chronic diseases. These foods contain bioactive compounds that can provide therapeutic effects, making them a promising area in preventive healthcare and nutrition science. The efficacies of bee products in this domain are particularly notable, fostering innovation in health-promoting dietary options [5, 6].

Honey is a natural sweet liquid substance with different colors, produced from the nectar and pollen of flowers [7], and not only used as food but also as a symbol of prosperity and health. Honey has been used extensively in traditional medicine because of its nutritional value and therapeutic qualities, in addition to its culinary purposes. Today's scientists and health enthusiasts are still fascinated by honey because of its complicated composition and endless health benefits. Honey has unparalleled versatility, being used for anything from relieving sore throats to moisturizing skin naturally. Its reputation as a material that promotes health is partly due to the natural antioxidants, vitamins, and minerals that it contains [8].

Propolis is a sticky substance collected by bees from the buds and exudates of trees, known as bee glue [9], and utilized by bees to seal the creaks of hives and humans have used it for traditional medicine because of its potent therapeutic properties demonstrating its natural antimicrobial properties [10]. Propolis contains various important compounds, including phenolic acids, terpenes, and flavonoids, which contribute to biological activities. Also, its antibacterial, antifungal, antiviral, and anti-inflammatory properties make it valuable as a natural remedy [11]. This review aims to provide a comprehensive overview of the biological activities and health benefits of honey and propolis, highlighting their significance in promoting human health and preventing diseases.

2. Composition of honey and propolis

Honey is composed of various compounds, but on average, it contains approximately 82.4 carbohydrates, 38.2% fructose, 31.3% glucose, and 17.2% water. Additionally, it has 7.1% maltose and 1.5% sucrose, with higher sugars like trisaccharides making up another 1.5%. The ash content, which includes minerals, is about 0.2%, while acids such as gluconic acid constitute roughly 0.57%. Honey also contains around 0.5% amino acids, proteins, and enzymes. Phenolic acids and flavonoids, which are antioxidants, are present in trace amounts, along with vitamins like the B complex and vitamin C [12, 13]. Pollen grains and other aromatic compounds also appear in trace amounts. These components collectively contribute to honey's unique taste, texture, and health benefits [14].

Propolis composition depends on its botanical source, and it consists of 50% resins and balsams, which include plant exudates such as flavonoids and phenolic acids, 30% wax, while 10% essential oils, pollen is present at approximately 5%, providing proteins and amino acids [15]. The remaining 5% comprises various organic and inorganic compounds, including vitamins (e.g., B1, B2, B6, C, and E) and minerals like magnesium, calcium, and potassium [16]. Propolis also contains 5–10% of other substances, such as terpenes, benzoic acid, and caffeic acid, which is contribute to its antimicrobial, anti-inflammatory, and antioxidant properties, making propolis valuable in traditional and modern medicine [17].

3. Bioactive compounds of honey and propolis

Both honey and propolis contain highly rich bioactive compounds, as shown in **Table 1**, many essential compounds are found in honey and propolis which are

Product	Bioactive compounds	Compounds	Properties	References
Honey	Flavonoids	Apigenin, quercetin, kaempferol, and galangin	Antioxidant and anti-inflammatory	[18]
	Phenolic acids	Caffeic acid, p-coumaric acid, and ferulic acid	Antioxidant activity	[19]
	Enzymes	Glucose oxidase	Antibacterial effects, and catalase	[20, 21]
	Organic acids	Gluconic acid	Honey acidic pH and antimicrobial properties	[22]
	Amino acids	Proline	Protein synthesis and metabolism	[23]
	Vitamins	B vitamins (B1, B2, and B6), vitamin C, and folic acid	metabolic functions	[24]
	Minerals	Potassium, calcium, magnesium, and zinc	Overall health	[25]
Propolis	Flavonoids	Pinocembrin, galangin, and chrysin	Antioxidant and antimicrobial effects	[26]
	Phenolic compounds	Caffeic acid phenethyl ester (CAPE) and p-coumaric acid	Anti-inflammatory and immunomodulatory properties	[26]
	Terpenes	Beta-caryophyllene and other sesquiterpenes	Anti-inflammatory and antimicrobial activities	[5]
	Aromatic acids	Benzoic acid and cinnamic acid	Antimicrobial properties	[5]
	Essential oils	Eucalyptol and limonene	Antiseptic and anti-inflammatory effects	[27]
	Amino acids	Arginine and proline	Tissue repair and immune function	[28]
	Vitamins	B complex (B1, B2, B6), vitamin C, and vitamin E	Immune support and antioxidant defense	[29]

Table 1.
The bioactive compounds of honey and propolis and further details of different function properties.

important for the biological activity of life and are the main part of our food chain including polyphenols and vitamins, and also hydrogenated compounds are occurred as corresponding function origin [30]. Honey and propolis contain Flavonoids (pinocembrin, galangin, and chrysin) with strong antioxidant and antimicrobial properties along with phenolic compounds (caffeic acid phenethyl ester (CAPE) and p-coumaric acid), which have anti-inflammatory and immunomodulatory properties [26, 31].

4. Biological activities of honey and propolis

In health benefits, honey and propolis exhibit a wide range of biological activities, including antimicrobial, anti-inflammatory, antioxidant, and immunomodulatory properties [32], as shown in **Figure 1**. Briefly, honey is broad-spectrum antimicrobial

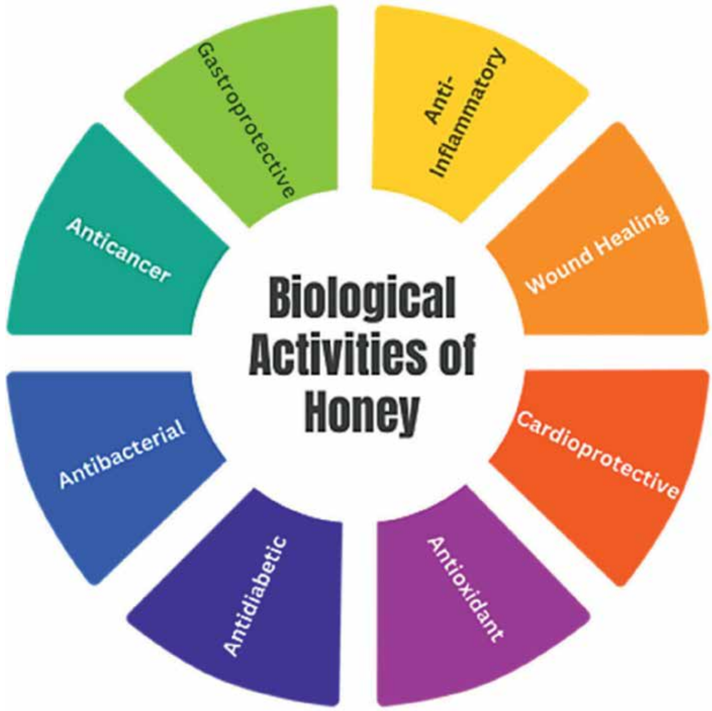

Figure 1.
Various types of biological activities of honey.

