Journal of Materials and Environmental Science
ISSN : 2028-2508
e-ISSN : 2737-890X
CODEN : JMESCN

J. Mater. Environ. Sci., 2024, Volume 15, Issue 2, Page 301-324

http://www.jmaterenvironsci.com

Biochemical Properties and Therapeutic Activities of Honey: A Review

Salama Y. [1,2]*, Chennaoui M. [2]

[1]*Department of Biology, Polydisciplinary Faculty of Khouribga, University Sultan Moulay Slimane, Khouribga, Morocco*
[2]*Laboratory of Life Science and Earth (SVT), Regional Centers for the Professions of Education and Training (CRMEF), El Jadida, Morocco*
**Corresponding author, Email address: salama.youssef@gmail.com*

Received *04 Feb 2024,*
Revised *20 Feb 2024,*
Accepted *29 Feb 2024*

Keywords:
- ✓ *Honey;*
- ✓ *Modern Medicine;*
- ✓ *Antibacterial;*
- ✓ *Biochemical properties;*
- ✓ *Healing properties*

Citation*: Salama Y. & Chennaoui M. (2024) Biochemical Properties and Therapeutic Activities of Honey: A Review, J. Mater. Environ. Sci., 15(2), 301-324*

Abstract: Honey has a rich history as a healing agent and a beloved food. It is produced by honey bees from the nectar and secretions of plants, serving as their primary food source. Additionally, honey is utilized to nourish bees during the winter season. Throughout the ages, the consumption of honey has served dual purposes - as a delectable sustenance and as a natural remedy. Esteemed by healers of diverse ancient civilizations, this golden nectar has long been recommended as a treatment for a myriad of maladies. Dating back to antiquity, honey has been revered for its remarkable ability to expedite the mending of wounds, a virtue repeatedly substantiated through compelling evidence. Honey, with its illustrious past as a potent remedy and a cherished culinary delight, holds a place of great significance. Crafted meticulously by diligent honey bees, this golden elixir emerges from the nectar and secretions of plants, acting as their vital sustenance. Moreover, honey is employed to nourish bees during the winter season. Across the centuries, the consumption of honey has served two-fold objectives - as a delightful sustenance and as an organic remedy. Revered by healers hailing from various ancient civilizations, this precious liquid gold has been hailed as a cure for a wide range of ailments. Tracing its roots in ancient times, honey has been highly regarded for its extraordinary power to accelerate the healing of wounds, a virtue consistently supported by compelling evidence.

1. Introduction

The traditional medicinal system, a time-honored practice, involves the utilization of natural products such as seaweeds, plants, and plant derivatives to address various ailments caused by microorganisms. Although antibiotics have largely replaced traditional medicines in recent times, the resurgence of antibiotic resistance has prompted a return to these age-old remedies. The abundance of bioactive compounds found in natural products provides an effective solution against microbial diseases, while minimizing the risk of adverse effects. In line with this, our current study focuses on harnessing the healing potential of honey-a precious component of the traditional medicinal system that has been employed by people from all walks of life, from antiquity to the present day (Nweze *et al.*, 2020; Zafar *et al.*, 2020). With the documented bacterial resistance to traditional antibacterial agents in both human and veterinary medicine, it has become imperative to explore alternatives to commercial pharmaceuticals. Honey harbors potent antibacterial compounds that demonstrate remarkable effectiveness in inhibiting or eradicating a wide range of bacteria (Brudzynski, 2020; Green *et al.*, 2022). Consequently, honey has emerged as a promising candidate for substituting pharmaceutical wound healing products in different regions across the globe.

For the past few decades, researchers have been exploring naturally occurring antimicrobial agents as substitutes for existing pharmaceutical antimicrobials and biocides. This trend has gained momentum due to the rising problem of bacterial resistance to conventional treatments (Yilmaz and Aygin, 2020). Interestingly, these natural alternatives have demonstrated comparable or even superior efficacy in numerous studies, testing their effectiveness against various bacterial species, including multidrug-resistant ones (Combarros-Fuertes *et al.*, 2020).

While many products have demonstrated antimicrobial activity, honey stands out as an exceptionally effective antimicrobial agent. The official recognition of honey's antibacterial properties dates back to 1892 when Dutch Scientist Van Ketel discovered its ability to "sterilize" wounds (Almasaudi, 2021). In the field of human medicine, honey has shown remarkable effectiveness in the treatment of burns, skin ulcers, and various other types of lesions (Aly *et al.*, 2021; da Rosa *et al.*, 2022). A veterinary laboratory study conducted on rabbits revealed that the application of raw honey on open surgical wounds resulted in faster healing compared to the control group. Both veterinary and human medical reviews have also highlighted the healing properties of honey in treating wounds, both in humans and animals (Martinotti *et al.*, 2019; McArdle *et al.*, 2023). Throughout history, humans have recognized the nutritional and medicinal value of honey and various plants.

It also has a role in religion and symbolism. Flavors of honey vary based on the nectar source, and various types and grades of honey are available. It is also used in various medicinal traditions to treat ailments. The health effects of honey have long been noted by humans. The nutritional and medicinal qualities of honey have been documented in Vedic, Greek, Roman, Christian, Islamic and other texts. Physicians of ancient times, such as Aristotle (384–322 BC), Aristoxenus (320 BC) Hippocrates, Porphyry, Cornelius Celsus (early first century AD) and Dioscorides (c. 50 AD), and Arab physicians have referred to the healing qualities of honey. Honey contains powerful antioxidants with antiseptic and antibacterial properties.