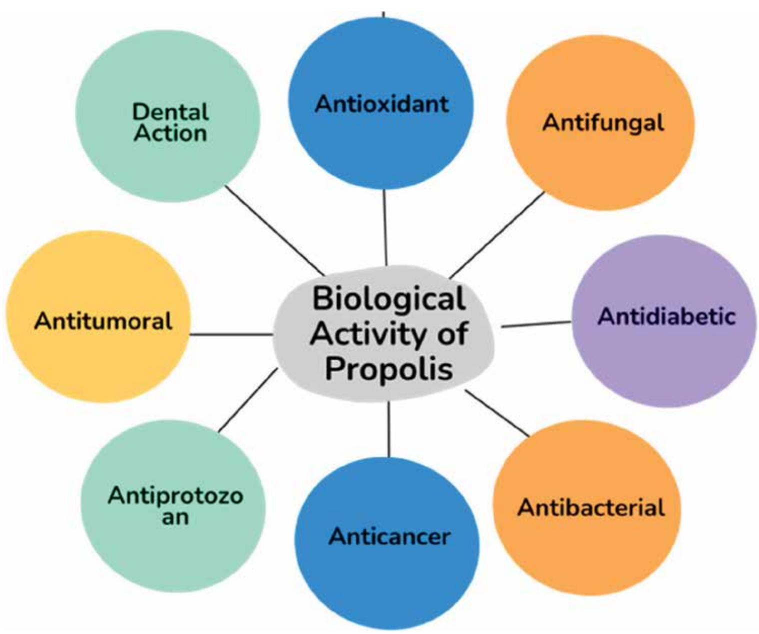

Figure 2.
Various types of biological activities of propolis.

properties against bacteria, fungus, etc., because of high acidity, low water activity, and percentage of hydrogen peroxide, which contribute as key factors of antimicrobial efficacy [33]. On the other hand, propolis important compounds including flavonoids and phenolic acids which is the high rate of antimicrobial properties, inhibit the microbial growth by disrupting the microbes' cell wall [34]. Additionally, both honey and propolis have the properties of antioxidant, which neutralize the free radicals and protect the cell from oxidative damage, and compounds like phenolic in propolis and enzymes (catalase and glucose oxidase) in honey have significantly high antioxidant properties [35]. Honey reduces inflammation by modifying the immune response and inhibiting proinflammatory cytokines and propolis containing flavonoids and phenolic compounds, suppressing the inflammatory pathway and reducing oxidative stress [36, 37]. Moreover, both are immunomodulatory properties because they are beneficial in controlling disorders related to the immune by enhancing the immune system by stimulating cell activities and producing antibodies, further reducing the immune response (**Figure 2**) [38].

5. Different health benefits of honey

5.1 Wound management

For centuries, people have used honey to heal boils, wounds, burns, skin conditions, and bug bites [39]. Scientific research has proven its efficacy in promoting wound healing and acting as an antibacterial agent. Honey stimulates latent plasminogen within the wound matrix, dynamically expresses the proteolytic enzyme plasmin, removes dead tissue from the wound bed, and aids in both blood clot retraction and fibrin breakdown. By encouraging tissue regeneration and lowering the danger of infection, this enzymatic activity improves wound healing [40]. Scientific research now supports honey's long-standing use as an effective natural treatment for a variety of skin conditions [41].

Clinical research supports honey's improved performance over current and conventional wound dressings, highlighting its effectiveness, specificity, and sensitivity in wound treatment [42]. According to Natarajan et al. [43, 44], honey has the capacity to promote wound-healing qualities in wounds that are resistant to antibiotics or antiseptics, including wounds infected with bacteria that are resistant to antibiotics, such as methicillin-resistant *Staphylococcus aureus* (MRSA). Honey speeds up the development of a healthy granulated wound bed and aids in autolytic debridement [42].

Anaerobic bacteria like *Peptostreptococcus* and *Bacteroides* spp. typically cause malodour, a prevalent feature of serious wounds [44]. As a result of the breakdown of serum and tissue proteins, these bacteria create sulfur, amines, and ammonia, which are malodorous chemicals. Honey masks this stench by offering a significant quantity of glucose, which bacteria preferentially metabolize over amino acids to produce lactic acids rather than foul-smelling chemicals (**Figure 3**) [45].

Quick wound healing, efficient wound cleaning, infection removal, tissue regeneration, decreased inflammation, and improved patient comfort from less tissue adhesion during dressing changes are among the therapeutic benefits of honey application [46]. Honey is a useful natural wound treatment because it has antibacterial qualities and the ability to encourage the production of granulation tissue and

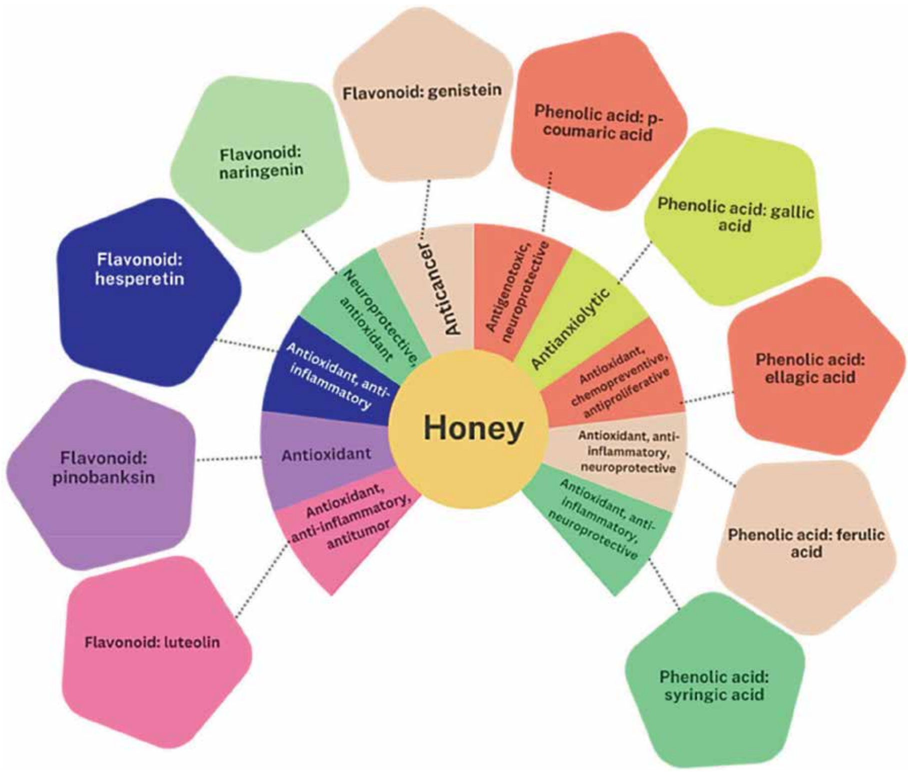

Figure 3.
Shown different honey activities in health benefits.

autolytic debridement. These therapeutic advantages highlight honey's advantages over conventional wound care techniques, particularly when it comes to managing malodorous wounds and treating infections involving microorganisms resistant to antibiotics [47].

6. Diabetic, foot ulcers, and pediatric care

Honey has the potential to treat diabetic foot ulcers (DFUs) and provide pediatric care. Despite its antibacterial properties and ability to soothe mucous membranes, pediatric care frequently uses honey as a natural remedy for cough and sore throat [47]. In addition to its therapeutic effects, honey's anti-inflammatory and antioxidant qualities help children with upper respiratory tract infections recuperate and have less discomfort [47]. Due to its special combination of methylglyoxal, hydrogen peroxide, and a high sugar content that inhibits microbial growth through an osmotic impact, honey has shown promise. Clinical research has shown that by promoting tissue regeneration, lowering inflammation, and acting as an infection-prevention barrier, honey can hasten the healing of wounds in diabetic foot ulcers. Researchers have linked its use to lower amputation rates and higher wound healing rates [48].

Moreover, honey's capacity to stimulate autolytic debridement, an important step in wound healing, aids in necrotic tissue clearance. Additionally, it keeps the site wet, which is necessary for the growth of new tissue [49]. Due to its affordability and availability, honey is particularly beneficial when used in DFU control, making it a viable choice in healthcare settings with resources both abundant and scarce [48].

7. Gastrointestinal disorders and oral health

Honey's natural healing properties have led to its long-standing use in treating gastrointestinal disorders. Prebiotics, such as oligosaccharides, help digestion and gut health. Antimicrobials can help treat infections like *Helicobacter pylori*, which is a common cause of peptic ulcers. Anti-inflammatory can soothe the digestive tract, easing the symptoms of gastritis and colitis. Antioxidants help fight free radicals, protecting the gut lining from oxidative stress [49]. Clinical studies have shown that honey is effective in reducing the severity of symptoms in conditions like diarrhea and irritable bowel syndrome (IBS). However, it is critical to use it as a complementary treatment in addition to traditional medical treatments [50].

Honey is beneficial for oral health because of its inherent antimicrobial properties, and they can prevent oral caries and gum disease by suppressing the growth of oral infections like *Porphyromonas gingivalis* and *Streptococcus mutans* [51]. Manuka honey has demonstrated a strong antibacterial effect against oral germs. Honey's anti-inflammatory qualities can lessen the signs and symptoms of periodontal disease and gingivitis [52]. However, honey has a high concentration of methylglyoxal and hydrogen peroxide, both of which help with tissue repair; it can also speed up the healing process in surgical and oral wounds [51]. By reducing unpleasant breath and supporting general oral hygiene, its enzymatic activity aids in the maintenance of a balanced oral flora. Despite having sweets, honey's special makeup and antibacterial properties reduce the chance of tooth decay, making it a natural supplement to oral health [52].

7.1 Pharyngitis and coughs

Honey is a natural substitute for synthetic cough syrups, as well as a well-known treatment for pharyngitis and coughs. Its sticky viscosity soothes and coats the lining of the throat, reducing inflammation and discomfort [53]. Honey's anti-inflammatory properties lessen pharyngitis-related throat swelling and pain. Honey also has a demulcent effect, which helps to relieve dry coughs and increase salivation. Research indicates that honey can be just as successful as some over-the-counter cough remedies in lessening the frequency and intensity of children's nightly coughs, thus enhancing the quality of their sleep [54].

7.2 Gastroenteritis

Regardless of its high sugar content, low pH, and hydrogen peroxide levels, which can stop the growth of bacteria that cause gastroenteritis, honey has antibacterial qualities [55]. According to studies, honey may calm the lining of the stomach, lowering inflammation and accelerating healing. Its prebiotic effects can enhance gut flora, aiding in the restoration of intestinal health. Furthermore, the antioxidants in honey reduce oxidative stress in the digestive system, which may alleviate gastroenteritis symptoms [56].

7.3 Constipation diarrhea

Honey has a natural laxative effect because of its fructose component, which draws water into the gut to soften stools and encourage bowel movements. Its prebiotic qualities improve intestinal regularity and function by promoting the growth of beneficial gut flora [55]. Honey's gentle osmotic action helps ease constipation without causing unpleasant side effects. Furthermore, the calming qualities of honey help lessen the discomfort brought on by firm stools and irregular bowel motions [56]. Although honey has antibacterial properties that target the germs that cause diarrhea, it can help manage the disease [57]. Its high sugar content gives you energy and aids in electrolyte balance, both of which are vital during diarrhea bouts. The anti-inflammatory qualities of honey can lessen intestinal irritation and hasten healing. Additionally, honey's prebiotic properties promote gut flora balance and aid in the recovery of regular bowel movements [58].

7.4 Liver diseases

The antioxidants in honey help shield liver cells from the oxidative damage that comes from free radicals [58]. Studies have demonstrated its ability to support detoxification procedures and enhance liver function. In cases of chronic liver illness, the anti-inflammatory properties of honey can lessen liver fibrosis and inflammation [59]. Furthermore, the hepatoprotective qualities of honey promote the general health of the liver by assisting in the regeneration of liver tissue [59].

7.5 Pancreatic diseases

Researchers have discovered that honey protects pancreatic cells, possibly due to its anti-inflammatory and antioxidant qualities [60]. It might aid in lowering the pancreas' oxidative stress and inflammation, two major contributors to pancreatic disorders. The natural sugars in honey can offer a more reliable energy source, lessening the pancreas' metabolic workload. Moreover, its ability to control insulin secretion and sensitivity may be advantageous for controlling pancreatic function [60].

7.6 Metabolic health

While honey has a lower glycemic index than processed carbohydrates, it can better regulate blood glucose levels, which is good for metabolic health. It can lessen oxidative stress and inflammation linked to metabolic diseases [61]. Furthermore, honey aids in lipid metabolism, potentially enhancing cholesterol profiles and reducing the risk of metabolic syndrome. Given the direct connection between gut health and overall metabolic function, its prebiotic properties bolster gut health [62].

7.7 Cardiovascular health

The antioxidant qualities of honey can lessen oxidative stress, one of the main causes of cardiovascular disease [63]. Honey's anti-inflammatory properties can reduce blood vessel inflammation, thereby enhancing vascular health. Research demonstrates that honey enhances lipid profiles by increasing HDL cholesterol and reducing LDL and total cholesterol levels. Furthermore, honey's polyphenols promote endothelial function, which lowers the risk of atherosclerosis and helps to maintain healthy blood pressure [64].

8. Propolis has health benefits

8.1 Gastrointestinal disorders

The resinous material called propolis, which bees create, has several advantages for digestive health. Propolis's anti-inflammatory properties contribute to the reduction of inflammation resulting from illnesses like inflammatory bowel disorders (IBD) and gastritis [65]. Studies have shown that propolis can inhibit the growth of Helicobacter pylori, a bacterium associated with stomach cancer and peptic ulcers [66]. Propolis also promotes mucosal regeneration and lowers oxidative stress, which improves the healing of stomach ulcers. Its antibacterial properties also include gut microbiota protection and intestinal environmental homeostasis. Propolis's flavonoids and phenolic components also help to reduce diarrheal symptoms and enhance digestive health in general (**Figure 4**) [67].

Furthermore, parasitic infection typically arises from direct contact with contaminated material. Common symptoms of gastrointestinal parasite infection encompass stomach pain, diarrhea, bloating, and nausea. Studies have documented the biological efficacies of propolis, including its anticancer, antioxidant, and anti-inflammatory actions. Several studies have demonstrated the clinical application of propolis in treating viral infections. Researchers conducted a study to investigate the effects of propolis ethanolic extract on the proliferation and adhesion of Giardia duodenalis trophozoites in a laboratory setting [68]. Propolis demonstrated the ability to impede the growth and attachment of trophozoites. Furthermore, it helped to separate these parasitic organisms. A clinical investigation has reported the effectiveness of propolis against giardiasis. This study administered propolis to both children and adults with giardiasis, resulting in a cure rate ranging from 52 to 60%. The standard medicine group experienced a cure rate of 40%. Further experimental investigation revealed that propolis possesses antihistaminergic, anti-inflammatory, antiacid, and anti-H. pylori properties, making it suitable for treating stomach ulcers [69].

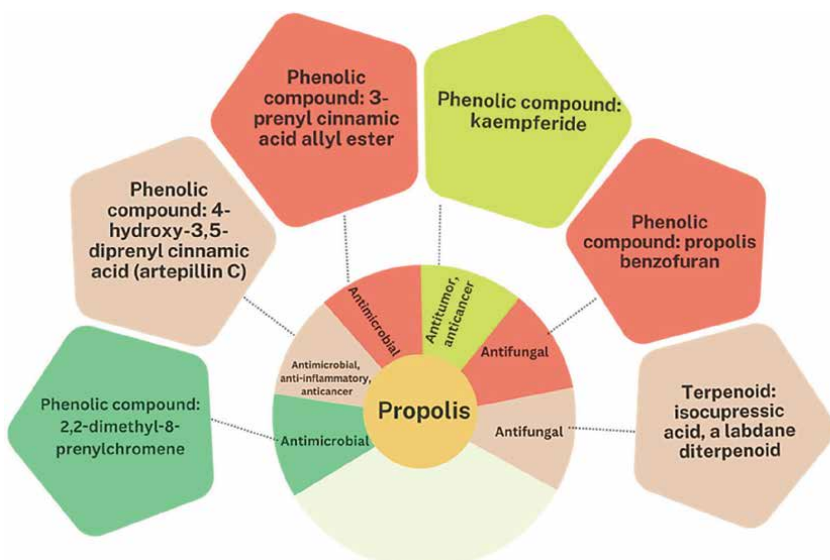

Figure 4.
Shown different propolis activities in health benefits.