Honey has also been used by humans since pre-Ancient Egyptian times to treat a variety of ailments through topical application, but only recently have the antiseptic and antibacterial properties of honey been chemically explained. Ancient Egyptian physicians used honey in medicinal compounds 5,000 years ago and the ancient Greeks believed that honey could promote virility and longevity. Honey has been used in Traditional Chinese Medicine for thousands of years and is still important today. Ancient Russian manuscripts attributed great importance to honey as a medicine.

In ancient Islamic literature, honey bees have been extolled for their "intelligence, industry and creativity". The Quran mentions it as medicine to cure human illness. It says "And thy Lord taught the Bee to build its cells in the hills, on trees, and in (men's) habitations; Then to eat of all the produce (of the earth), and find with skill the spacious paths of its lord: there issues from within their bodies a drink of varying colors, wherein is healing for men: verily in this is a sign for those who give thought." [Al-Quran 16:68-69]. Prophet Mohammad himself spoke of the healing power of honey as a cure for all mental illness. In the later part of the 12th century, a Muslim physician described the healing powers of honey to disperse body fluids, soothing the bowels, curing dropsy, checking facial twitches, improving appetite, preventing the breakdown of muscles and preserving them. In 1000 BC, it was a Saxon herbal treatment for wounds, sties and amputated limbs. In 1446, it was used as a therapeutic drug, in combination with alum, to treat ulcers. And in 1623, it was used as an antiseptic and a mouthwash. The use of honey as a therapeutic cure in various combinations was popularized in

Medieval Europe, particularly in England, Germany, Finland, and Ireland. It was also extended to Ghana, the USA, Nepal, Nigeria, Russia, and Brazil. It was a gourmet medicine during the Second Balkan War in 1913, healing the wounds of soldiers. Honey from several species of stingless bees was consumed to cure flu, to cure the cataract, glaucoma and cough. In modern times, an increasing body of literature supports the effectiveness of honey in promoting various aspects of health, particularly as a novel approach to wound management. For centuries, specific honeys have been selected to treat certain ailments, and recent research has confirmed that these honeys possess unique antimicrobial properties. As a result, they have become the preferred choice for wound management.

In this review article, we explore the biochemical and medicinal properties of honey. The paper delves into the biochemical properties of honey, such as its sugar content, vitamins, minerals, and amino acids. It further explores the antioxidant and antimicrobial properties of honey, along with its potential therapeutic benefits in wound healing, cough suppression, and immune system support.

2. History of drug discovery

Over the course of history, humanity has consistently turned to nature for a multitude of traditional remedies and therapeutics. As far back as 2400BCE, ancient Egyptian records indicate the utilization of oils and plant materials for their medicinal properties (Bernardini *et al.*, 2018). The Greeks and Romans similarly embraced nature as a wellspring of drug discovery (Thomford *et al.*, 2018), a tradition that persists even in modern medicine, where numerous nutraceuticals and pharmaceuticals are sourced from plants (Yang *et al.*, 2019).

In the early 19th century, there was a profound exploration of plants with the aim of uncovering their healing properties. Likewise, in the 1970s, researchers turned their attention towards the vast ocean as a potential source of natural substances with medicinal value (Bernardini *et al.*, 2018). Astonishingly, approximately 50% of the drugs that have been approved for market use between 1981 and 2010 originate from natural products (Hauer, 2020; Newman and Cragg, 2020). During this period, the discovery of new drugs primarily relied on chance discoveries, prior knowledge passed down through generations, or the arduous process of trial and error. However, the field experienced a significant breakthrough with the emergence of rational drug design. This approach starts with a hypothesis that a specific biological molecule may possess therapeutic potential. Conventionally, bioactive compounds were identified through a series of steps involving separation and purification of extracts (Yang *et al.*, 2019). In the mid-1990s, major pharmaceutical companies began employing fragment-based molecular modeling and computational chemistry techniques as innovative tools to uncover and synthesize novel drugs (Konteatis, 2021).

The development and screening of synthetic compounds have become more accessible with the introduction of high-throughput screening methods (HTS) and advancements in synthetic chemistry. This has resulted in a growing emphasis on laboratory-driven drug development (Atanasov, Zotchev, *et al.*, 2021). Combinatorial chemistry, a high throughput technique, has been instrumental in the identification of new therapeutic options. It involves assessing various points of diversity within an initial compound or pharmacophore and generating different constructs using mathematical models and starting materials (Thomford *et al.*, 2018). Through this approach, vast libraries of compounds can be synthesized and analyzed for their potential activity.

However, it is important to acknowledge some disadvantages associated with this method. These include limiting yields, poor solubility, and low purity of the synthesized compounds (Thomford *et al.*, 2018). Consequently, the success rate of drug discovery has been lower than initially anticipated

(Newman and Cragg, 2020). The realm of natural product structures transcends the boundaries of a chemist's imagination and captivate the realm of drug discovery with their inherent potential to yield unique and impactful bioactive secondary metabolites (Thomford *et al.*, 2018). Nonetheless, the utilization of High-Throughput Screening (HTS) and natural products as primary avenues for drug exploration has waned over the last two decades (Baltz, 2019). However, natural products as a source of novel drugs are re-emerging and pharmaceutical companies are realizing that these sources need to be re-explored and combined with diversity-orientated synthetic methodologies (Newman and Cragg, 2020; Atanasov, Zotchev, *et al.*, 2021). Due to the significant advances in our understanding of natural product biosynthesis, with considerable developments in approaches for natural-product isolation and synthesis new paradigms and new enterprises have recently evolved (Thomford *et al.*, 2018). Transcriptomics, proteomics, and metabolomics studies have recently unveiled novel insights into the biosynthesis of bioactive molecules (Baltz, 2019; Yang *et al.*, 2019). The production of artemisinic acid has been induced in the tobacco plant Nicotiana benthamiana for the treatment of malaria (Beyraghdar Kashkooli *et al.*, 2022). With the advancements in high-throughput screening (HTS) technologies like high-performance liquid chromatography (HPLC), mass spectrometry (MS), and nuclear magnetic resonance (NMR), the capability to unravel chemical structures of natural products has been greatly enhanced (Baltz, 2019; Atanasov, Zotchev, *et al.*, 2021). With the advent of high-throughput drug screening technologies associated with genetic information, novel avenues of research are emerging to swiftly and efficiently detect innovative lead compounds (Ahmad *et al.*, 2019; Atanasov, Zotchev, & Dirsch, 2021).

3. Natural antimicrobial products

Microorganisms are common sources of novel drugs and lead compounds, which are extensively used in modern medicine (Khatabi *et al.*, 2023). The modern era of antimicrobial therapy began in 1929, with Fleming's accidental discovery of the bactericidal substance, penicillin (Lalchhandama, 2021). It was observed that the growth of a fungus, from the *Penicillium* genus, had a bactericidal effect on neighboring *Staphylococcus* sp. an observation which eventually resulted in the production of many antibiotic derivatives of penicillin (Rodriguez-Herrera *et al.*, 2019). The discovery of penicillin prompted increased interest in identifying novel classes of antibiotics from natural products and up till 1962 nearly all new antibiotics came from this source (Ahmad *et al.*, 2019). *Streptomyces* is the largest antibiotic-producing genus of bacteria, producing various antimicrobials including Streptomycin and Chloramphenicol. Antifungal-including nystatin, have also been isolated from *Streptomyces noursei*. These are a few of many natural products derived from microorganisms. There is also a diverse array of unexplored potential for microbial diversity; environmental samples, extremeophiles, endophytes, marine microbes and microbial symbionts are yet to be explored (Newman and Cragg, 2020). Evolutionarily preserved antimicrobial peptides (host defense peptides) are a diverse family of cysteine-rich cationic molecules which act against a range of different microorganisms. Defensins are key elements of the innate immune response and are produced upon infection or injury to protect the host (Deyrup *et al.*, 2021). Naturally occurring peptides from various biological sources are utilized in modern medical therapeutics (Tian *et al.*, 2018; Ramalingam, 2021).

Defensins kill bacteria by increasing the permeability of their cytoplasmic membrane resulting in a reduction of cellular cytoplasmic content (Cabezas-Cruz *et al.*, 2019). Peptides have a broad antimicrobial spectrum and disrupt microbial membranes via peptides–lipid interactions by defensin oligomers. Cationic peptides interact with the negative charge of the outer membrane, disruption occurs and peptides can enter the cell. Peptides can also aggregate into the membrane forming barrel-like structures which span the membrane causing disruption of cell death (Gao *et al.*, 2021). The inner membrane is also depolarized, cytoplasmic ATP is reduced and respiration is inhibited resulting in bacterial cell death. Three antimicrobial peptides from the marine sponge *Discodermia kiiensis*, discodermins models were among the first peptide antibiotics to be discovered and were shown to have antibacterial activity against a range of bacteria including *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus subtilis*, and *Mycobatcerium smegmatis*. Antimicrobial insect defensins are a large family of peptides commonly found in the hemolymph or fat cells of several insect orders, including honey bees (Pluta and Sokol, 2020). Honey bees produce antimicrobial defense peptides when responding to an infection. Four immune system peptides have been isolated from honey bees; apidaecin, abaecin hymenoptaecin and defensins (Wu *et al.*, 2020). These honey bee defensins are known to leak into naturally produced bee products. Antimicrobial defensin molecules have been isolated from royal jelly and more recently in Revamil® (RS) honey (Combarros-Fuertes *et al.*, 2020).

4. Floral origins of Honey

Ever since the remarkable findings on the potent antimicrobial properties of Manuka honey, numerous studies have undertaken research into the floral sources and antibacterial efficacy of various honeys obtained from different regions around the world. It is crucial to identify the specific floral origins of honeys exhibiting substantial antibacterial activity in order to understand their mechanisms and cultivate them for medicinal purposes. Currently, melissopalynological analysis (visual pollen identification) stands as the approved method for discerning the botanical and geographic origins of honey (Maione *et al.*, 2019). Many studies have employed this technique to assess the effectiveness of honey, highlighting correlations between phytochemical levels and antimicrobial properties based on the botanical origin (Johnston *et al.*, 2018; Schmidt *et al.*, 2021).

An innovative approach for determining the botanical origins of honey has been recently introduced using DNA barcoding technology, specifically metagenomics. Metagenomics is a relatively novel field that has demonstrated a comparable level of accuracy to visual pollen identification in establishing the botanical sources of honey. This technique is reported to offer enhanced reliability, efficiency, and simplicity compared to traditional visual methods. The proposed approach employs a combination of universal primers and high-throughput pyrosequencing, enabling DNA barcoding. However, additional investigation is necessary to ensure consistent and precise identification of the floral origins of honey (Garlapati *et al.*, 2019; Liu *et al.*, 2022).

The incorporation of honey as a valuable wound care product in contemporary medicine has been facilitated by the marketization of 'therapeutic honeys' like manuka honey and Revamil. Nevertheless, it is imperative to conduct additional research on various types of honeys and their floral/geographical origins to ascertain their antimicrobial efficacy and worldwide accessibility.