8.2 Gynecological care

The most common types of vaginitis are bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC). A notable feature of vaginal infections is the decrease in the presence of Lactobacillus spp. in the vagina. The infection is characterized by an abnormal growth of vaginal pathogens, such as yeast-like fungi, and an elevated vaginal pH level. Diabetic individuals have an increased susceptibility to vaginal infections caused by the fungus *Candida albicans*. A research investigation examining the efficacy of a 5% aqueous solution of propolis revealed its positive impact on vaginal well-being [70]. Propolis possesses both antibacterial and antimycotic properties, in addition to providing prompt symptom alleviation due to its anesthetic qualities. Individuals who cannot take antibiotics because they are also taking other medications should consider using propolis as a suitable substitute for treating recurrent vulvovaginal candidiasis (RVVC). Propolis has shown excellent effects when compared to the standard antifungal nystatin, indicating its efficacy. Propolis extract solution (PES) exhibits low cytotoxicity toward human cells, making it a potential therapeutic option for chronic vaginitis. Furthermore, PES has antifungal properties and can be used as an antibiofilm agent to treat recurrent vulvovaginal candidiasis (RVVC). It effectively combats *Candida albicans*' biofilm formation and counteracts resistance to antifungal drugs [71].

8.3 Cancer therapy

One study suggests that propolis holds promising potential in treating human breast cancer. Propolis induces apoptosis in human breast cancer cells, resulting in an anticancer effect. Propolis has preferential toxicity against tumor cells while demonstrating no toxicity toward normal cells. Therefore, it is a highly favorable option for the management of breast cancer [72]. A recent study examined the impact of an ethanolic extract derived from Algerian propolis on the formation of melanoma tumors. The study found that galangin, a flavonoid that is often found in propolis, effectively caused apoptosis and stopped the growth of melanoma cells in a lab setting [73]. Studies have demonstrated that Turkish propolis effectively eliminates lung cancer cells in people by intensifying pressure on the endoplasmic reticulum, triggering apoptosis and caspase activity, and reducing the mitochondrial membrane's potential. Research has shown that propolis has a significant inhibitory effect on the proliferation of cancer cells (**Figure 5**) [74].

8.4 Treatment for skin problems

Dermatological formulations, including lotions and ointments, extensively use propolis. This substance's ability to combat allergies, reduce inflammation, inhibit the growth of microorganisms, and stimulate collagen production is the foundation for its use in skincare products. A recent study conducted a comparative analysis between propolis and the standard medicine silver sulfadiazine. The results demonstrated that propolis effectively reduced free radical activity (FRA) in the wound beds, thereby facilitating the healing process. A clinical trial on acne sufferers found an ethanolic extract of propolis to be highly effective in treating acne vulgaris [75, 76]. Propolis improves collagen metabolism in the wound during the healing phase by increasing tissue collagen content [77]. A study found that propolis is effective as a substitute treatment for wound healing, especially in cases of human diabetic foot ulcers (DFU) (**Figure 6**) [78].

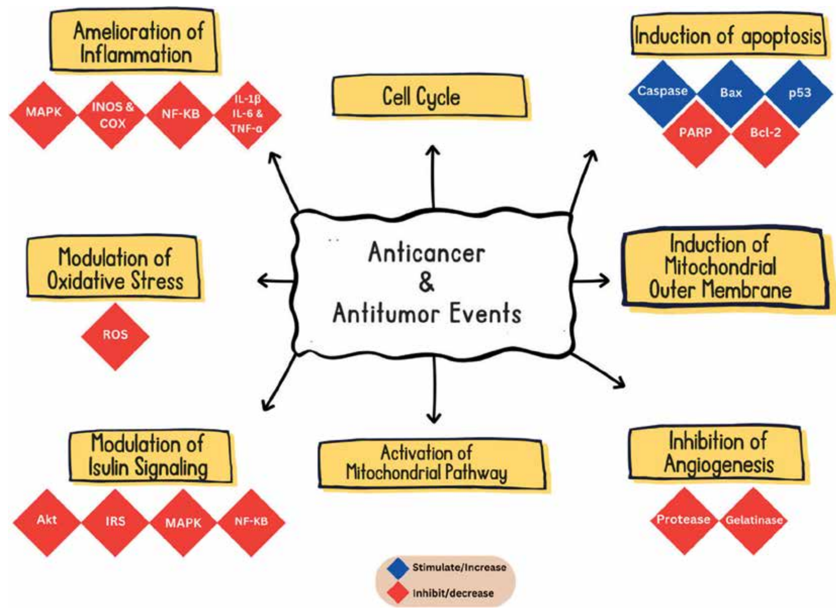

Figure 5.
The molecular pathways that underlie honey products' antitumor and anticancer properties.

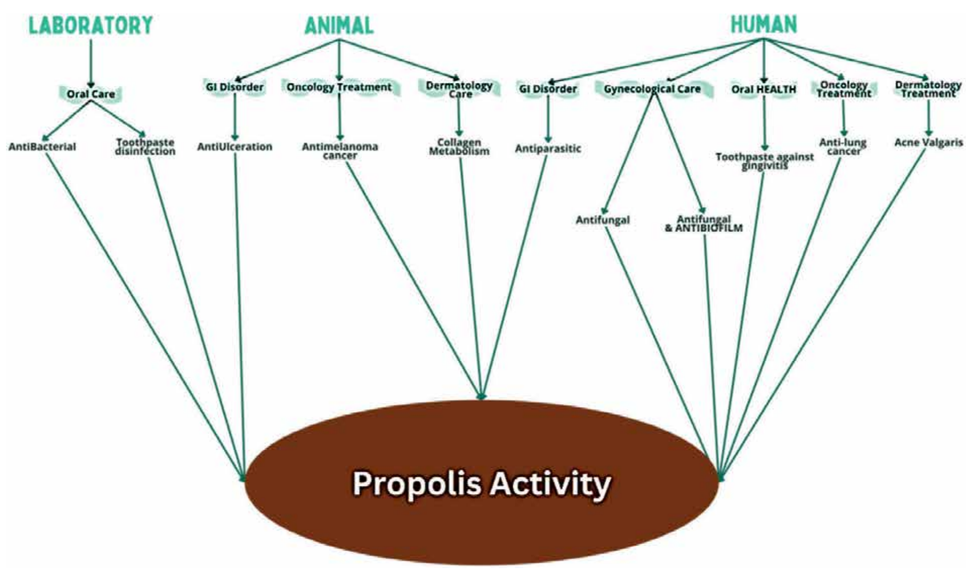

Figure 6.
Shown different propolis activity according to health benefits.

9. Conclusion and recommendation

In the current review, the prospective benefits of honey, and propolis, were the primary focus of attention. For example, flavonoids, phenolic acid, phenolic compounds, terpenes, and enzymes are all examples of active components that are abundant in these items. These components have biological roles that include preventing certain diseases and promoting good health. There are unique efficacies associated with honey, and propolis each of which possesses substantial nutritional characteristics and functional values. It is therefore possible to transform these bee products into highly effective apitherapeutic medicines. However, if allergens are associated with bee products, we need to take certain considerations into account when determining the appropriate dosage for consumption. it is important to emphasize the benefits of honey and propolis for various health conditions, including allergies, oral problems, dermatological issues, and gastrointestinal disorders, as well as their antimicrobial, anti-inflammatory, immunomodulatory, antioxidant, anti-tumor, and cardiovascular properties. Therefore, it is crucial to do further research to identify the key mechanisms behind the pharmacological effects of porpolis and to determine the ideal dosages for achieving the intended health benefits.