5. Nomenclature and classification of Honey

Honey is a saturated or supersaturated sugar solution created by social bees and certain other social insects. These insects collect nectar or honeydew from living plant flowers and enzymatically process it into honey, which they store as food for times of scarcity (Howard and Zimmerman, 2020). Although a few other insects also contribute, honey is primarily produced by bees, which are social insects with a lifelong cycle. The bee population is divided into various groups, including honey bees (*Apis* spp.), stingless bees (Melipona and Trigona spp.), Nectarina wasps in South America, and certain species of honey ants, particularly Melophorus inflatus in Australia. There are also other social wasps and bumblebees (Bombus spp.) with annual life cycles that produce small amounts of honey (Thapa *et al.*, 2018).

5.1. Nectar Honey

The European Commission Council Directive provides the definition of nectar, honey. According to this directive, nectar honey is a delightful, natural sweet substance created by the incredible Apis mellifera bees. These remarkable bees collect nectar from various plants, blend it with unique substances of their own, and then deposit, dehydrate, store, and ultimately leave it in honeycombs for the purpose of ripening and maturing (Moumeh *et al.*, 2020).

5.2. Honeydew honey

European Commission Council Directive defines honeydew honey as a delectable substance derived from the secretions of living plant parts or the excretion of small insects that feed on plant sap. These plant-sucking insects, scientifically known as Hemiptera, puncture foliage or other plant coverings, extract sap, and expel surplus droplets of honeydew. The resourceful bees diligently collect these honeydew droplets for our consumption (Mădaş *et al.*, 2020).

Although pollen analysis can aid in distinguishing between honeydew honeys and nectar honeys, their distinctiveness is better characterized by examining their physicochemical profiles (Mehanned and Dehbi, 2022). Honeydew honeys exhibit higher pH levels, acidity, ash content, electrical conductivity, and possess a darker color (Abselami *et al.*, 2018). Additionally, they contain lower levels of monosaccharides, while showcasing higher levels of di- and trisaccharides (Mateo *et al.*, 2021). It is worth noting that honeydew may also contain cells of algae and fungi, although these elements are not exclusive to its origin (Vilas-Boas *et al.*, 2023).

6. Honey applications – A historical perspective

Honey holds a significant place in the realms of nourishment, healing, and delight since time immemorial. Unraveling the precise origins of the enduring bond between humanity and the bees poses challenges, as ancient civilizations tirelessly endeavored to tame these remarkable creatures. Yet, from the annals of literature, we can glean intriguing accounts that showcase the manifold applications of this golden elixir.

6.1. Honey in ancient times

The utilization of honey for therapeutic purposes has been widely recognized in both ancient and modern medical practices. Dating back to 1900 to 1250 BC, the use of honey can be found in Egyptian Papyri and Sumerian clay tablets, comprising around one third of their prescriptions (Almasaudi, 2021). The ancient Egyptians employed honey not only for wound management but also for treating eye and skin conditions, as well as in embalming processes.

During the time of Hippocrates (460-357 BC), it was discovered that honey possessed cleansing properties for sores, ulcers, and busted lip, promoting their healing (Nong *et al.*, 2023). Aristotle (384-322 BC) even acknowledged the efficacy of pale honey as a salve for soothing sore eyes. In ancient Greece, athletes would consume a combination of honey and water before significant athletic competitions to combat fatigue (Wyndham Lewis, 2021). Moreover, the Babylonians employed honey as an ointment for skin ailments, as well as for treating ear and eye infections (Almasaudi, 2021).

The healing properties of honey, both on its own and when combined with herbs and essential oils, have been utilized for centuries. It can be traced back to ancient civilizations such as the Egyptians, Assyrians, Greeks, and Romans (Boukraâ, 2023). Around 50 AD, Dioscorides specifically mentioned honey's effectiveness in treating ulcers and sunburn, as well as facial blemishes (Yilmaz and Aygin, 2020). Many African tribes have long relied on the medicinal properties of honey. It has been used to treat snakebites, alleviate fever, and even as a laxative. Interestingly, the Masai warriors have discovered that honey can also enhance their power and strength, likely owing to its high sugar content (Albaridi, 2019).

The historical use of honey extends beyond Africa. In ancient Egypt, honey played a vital role in their culinary delights. Egyptians incorporated honey into their spiced breads, cakes, pastries, and even used it for priming beer and wine. Similarly, the Ancient Romans embraced honey for a wide array of dishes. It found its way into salad dressings to balance the acidity of vinegar and became an essential ingredient in numerous sauces (Carreck, 2018).

Honey's versatility continued to manifest in various culinary practices. Historical accounts reveal that sweetened wines, often sweetened with honey, were commonly consumed at the beginning and end of meals. Moreover, honey served as a preservation method for fruits, vegetables, and even meat. Refined sugar, a common cooking ingredient today, was recognized and utilized for medicinal purposes but had no place in cooking during those times (Boukraâ, 2023).

The appreciation for honey's distinct flavor and properties is evident in historical records. In fact, almost half of a late Roman cookery book was dedicated to recipes incorporating honey, totaling nearly 500 unique preparations (Sandhya and Pai, 2022).

6.2. Honey use in Middle Ages

During the Middle Ages, honey played a significant role in sweetening a wide range of dishes, including appetizers, soups, cheese, fish dishes, roast meats, and vegetables. Interestingly, distinguishing whether a dish was savory or sweet based on its title in a recipe was challenging. In contrast to today's conventions where meat or cheese dishes are typically savory, Middle Ages cuisine often incorporated sweet elements. For instance, meat, fish dishes, and even the pastry lids of "savoury" pies were often sweetened (Milburn, 2020).