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Chapter 7

Utilization of Apiary Product for Boosting Human Health

Subhalaxmi Roy, Bijoy Kumar Mishra, Manasa Shastri Pattnaik and Sushree Suparna Mahapatra

Abstract

Honeybees are vital pollinators that contribute significantly to global agriculture and biodiversity. Their role extends beyond pollination to the production of various valuable products, including honey, beeswax, propolis, royal jelly, and bee venom. Honey, a natural sweetener, and source of bioactive compounds, is renowned for its antimicrobial, antioxidant, and anti-inflammatory properties. It has been used historically for its medicinal benefits and continues to be studied for its potential in treating wounds and digestive issues. Beeswax, a natural wax produced by honeybees, finds applications in cosmetics, pharmaceuticals, and candles owing to its emollient and barrier properties. Propolis, a resinous substance collected by bees from tree buds and used to seal their hives, exhibits antimicrobial and antiviral effects making it a valuable component in traditional medicine and modern health supplements. Royal jelly, a protein-rich secretion used to nourish queen bees, is consumed as a dietary supplement for its purported health benefits, including enhanced immunity and improved skin health. Bee venom, though less commonly utilized, is gaining attention for its potential in treating arthritis and other inflammatory conditions due to its complex biochemical profile. This abstract underscores the significance of honeybees beyond their ecological roles emphasizing the diverse applications and therapeutic potentials of their products, which continue to be subjects of scientific investigation and commercial interest.

Keywords: *Apis*, bee wax, biproducts, honey, propolis

1. Introduction

A vast collection of gregarious insects, bees are members of the Apidae family which also includes stingless bees, honey or domestic bees, and other specialized species. Specifically, the two most well-known domesticated species utilized in contemporary beekeeping are honeybees (western *Apis mellifera* which is mostly found in Europe, America, Africa, and Asia, and eastern *Apis cerana* which is endemic to Southeast Asia). Beekeeping integrates forestry, social forestry, and agricultural aid operations, making it a notable, environmentally friendly and sustainable activity [1].

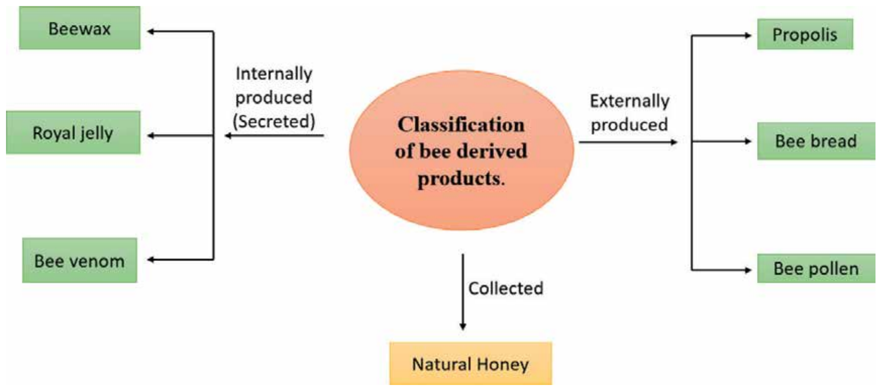

Figure 1.
Bee-derived products.

Together with bringing in money and jobs, it maintains the ecological, economic, and nutritional balance. There is a significant chance that India will become a big exporter of honey and take the lead in beekeeping. In India, beekeeping has been practiced for many centuries. Thousands of people might potentially find direct employment in beekeeping, particularly among hill dwellers, tribe members, jobless young, and farmers. Beekeeping is an industry with low skill and investment requirements. For the sake of the nation's economic growth and well-being, this sector needs to be sustainable. Products from bees may often be divided into two categories according to how they are harvested: those that are generated outwardly and those that are created inside and subsequently secreted (**Figure 1**) [2].

Bees use nectar and honeydew to make honey, a naturally occurring substance. Honey is a supersaturated carbohydrate solution with a variety of uses and qualities. Bees gather propolis, often known as "bee glue," a resinous material, from the buds of trees, shrubs, and other plants [3]. While honey was used in traditional medicine to treat wounds and relieve pain, propolis and honey were both utilized in antiquity to embalm bodies. Pollen loads are used to carry the pollen that bees harvest from plants to the hive. Pollen must be moistened with nectar or honey in order for loads to develop. Bee bread is created when pollen for winter supplies is placed within honeycomb cells and undergoes lactic fermentation. Bacteriostatic and bactericidal substances are bee pollen and bread. A material called beeswax is generated by glands in the abdomen of bees [4]. Honeycomb-derived wax is an important component found in cosmetics and pharmaceuticals. Apitoxin is another name for the venom secreted by honeybees. Its complex blend of several peptides, including the mast cell degranulating peptide, is employed in numerous fields for its medicinal and cosmetic qualities.

The utilization of bee products for medicinal purposes is known as *apitherapy* [3]. It includes many different forms of medical care that make use of materials made by bees.

2. Key components of apitherapy

i. *Honey*—Bees collect nectar, a mixture of sugars, and other trace ingredients, from flowers and use it to produce concentrated honey. It is a thick, delicious liquid that is made by honeybees (**Table 1**) [6].

Constituents	Percentage (%)
Levulose	41.0
Dextrose	35.0
Sucrose	1.9
Dextrins	1.5
Minerals	2.0
Water	17.0
Undetermined (Enzymes, vitamins, pigments, etc.)	16.0

Source: [5].

Table 1.
Composition of fully ripened honey.

ii. *Bee wax*—The substance used by bees to construct their nests is called beeswax. It is created by immature honeybees, who release it as a liquid from certain wax glands. When worker bees reach the age of 14–18 days, they begin to exude wax. When honey is extracted, the cappings are collected and used to make bee wax. Old, useless combs and combs damaged during the extraction of honey are used to make wax. Wax of the highest grade is extracted from cappings with a greater recovery percentage. In India, a significant amount of wax comes from *Apis dorsata* combs [7].

iii. *Bee venom*—Electric shock is a method used in the commercial extraction of bee venom. Copper wires are subjected to a 12-volt electric current. After being shocked and agitated, the bees attack a thin nylon fabric beneath the copper wires to discharge their venom. The glass plate with the venom on it is positioned beneath the nylon sheet. When the venom dries, it is scraped from the glass plate [8, 9].

iv. *Propolis*—Bees collect propolis from the resinous tree exudates. Propolis is used in bee colonies to seal gaps and crevices and stick frames, however, it contaminates comb wax. It can be extracted by scraping the frames. Its contents are as follows: 55% resins and balsams, 10% scented oils, 5% pollen, and 10% ethanol. Consequently, it possesses potent antiviral, antifungal, anti-inflammatory, and antibacterial effects [10].

3. Uses of apitherapy

a. Heal wounds: Honey can be topically applied to treat wounds, including both open cuts and burns because of its antibacterial, anti-inflammatory, and pain-relieving properties [3].

b. Ease arthritis pain: Rheumatoid arthritis pain has been managed with bee venom treatment (BVT) since ancient Greece because of its anti-inflammatory and analgesic properties. It reduces swelling, stiffness, and pain in people suffering from arthritis.

c. Reduce gingivitis and plaque: When added to mouthwash, propolis can help prevent gingivitis and plaque while also acting as a natural defense against other oral health issues. It may possibly aid in the prevention and healing of canker sores.

d. Serve as a multivitamin: Numerous vitamins and elements included in propolis and royal jelly can be used as multivitamins to enhance general health. Propolis is offered as an extract and as an oral supplement. Soft gel and pill forms are available for royal jelly.

e. Regulate thyroid functions and treat neurological conditions: Many illnesses, including Alzheimer's, multiple sclerosis, and Parkinson's disease, are treated using bee venom. It has also been discovered to regulate thyroid activity in female hyperthyroidism patients.