Honey also had a longstanding history in folk medicine during that period. Around 1200 AD, Daude de Pradas documented the use of honey in folk remedies (Wyndham Lewis, 2021). In the book "Honey," Boukraâ (2023) mentioned that honey had been employed as a remedy for various gastric and intestinal complaints. Its diuretic properties were also recognized and favored as a treatment for kidney inflammations and stones. Hindu cultures placed significant faith in the medicinal properties of honey, particularly in treating coughs, pulmonary issues, and gastric disorders. Specific types of honey were even recommended for certain ailments, while honey, in general, was used in the treatment of skin diseases, smallpox, and as a component in surgical dressings. German women also utilized a mixture of honey and crushed bees to regulate menstrual flow and for its energetic and cosmetic benefits (Boukraâ, 2023).

6.3. Honey in modern medicine

In more recent times, honey has played a relatively minor role in medicine in the developed countries mostly due to it not being accepted by Western practitioners who preferred to use antibiotics since they were not sure of the honey's mode of action (Jassam *et al*., 2021). However, the applications of honey have persisted in the Middle East, China, Africa, and Indian nations, as they recognize honey as a precious resource for treating both internal and external ailments. Throughout history, rural communities from various nations have extensively documented the use of honey for managing wounds and addressing other health issues. Honey has demonstrated effectiveness in combating bacterial diarrhea and assisting in the management of eye infections, according to a clinical trial (Kuropatnicki *et al.*, 2018). Nevertheless, since the advent of penicillin and other antibiotics, which were hailed as miraculous, honey has played a relatively minor role in Western medicine. However, the re-emergence of antibiotic-resistant pathogens like methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and *Pseudomonas aeruginosa* has compelled researchers to rediscover the antibacterial potential of honey (Almasaudi, 2021).

Throughout the past two decades, extensive research has been conducted to delve into the enigmatic role of honey in wound and burn management. This relentless pursuit of knowledge has yielded compelling scientific evidence, underscoring honey's prowess as an effective antibacterial agent (Gambo *et al.*, 2018; Aly *et al.*, 2021). In vitro studies have unequivocally revealed honey's superior antibacterial qualities, surpassing several antiseptics and antibiotics. Remarkably, these findings align harmoniously with clinical trials, in vivo experiments, and numerous cases where honey triumphantly eliminated antibiotic-resistant and sensitive strains, defying the limitations of conventional therapy (Yilmaz and Aygin, 2020; Chikhaoui *et al.*, 2023). Medicinally, honey is used to enhance wound healing in humans, treat gastric ulcers, and shorten the duration of diarrhea. The use of honey was traditionally based on empirical knowledge rather than scientific understanding. People were aware that honey could cure infections without fully comprehending how it worked, which eventually led to the dominance of antibiotics over honey as a medical treatment (Boukraâ, 2023). However, recent research has shed light on the therapeutic and beneficial potential of honey, providing insights into why it has been considered an elixir by ancient civilizations (Aly *et al.*, 2021). Studies have indicated various health-related advantages of honey, such as its laxative effect, positive impact on blood glucose levels, anti-inflammatory and immune-stimulating properties, and potential cancer-preventative action (Abbas *et al.*, 2021).

7. Production of Honey

The honey bee (*Apis mellifera*) is of great significance to humans as it serves as a crucial pollinator for both commercial and domestic crops. Additionally, honey bees provide us with honey, which is a valuable and nutritious commodity (Gupta *et al.*, 2019; Osterman *et al.*, 2021). Unfortunately, honey bee populations have been facing numerous challenges, such as pests and diseases, exposure to agrochemicals, mismanagement in beekeeping practices, and lack of genetic diversity. These factors have raised concerns regarding the future sustainability of honey bee populations and their ability to continue providing these vital services (Gupta *et al.*, 2019).

The quality and composition of honey are influenced by various factors, including the types of flowers in the vicinity, the geographical location of the hive, the health of the bees, and annual changes in local flora and flowering patterns (Kamo *et al.*, 2018). Moreover, honey comes in different physical forms for commercial purposes, such as combs, chunks, crystallized or granulated, and creamed honey. It also undergoes processing techniques like pressing, centrifuging, draining, and heat processing (Chin and Sowndhararajan, 2020). Within a honey bee hive, there are three distinct castes: the queen (alpha), the worker (beta), and the drone (gamma) bees (Qamar and Rehman, 2020). Through their collective efforts, honey production is made possible. Honey bees produce honey by collecting nectar from flowering plants. Nectar, a sugary liquid, is sourced from specialized glands called nectaries.

Nectar is collected by worker bees, traveling up to 9 km in one trip. Sucrose in nectar is hydrolyzed to produce glucose and fructose (Lewkowski *et al.*, 2019). Upon his return to the hive, thousands of worker bees swallow and regurgitate the nectar within the honeycomb. This regurgitation process, along with wing fanning, causes evaporation and reduces the water content, ripening the honey over time. Honey bees store the honey as food reserves for the winter when nectar or pollen is scarce. Any surplus honey can be taken out for human consumption (Qamar and Rehman, 2020). Lewkowski et al. (2019) discussed the production of glucosidase III in the hypopharyngeal gland of European honey bees. This enzyme is secreted into the nectar and is responsible for the production of hydrogen peroxide (Bugarova *et al.*, 2021). Honey bees collect pollen grains as they visit flowering plants to feed the bee larvae (Kamo *et al.*, 2018). Using a mixture of nectar and saliva, dense pollen pellets are created from these grains. In addition to nectar, honey bees also gather exudate from sap-sucking insects as an alternative. Honeydew collection is commonly observed from sap-feeding insects on conifers and other anemophilous species (Mateo *et al.*, 2021). The tree resin is actively collected from various species and, when combined with wax, is used to create propolis. This propolis possesses antimicrobial properties and is deposited within the hive (Shanahan and Spivak, 2021).