4. Honey: Biological activities and medicinal properties

One of the most treasured and cherished natural items given to humanity since ancient times is honey. In addition to being used as a dietary supplement, honey is also utilized in traditional medicine to treat a variety of clinical ailments, from cancer to wound healing. As a nutritional supplement, honey has been traditionally used to cure a variety of conditions, including worm infestation, piles, eczema, hepatitis, bronchial asthma, throat infections, TB, thirst, hiccups, weariness, dizziness, and hepatitis. Antioxidant, antibacterial, anti-inflammatory, antiproliferative, anticancer, and antimetastatic properties have all been linked to the components of honey. Honey may be used to treat and manage wounds, diabetes mellitus, cancer, and asthma, as well as neurological, gastrointestinal, and cardiovascular conditions. Honey's phytochemical, anti-inflammatory, antibacterial, and antioxidant qualities make it a promising medicinal for treating various ailments. It has two primary bioactive molecules: flavonoids and polyphenols, both of which function as antioxidants [11]. Current research indicates that honey may be protective and beneficial for the management of a number of illnesses, such as diabetes mellitus, disorders of the neurological, gastrointestinal, respiratory, and cardiovascular systems. Honey has a wide range of antioxidants, which means that it could potentially help treat cancer [12, 13].

4.1 Antioxidant activity

Honey's capacity to exhibit antioxidant properties is correlated with its brightness; thus, darker honey has a higher antioxidant value. Research has demonstrated that the primary factor responsible for honey's antioxidant activity is its phenolic content, as phenolic levels are related to the honey's radical absorbance activity values [14]. Studies have shown that the antioxidant activity is related to the combination of a wide range of active compounds present in honey; hence, honey can function as a dietary antioxidant.

4.2 Antimicrobial activity

The primary contributors to honey's antimicrobial properties are the enzyme-mediated glucose oxidation reaction and certain physical aspects. Other elements that may also exhibit the antimicrobial activity of honey include low protein content, high carbon-to-nitrogen ratio, low pH/acidic environment, high osmotic pressure, low redox potential owing to high reducing sugar content, a viscosity that restricts dissolved oxygen, and additional chemical agents [15, 16]. Honey's low water content, hydrogen peroxide, glucose oxidase, and other characteristics prevent yeast and bacteria from growing.

4.3 Apoptotic activity

Cancer cells are characterized by inadequate apoptotic turnover and uncontrolled cellular proliferation. Inadequate programmed cell death and unchecked cell division are hallmarks of cancerous cells. Inducers of apoptosis are chemicals used in cancer therapy [17]. Through the depolarization of the mitochondrial membrane, honey induces apoptosis in a variety of cancerous cells. Owing to its high phenolic content, honey has been shown to promote caspase 3 activation and poly (ADP-ribose) polymerase (PARP) cleavage in human colon cancer cell lines. When honey is orally consumed, it raises the expression of the pro-apoptotic protein Bax and decreases the expression of the anti-apoptotic protein Bcl-2 in the tumor tissue of Wistar rats. In those tissues, oral administration of honey results in increased expression of the pro-apoptotic protein Bax and decreased expression of the anti-apoptotic protein Bcl-2 [18]. When manuka honey is injected intravenously, it triggers the death of cancer cell lines by activating caspase 9, which in turn triggers caspase 3, the executor protein. Manuka honey induces apoptosis, which also involves DNA fragmentation, loss of Bcl-2 expression, and PARP activation. Honey possesses natural anticancer capabilities due to its apoptotic qualities [19].

4.4 Anti-inflammatory and immunomodulatory activities

Various studies reflect that honey lowers the inflammatory response in cell cultures, animal models, and human clinical trials. The phenolic content attributes to honey's anti-inflammatory properties [20]. It impedes recovery in damaged tissues and chronic inflammation.

4.5 Wound healing agent

The cascades of tissue healing start when honey stimulates leukocytes to produce cytokines. It also stimulates the immune system's reaction to infection. It is also suggested that honey stimulates other aspects of the immune response, such as the activity of phagocytes and the proliferation of B- and T-lymphocytes [21]. Antibodies are generated in response to honey. Honey may be used to treat and manage acute wounds as well as mild to severe surface burns and partial thickness burns, according to a wealth of research. Honey is effective in treating wounds and leg ulcers (**Figure 2**).

4.6 Honey and diabetes

Honey being a complex structure and a natural sweet product, it has a lower glycaemic index and energy value than sugar. When compared to dextran, honey can dramatically lower plasma glucose levels in diabetic individuals [22]. In those with normal or hyperlipidaemic blood, it also lowers homocysteine, C-reactive protein, and blood lipid levels. Honey also helps in healing diabetic wounds. Mostly, the wounds are slower in healing and sometimes lead to complications [23]. Since honey is readily available, inexpensive, and natural, it may be utilized in these therapies. When honey is diluted with water or other bodily fluids, it produces hypochlorite anions and hydroxyl

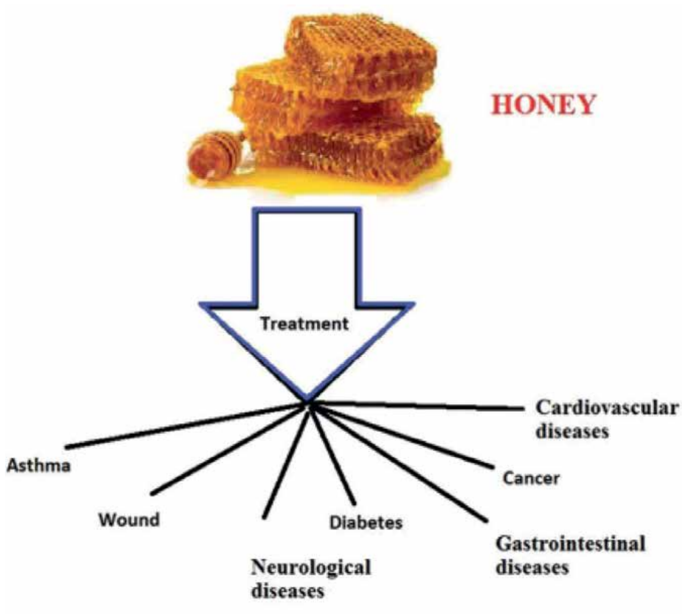

Figure 2.
Benefits of honey for human health.

radicals at the site of the wound [24]. The antioxidants found in honey work in a wound in two different ways: first, they combat microbes and lessen infection; second, they lessen inflammation and reactive oxygen species which aid in the healing process.

4.7 Anticancer effects of honey

Honey has anticancer properties via interfering with many cell-signaling pathways, such as those that induce apoptosis, are antimutagenic, antiproliferative, and anti-inflammatory. The immunological responses are altered by honey [4]. It has been demonstrated to suppress cell proliferation, induce apoptosis, alter cell cycle progression, and cause mitochondrial membrane depolarization in a variety of cancer types, including skin cancer (melanoma), adenocarcinoma epithelial cells, cervical cancer cells, endometrial cancer cells, liver cancer cells, colon rectal cancer cells, prostate cancer cells, renal cell carcinoma, bladder cancer cells, human non-small cell lung cancer, bone cancer cells (osteosarcoma), leukemia, and mouth cancer cells (oral squamous cell carcinoma) [25]. Moreover, in animal models, honey may be able to suppress several tumor types, such as bladder cancer, melanoma, colon carcinoma, hepatic cancer, breast cancer, and carcinoma. To further our understanding of honey's protective effects against cancer, additional research is necessary. Furthermore, in animal models of several cancers, honey may be able to suppress the growth of breast cancer, carcinoma, melanoma, colon carcinoma, hepatic cancer, and bladder cancer [26].

4.8 Anti-inflammatory effect of honey to treat asthma

Honey is a traditional folk remedy for fever, coughing, and inflammation. Honey's capacity to mitigate asthma-related symptoms or function as a prophylactic to avert the onset of asthma was demonstrated. Oral honey ingestion was used in animal models to treat bronchial asthma and chronic bronchitis [12]. It has also been found that goblet cell hyperplasia that secretes mucus may be successfully removed by honey inhalation. To learn more about the processes by which honey lessens asthma symptoms, more research on the benefits of honey is necessary [27].

4.9 Effective to treat cardiovascular diseases

Flavonoids, polyphenolics, vitamin C, and monophenolics—antioxidants found in honey—may be linked to a lower incidence of heart attacks [28]. Flavonoids have protective properties against coronary heart disease, including antioxidant, antithrombotic, anti-ischemic, and vasorelaxant effects. These methods improve coronary vasodilatation, inhibit blood platelet clotting, and stop low-density lipoproteins from oxidizing, all of which reduce the incidence of coronary heart diseases [29].

4.10 Honey for neurological disorders

Honey reduces the oxidative content of the central nervous system and has anxiolytic, depressive, anticonvulsant, and antinociceptive properties [3]. Honey's polyphenolic components neutralize biological ROS, which causes aging, neurotoxicity, and the pathological buildup of misfolded proteins, such as amyloid beta. Through excitotoxins, such as quinolinic acid and kainic acid, and neurotoxins, such as 5-S-cysteinyl-dopamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, the polyphenol components of honey counteract oxidative stress [30]. The neuroinflammation caused by immunogenic neurotoxins or ischemic damage that is created in microglia is reduced by raw honey and honey polyphenol. The primary effect of honey polyphenols is to reduce neuroinflammation in the hippocampus, a region of the brain related to memory [31].

4.11 Honey and gastrointestinal diseases

Several gastrointestinal tract conditions, such as dyspepsia, periodontal disease, and other dental disorders, have been linked to honey as a potential therapy. Additionally, it has been thought of as a part of oral rehydration treatment [32, 33]. A clinical trial demonstrating honey's therapeutic effects in treating infants and children hospitalized for gastroenteritis revealed a significantly shorter duration of diarrhea in patients receiving honey treatment. Honey may also be useful as a component of oral rehydration therapy [31, 34].

5. Bee venom: A potential therapeutant

- The synergy between the bee venom components may provide a route for treating several disorders that are now the focus of modern therapy. Bee venom contains a variety of biological properties that are important for looking for potential uses and therapeutic benefits [35].

- Additionally, it exhibits biological actions such as anti-secretory, anti-apoptotic, and antimicrobial properties [36].

- Melittin, a peptide that is more abundant in bee venom, has the capacity to interact with so many types of cancer cells. For example, melittin can stop the development of human ovarian cancer cells by expressing more death receptors (DR3, DR4, and DR6) and deactivating the STAT3 signal transducers and activators, which causes the cells to undergo apoptosis [37].

- Furthermore, melittin can cause stomach cancer cells to undergo apoptosis via the mitochondria pathways, which increases the production of free radicals. By demonstrating downregulation of the phosphoinositide 3-kinase (PI3K), protein kinase B (AKT), mammalian target of Rapamycin (mTOR), and 5′ adenosine monophosphate-activated protein kinase (MAPK) signaling pathways, melittin can also cause caspase-dependent death in melanoma cells [38].

- Inhibiting the production of vascular endothelial growth factor (VEGF) and the protein hypoxia-inducible factor-1α (HIF-1α) in human cervical cancer cells, melittin demonstrates antiangiogenic effects [39].

- The concentrations of melittin, PLA2, and apamin are often correlated with the effectiveness of antioxidant activity. These chemicals may have antioxidant properties because they can boost superoxidase dismutase activity and suppress the lipid peroxidation process. Apart from these, BV has a number of antioxidant-rich compounds. For example, vitellogenin has antioxidant action in mammalian cells through a direct shielding mechanism that protects the cell from oxidative stress and reactive oxygen species [40].

- Melittin, an antimicrobial peptide, is primarily responsible for its antibacterial action. Its primary method of antibacterial activity involves breaking down cellular membranes. In addition, several constituents exhibit antimicrobial properties. For example, vitellogenin functions as an antimicrobial peptide by causing harm to bacteria's cell membranes. Compounds, such as secapin, have proved antibacterial and antifungal effects [41].

- At least four of bee venom's primary constituents have anti-inflammatory qualities. Melittin's ability to reduce inflammation was evaluated in relation to liver inflammation, neuroinflammation, atherosclerosis, acne vulgaris, and amyotrophic lateral sclerosis [42].

- The neuroinflammation resulting from the persistent activation of microglia and glia cells is associated with neurodegenerative diseases. Among the most significant neurological conditions are amyotrophic lateral sclerosis, Parkinson's disease (PD), and Alzheimer's disease (AD) [43]. To increase the effectiveness of some medications against neurodegenerative illnesses, several BV constituents, including apamin and PLA2, have been investigated as anti-neuroinflammation agents.

- Melittin and PLA2 are the primary components of bee venom that possess anticancer activity. The most appealing method of slowing the development of tumor cells is to induce apoptosis in cancerous cells [43]. Melittin has the most cytotoxic action against malignant cells.

- Given the biological activities of bee venom and the mechanisms in which it can operate as a mediator, therapeutic applications for BV are possible. Though BV has historically been recognized for its anti-inflammatory, anti-apoptotic, anti-fibrosis, and anti-arthrosclerosis properties, additional methods have lately come to light, such as their impact on circulatory and neurological disorders [39]. Because of its biological characteristics, bee venom is a complex blend of chemicals that has been utilized in traditional medicine and thoroughly studied. Proteins and peptides make up most of its content, whereas other molecules are also present, albeit in trace amounts. Melittin is the most prevalent and researched component of bee venom among its constituents, with PLA2—an enzyme—and histamine being the primary allergenic substances of bee venom. Because BV has beneficial effects on some disorders, including musculoskeletal and neurological ailments, its primary uses would be for medicinal purposes [44].

6. Effects of bee products on the skin

6.1 Honey

Honey's antibacterial properties, which come from hydrogen peroxide, high osmotic pressure, high acidity, and the presence of flavonoids, lysozyme, and phenolic acids, are among the reasons honey is utilized in medicine. It reduces the formation of germs and fungus on the skin's surface, therefore preventing their growth [28]. Honey has been used in treatments for pityriasis, tinea, seborrhoea, dandruff, diaper dermatitis, psoriasis, hemorrhoids, and anal fissure [45]. It is very useful as a bandage for wounds and burns. Honey is a bee product that is utilized in skin care products because of its high nutritional content and healing qualities. Its nutritive and restorative properties are caused by a high carbohydrate content, fruit acids, and trace elements. Due to its hygroscopic qualities, honey can absorb metabolites and help the skin become more detoxified. This causes the suppleness, color, and tension of the skin to all improve as well as the wrinkles to disappear. When honey is sugared, it can be used as a peeling agent. This facilitates the easier diffusion of several beneficial nutrients, such as vitamins, via the skin. Honey's fatty acids and mineral salts help to treat xerosis [46]. Honey is a fantastic cosmetic for rough, cracked hands, chapped lips, and frostbites. It also relieves skin irritations. Because of its high simple sugar concentration, essential oil content, and bio-element content, honey has toning, soothing, and conditioning properties that make it a popular ingredient in balms and bath treatments. Honey's flavonoid content makes it an effective sun protection ingredient by reducing skin sensitivity [20].