8. Composition of Honey

Honey possesses a wide range of minor constituents, such as carbohydrates, volatile, and phenolic compounds, including flavonoids and non-flavonoid phenolic compounds (Bonometti *et al.*, 2022). These compounds can be sourced from the plants that bees gather nectar to and from the bees themselves. The presence and composition of phenolic compounds in honey can be influenced by various factors, including storage and processing methods, microbial or environmental contamination, geographical distribution, and the specific types of plants from which nectar and pollen are collected. It is important to note that while honey is a distinctive and saturated complex solution, not all types of honey are identical. The chemical profile of honey can vary significantly based on factors such as the botanical source, geographical location, bee species, storage conditions, beekeeping practices, as well as the year and time of collection (Abbas *et al.*, 2021).

8.1. Osmalarity

Due to the high sugar content of honey, the osmotic pressure of honey is typically high, resulting in low water activity (aw). According to Thakur et al. (2022), the reported range of aw is 0.562–0.62. This highlights the crucial role of osmolarity in the antimicrobial activity of undiluted honeys. In fact, the growth of numerous bacterial species is completely inhibited when the aw falls between 0.94 and 0.99 (Johnston *et al.*, 2018).

8.2. Water content

Honey's water content holds significant importance as a quality factor, crucial for preventing spoilage caused by fermentation. Unlike other parameters, the moisture content of honey cannot be overlooked, as it directly impacts both the overall quality and shelf life of the product (Thakur *et al.*, 2022). The International Honey Commission (IHC) has established a maximum limit of 20g water/100g of honey for any honey sample to be deemed suitable for trading purposes. The moisture content also influences other properties of honey, such as glucose crystallization and viscosity, rendering it pivotal (Thakur *et al.*, 2022). Evaluation of honey moisture content can be conducted using various methods, including refractive index, gravimetric technique, or Karl Fischer titration (Pascual-Mate *et al.*, 2018).

8.3. Acidity

Acidity is an additional aspect that contributes to the antimicrobial potency of honey. While it was previously believed to play a significant role, recent research indicates that acidity actually has a minor impact on the antibacterial properties of honey (Johnston *et al.*, 2018). Honey consists of approximately 30 organic acids (Rahman *et al.*, 2023). Among these acids, gluconic acid is the primary organic acid present in honey, ranging from 0.23% to 0.98%, and it is produced through the activity of the enzyme glucose oxidase (Mohamadzade Namin *et al.*, 2023).

8.4. Sugar content (Carbohydrates)

Honey is a complex saturated or supersaturated solution which mainly made up of two components sugars and water. The sugars or carbohydrates make up more than 90% of the honey's total dry matter (Chin and Sowndhararajan, 2020). It has been reported that honey is made up of more than 180 substances (Kuropatnicki *et al.*, 2018) which Bogdanov has estimated to be actually even closer to 600 substances (Thakur *et al.*, 2022). The carbohydrate content of honeys includes a variety of sugars such as the monosaccharides fructose (levulose) as well as glucose (dextrose), sucrose and maltose and disaccharide oligosaccharides which seem to differ according to the floral source of the honey (Almasaudi, 2021). Sugars (saccharides) comprise the major portion of honey approximately 85-95% (w/v) of the total honey. Honey consists mostly of the monosaccharides fructose and glucose. Twenty-five other oligosaccharides (di, tri and tetrasaccharides) have also been described. Invert syrup (IS), conventional corn syrup (CCS) and high fructose corn syrup (HFCS) are also used in honey adulteration (Chin and Sowndhararajan, 2020). Honey is a variable and complex mixture of sugars and other components. At its very basic level, honey consists of a mixture of simple carbohydrates which create a highly osmotic environment. The combination of low levels of water (~18%) and high levels of sugar (~80%) are enough in themselves to prevent the spoilage of honey by microorganisms (Hussain, 2018). Disruption of the bacterial cell wall occurs due to the osmotic effect. The osmotic effect has been shown to be an important parameter for killing *Helicobacter pylori*. However honey has other antibacterial factors beyond the osmotic effect (Almasaudi, 2021). An artificial honey solution is used to distinguish between the osmotic effects of sugars and antibacterial activity in a study by Albaridi (2019).

8.5. Proteins and Amino acids

Honey typically contains approximately 0.1-0.5% proteins, as reported by Alp (2018). Among the eighteen amino acids present in honey, proline accounts for 50-85% of the total amino acid profile. Some specific types of honey exhibit characteristic amino acids such as arginine, tryptophan, and cystine (Chin and Sowndhararajan, 2020). The proteins in honey consist mainly of enzymes, which originate from both the nectar and the bees themselves (Bucekova *et al.*, 2019). The primary enzymes found in honey are diastase (amylase), responsible for breaking down starch into smaller units; invertase (glucosidase), which converts glucose to fructose; and glucose oxidase, which facilitates the conversion of glucose to gluconolactone, resulting in the production of gluconic acid and hydrogen peroxide (Bugarova *et al.*, 2021). Additionally, catalase naturally occurs in certain pollen grains and helps neutralize hydrogen peroxide (Ayad *et al.*, 2021).

8.6. Vitamins and Minerals

Trace amounts of B vitamins (riboflavin, niacin, folic acid, pantothenic acid and vitamin B6) and C vitamins (ascorbic acid) are found in honey. Many different minerals (calcium, iron, zinc, potassium, chromium, phosphorous, magnesium and manganese) are found in unprocessed honey.

8.7. Volatile compounds

More than 600 volatile organic compounds (VOCs) have been identified in honey. Volatile are organic chemicals that have a high vapor pressure at standard room temperature. Honey has been categorized into seven major groups based on its composition; these include hydrocarbons, terpens, acids, alcohol, organic acids, ketons, furans, aldehyde and miscellaneous (Abbas *et al.*, 2021; Wang *et al.*, 2022; Rahman *et al.*, 2023).

The presence of VOCs in honey, although in low concentrations, significantly affects its sensory characteristics such as flavor, aroma, color, and texture. These characteristics are influenced by the specific types of plants and flowers visited by bees during the honey-making process (Abbas *et al.*, 2021). While some VOCs originate directly from the plants or nectar sources, others are produced during the honey's processing or storage stages (Machado *et al.*, 2020; Tedesco *et al.*, 2022; da Silva Cruz *et al.*, 2023).

When honey undergoes heat treatment, the Maillard reaction takes place. This non-enzymatic browning reaction occurs between sugars and amino acids, leading to the production or transformation of VOCs (da Silva Cruz *et al.*, 2023). Additionally, the presence of microbial and environmental contaminants can contribute to the variety of VOCs detected in honey (Abbas *et al.*, 2021).

8.8. Hydroxymethylfurfuraldehyde (HMF)

Hydroxymethylfurfuraldehyde (HMF) is also present in minor quantities. HMF which could be formed in the presence of acid due to the breakdown of fructose has been considered as evidence for the adulteration of honey; however, it has been proved that even fresh honeys do contain minor amounts of HMF (Pascual-Mate *et al.*, 2018) which could easily be elevated if the honey is stored in moderate or high temperatures; hence, it is necessary to store honey in a refrigerator or a cool place (Mohamadzade Namin *et al.*, 2023) so as to keep the levels of HMF to the minimum since, HMF is one of the main factors which are considered for the quality and marketing of honey.

8.9. Enzymes

Moreover, honey contains a number of enzymes including glucose oxidase, invertase, and amylase, which appear to originate from honeybees (Johnston *et al.*, 2018). The glucose oxidase plays an essential role in the antibacterial activity of honeys as well as the generation of gluconic acid. The enzyme invertase catalyzes the conversion of sucrose obtained from the nectar and into the monosaccharides fructose and glucose in a ratio of 1.2:1 between glucose and fructose (Chin and Sowndhararajan, 2020). There are other enzymes such as catalase and acid phosphatase (Mohamadzade Namin *et al.*, 2023) which are also present in some honeys, but these are likely to be derived from the pollen and nectar of plants.

8.10. Phenolic compounds

The major phenolic compounds identified in honey are flavonoids: quercetin, pinocembrin, pinobanksin, chrysin, galangin, kaempferol and luteolin (Cheung *et al.*, 2019; Wang *et al.*, 2022). Aromatic acids contain an aromatic ring and an organic acid function (C6-C1 skeleton). Phenolic compounds are an example of aromatic acids as they contain a phenolic ring and an organic carboxylic acid function. Phenolic acids can be found in many plant species (Li *et al.*, 2018). Flavonoids are plant specialized metabolites which fulfill many functions and are important for plant pigmentation, UV filtration and symbiotic nitrogen fixation (Shah and Smith, 2020). Flavonoids are widely distributed in plants and their basic molecular structure is 2-phenyl-1,4-benzopyrone. Plant derived phenolic acids include benzoic, ferulic, gallic, chlorogenic, caffeic, p-coumaric, ellagic and syringes acids. Phenolic compounds have antibacterial, anti-inflammatory and antioxidant activities. The composition of phytochemicals has an effect on the bioactivity of honey (Wang *et al.*, 2022).

8.11. Pollen, Propolis and Royal jelly

Honey bees collect pollen and nectar from flowering plants, supplying the hive with protein for nourishment. Pollen is commonly found in honey. Wind pollinated pollen from trees and plants also frequently feature within honey (Saravanan *et al.*, 2019). Pollen contains contain carbohydrates, amino acids, DNA, nucleic acids, proteins, lipids, vitamins, minerals, phenolic compounds and flavonoids (Gercek *et al.*, 2021). Propolis is produced from the exudates of plants ; bees seal the hive with the resinous substance creating a protective barrier against intruders (Vazhacharickal, 2021). Propolis is comprised of resin (50%), wax (30%), essential oils (10%), pollen (5%), and other organic compounds (5%). More than 300 compounds including phenolic compounds, esters, flavonoids, terpenes and anthraquinones have been found in propolis (Özkök *et al.*, 2021; Nalbantsoy *et al.*, 2022). Royal jelly is a protein liquid secreted by glands in the hypopharynx of worker bees; it is produced exclusively for the adult queen bees, it is a vital nutritional source (Vazhacharickal, 2021). More than 50 % of the dry mass of royal jelly is proteins, major royal jelly proteins (MRJPs) have been researched and analyzed (Alp, 2018). Royal jelly is used as a dietary supplement for the treatment of many conditions including asthma, high cholesterol and seasonal allergies.

8.12. Hydrogen peroxide

In the 1960s, hydrogen peroxide (H_2O_2) was identified as a major antibacterial compound in honey. Hydrogen peroxide is commonly used in cleaning products such as bleach, but it is also produced naturally during glucose oxidation of honey (Farkasovska *et al.*, 2019). Hydrogen peroxide is also a contributing factor to a honey's acidity and sterility. Hydrogen peroxide and honey phenolics with pro-oxidant activities are involved in oxidative damage resulting in bacterial growth inhibition and DNA degradation (Farkasovska *et al.*, 2019; Rane *et al.*, 2021). Rane et al. (2021) concluded that hydrogen peroxide is involved in oxidative damage, which causes bacterial DNA degradation and growth inhibition. Further studies revealed the bacteriostatic effect was directly related to the generation, and therefore the concentration of hydroxyl radicals generated from the hydrogen peroxide (Rane *et al.*, 2021). It is believed that the hydrogen peroxide effects are modulated by other honey components (Farkasovska *et al.*, 2019).