Propolis—Propolis is a common medical ingredient. It is used in dermatology to treat fungal, streptococcal, and staphylococcal infections because of its antiseptic qualities. Propolis is used to treat a variety of conditions, including thrush, cheilosis, intertrigo, hidradenitis, and purulent skin infections [3]. It has antibacterial and anti-inflammatory properties, but it also lessens pain and accelerates cicatrization. Chrysin, which is a flavonoid, provides an analgesic effect. It promotes the accumulation of glycosaminoglycan, which is necessary for tissue development, granulation, and wound healing. Propolis works better as an apitherapy agent than silver sulfadiazine.

Because collagen type I is essential for keratinocyte migration and reepithelization, its accumulation in the injury matrix promotes the healing process [47].

Additionally, propolis accelerated the process of wellness by increasing the deposition of collagen type III. Reepithelization may be aided by the topical apitherapeutic product propolis ointment, which is used to treat burns. At concentrations of 5–20%, propolis possesses protective and regenerative properties as well as the ability to repair itself. Because it tightens the dermal tissue and shields it from harmful microorganisms, it can be utilized to create treatments that treat bed sores. Propolis has anti-UV properties as well since it contains ferulic acid, coumaric acid, and caffeic acid, which allow it to absorb UV rays [48]. Propolis has antioxidative, anti-inflammatory, and regenerative qualities that make it a useful addition to sun blockers (creams, lotions, sticks, and lipsticks) [9]. Propolis offers antiaging qualities and reduces wrinkles. Antioxidants like flavonoids and phenolic substances, which counteract the damaging effects of free radicals on the skin, are crucial in this situation. Bee glue hydrates, soothes, and lightens the skin. It also lessens indications of weariness.

6.2 Royal jelly

Numerous biological activities, such as antibacterial, anti-inflammatory, immunomodulatory, anti-allergic, antioxidant, toning, moisturizing, and antiaging qualities, influence how royal jelly affects skin [49]. At 20% concentration, royal jelly, a product of bees, has substantial antibacterial action within skin tissue. Royal jelly reduces inflammation of the tongue, throat, and oral cavity as well as periodontal disorders because of its anti-inflammatory properties. Because of its capacity to prevent the synthesis of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1), it has anti-inflammatory properties and promotes wound healing [50]. Royal jelly cures hemorrhoids and varicose veins in the lower limbs while also protecting blood vessels. It is used to treat lichen, ulcers, burns, bed sores, shingles, wound epithelialization, healing, and antibacterial activity in all situations where the regeneration of the epidermis is anticipated. Royal jelly promotes wound reepithelization [51]. Royal jelly works well as a wound therapy agent and is a popular ingredient in skin care products. Royal jelly is a component of products that normalize sebum production and are used to treat seborrheic skin, acne-prone skin, skin lesions, and minor wounds. Royal jelly enhances tissue regeneration by boosting metabolism in the tissues. Balms, creams, and lotions include ingredients with nutritional, medicinal, and restorative qualities. The characteristics of the fatty acids that are separated from royal jelly are linked to its immunomodulatory and anti-allergenic capabilities. Both 3-10-dihydroxydecanoic acid and 10 HDA regulate the immune system and reduce the amounts of IL-2 and IL-10 [52]. Atopic dermatitis, hypertrophy, hyperkeratosis, and epidermis and dermis inflammation were treated with royal jelly's anti-inflammatory and immunomodulatory properties. This may have been accomplished by combining TNF-specific low adjustment of IFN-gamma-specific production with high adjustment of nitric-oxide synthase (NOS) expression. Royal jelly contains 10-hydroxy-trans-2-decenoic acid, which induces the fibroblasts to produce collagen by means of transforming growth factor. Consequently, royal jelly has an impact on the synthesis of collagen, a crucial component that maintains the skin. Due to its high moisture content, royal jelly influences the stratum corneum's hydration by keeping water in it. Consequently, the skin becomes more supple and more hydrated [53].

6.3 Bee pollen

Bee pollen can have an impact on the skin as well. Bee pollen, a strong antifungal, antibacterial, antiviral, anti-inflammatory, and immunostimulant, also helps with the granulation process involved in burn healing. Pollen ethanol extract exhibits antifungal properties against Candida albicans and antibacterial properties against *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa.* The antifungal and antibacterial properties of bee pollen are attributed to flavonoids and phenolic acids. The anti-inflammatory properties of bee pollen stem from its ability to decrease the activity of two key enzymes involved in the genesis of inflammation: lipoxygenase and cyclooxygenase II. The anti-inflammatory properties of phytosterols, fatty acids, and phenolic acids are to blame [54]. Furthermore, kaempferol inhibits elastase and hyaluronidase which reduces the inflammatory response. The topical administration of ointment containing pollen extract can heal burns and repair injured tissues. Bee pollen is an active component of cosmetics, often found in 0.5–5% concentrations [55, 56]. Its high flavonoid concentration accounts for its notable effects on skin tissue. Because of their existence, bee pollen's high vitamin C concentration helps to seal and strengthen capillaries, which is why bee pollen is utilized in lotions for coupe rose skin [57]. Bee pollen influences mitotic division, increases regeneration, and has an impact on cell metabolism. A common ingredient in shampoos and conditioners is bee pollen. Oily hair products employ its sebum-balancing action, which lowers sebum output. Because bee pollen contains phospholipids, zinc, and methionine, it restores normalcy to the action of sebaceous glands [55]. Additionally, the sulfur-containing amino acids in bee pollen, particularly cysteine, strengthen the hair shaft. In addition, bee pollen is used in anti-dandruff shampoos because it inhibits the formation of fungi and reduces scalp irritation while maintaining its moisturizing, conditioning, and regenerative qualities.

7. Conclusion

A wealth of vitamins, minerals, antioxidants, and other advantageous substances may be found in apiary products like honey, pollen, and propolis. These items can improve general nutrition and assist several body processes. Because of its antibacterial and anti-inflammatory qualities, honey and propolis can be regularly consumed to boost immunity, perhaps lowering the risk of common illnesses and enhancing immune response in general. Prebiotics, found in raw honey, help intestinal health by encouraging the growth of healthy bacteria. It also helps in detoxification and maintaining the general gut. Strong antioxidant and anti-inflammatory qualities found in many apiculture products can help minimize oxidative stress and inflammation in the body which may lessen the risk of chronic illnesses including cancer and cardiovascular disease. Because of its inherent antibacterial qualities, which help hasten the healing process and lower the risk of infection in small wounds and burns, honey has long been used for wound care. By progressively desensitizing the body to local pollen, local honey may help reduce seasonal allergies; however, further research is required to completely appreciate its usefulness in this area. Although apiary products have numerous health advantages, they should be used cautiously in some groups, such as small children or those who are allergic to bee products (since honey can cause botulism). Using products from apiaries helps to preserve bee numbers and encourage biodiversity via sustainable beekeeping methods. Food security and ecology both gain from this. Further investigation into the health advantages of apiculture products may result in new uses and a deeper comprehension of the subject, which might improve its implementation in therapeutic and preventative health approaches. Supplementary health advantages can be obtained by including apiary products in a well-rounded diet and lifestyle, but they should not take the place of traditional medical care or a balanced diet.

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Health Benefits of Honey and Propolis - Scientific Evidence and Medicinal Uses comprehensively explores the richness and potential of honey and propolis. The book covers honey's microbial diversity and antimicrobial activity, its effects on burn treatment, the ecological and botanical aspects related to the safe production of medicinal honey, and the benefits of Brazilian honey with geographical indication, highlighting its unique floral origin. Additionally, it discusses the therapeutic properties of honey, propolis, and other bee products for promoting human health. This work provides an essential source of knowledge written by experts, supporting scientific investigations, in-depth discussions, and the advancement of research on using these valuable natural products.

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