8.13. Bee derived antimicrobial peptides

Bee derived defensins are cysteine-rich cationic peptides produced in the salivary glands and fat body cells and are involved in social and individual immunity (Maitip *et al.*, 2021). Two defensins have been characterized, royalisin (from royal jelly) and defensin (from the haemolymph), which are both encoded by Defensin-1. The Defensin-2 which shows 55% similarity to Defensin-1, has also been identified (Pluta and Sokol, 2020). Defensin-1 (5.5 KDa) has been shown to possess potent antibacterial activity against Gram-positive microorganisms including *Staphylococcus aureus* and *Bacillus subtilis* (Hussain, 2018; Bugarova *et al.*, 2021) and *Paenibacillus* larvae. This is the causative agent of American Foulbrood (AFB) which is a major pathogen of bees (Ullah *et al.*, 2023). The

honey is not registered as an antimicrobial but as a wound healing stimulant where it is claimed to stimulate tissue regeneration and reduce inflammation. I*n vitro* bactericidal activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus epidermidis*, *Escherichia coli* and *Pseudomonas aeruginosa* was assessed and a bactericidal effect was seen within
24 h by 10-40% (v/v) honey (Hussain, 2018). The peptide (defensin-1) and the other factors contributing to this bactericidal effect were also characterized**.** Other proteinaceous antibacterial compounds have previously been reported in six of twenty-six honeys, but identification of these proteins was not performed (Żebracka *et al.*, 2022).

8.14. Plant derived antimicrobial phytochemicals

Plant derived phytochemicals play an important role in the antibacterial activity of honey; methylglyoxal (MGO) from Manuka honey is an example of honey which attributes its activity to plant derived chemicals. Non-peroxide activity has been described in investigations of bactericidal factors within honey (Lima *et al.*, 2023), particular attention has been paid to Manuka honey (Green *et al.*, 2022). Plant derived phenolic compounds isolated from honey have been investigated and identified by different research groups, but the contribution to the overall activity remains unclear (Quraisiah *et al.*, 2020; Almasaudi, 2021; Al-Kafaween *et al.*, 2023). It has been suggested that the contribution of plant-derived components to the antibacterial activity of honey is too low to detect (Hussain, 2018), but when extracted phenolics and flavonoids are regarded as a very promising source of natural medicinal therapeutics. Solid phase extraction (SPE) and HPLC analysis was used to extract phenolic compounds and antimicrobial agents from *Rubus,* honey.

The caffeic phenolics, *p*-coumaric and ellagic acids and the flavonoids chrysin, galangin, pinocembrin, kaempferol and tectochrysin were isolated (Straumite *et al.*, 2022). The phenolic fraction samples showed antimicrobial activity against various organisms including *Salmonella typhimurium, Proteus mirabilis* and *Pseudomonas aeruginosa*. The most susceptible species were *Proteus mirabilis* and *Bacillus cereus*. The antioxidant and antimicrobial activities of phenolics extracted from *Rhododendron* honeys from the Black Sea region of Turkey have also been studied (Gül and Pehlivan, 2018).

High levels of antimicrobial activity were described against *Pseudomonas aeruginosa* and *Proteus mirabilis* (Gül and Pehlivan, 2018). The combination of different phenolics, instead of individual compounds may contribute to the activity of honey, but further investigations are required in order to assess these interactions (Quraisiah *et al.*, 2020). The minor constituents in honey have high levels of antimicrobial activity due to a combination of these factors, often working in unison. These plant-derived compounds have high potential to be used as therapeutics in human health. It has been shown that the flavonoids, phenolic and organic acids in honey may act in various processes including hydrogen donating, oxygen quenching, radical scavenging and metal ion chelation resulting in bacterial growth inhibition (Quraisiah *et al.*, 2020).

The antibacterial activity of phenolic compounds should not be dismissed; phytochemicals have an influence on the antimicrobial activity of honey (Cianciosi *et al.*, 2018). Peroxide and non-peroxide factors may also be working in synergy and inhibiting bacterial growth (Abbas *et al.*, 2021). In order to analyze these compounds, the sugars which are the major components of honey must be removed. Various analytical techniques can be used to identify these components (Mamedova and Alimzhanova, 2023).

Thin Layer Chromatography (TLC) and Gas Chromatography-Mass Spectrometry (GC-MS) have been used to extract the phenolic compounds which have demonstrated antibacterial activity against

Helicobacter pylori. The *Helicobacter pylori*, which cause chronic active gastritis and peptic ulcers, showed susceptibility to various fractions of South African honey. The activity was attributed to the combination or separate action of volatile compounds including acetic acid (Quraisiah *et al.*, 2020). Other VOCs have been identified in honey; (±)-3- Hydroxy-4-phenyl-2-butanone and (+)-8-hydroxylinalool show high levels of antimicrobial activity against bacteria including *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae* and human pathogen fungi *Candida albicans* (Mărgăoan *et al.*, 2021). Despite only being present in low concentrations, the VOCs may contribute to the overall antimicrobial activity and have the potential to be used as natural therapeutics to treat a range of pathogenic microbial organisms.

9. Other minor components

Furthermore, honey is rich with other components although in a minor amount. These include amino acids (mainly proline), vitamins including vitamin A, B-vitamins (riboflavin, niacin, pyridoxine, pantothenic acid, and folic acid), vitamin-C (ascorbic acid), vitamin D, and vitamin E, Honey also contains a significant number of minerals, including calcium, phosphorous, iron, zinc, selenium, chromium, potassium, magnesium, and manganese and organic acids (Srećković *et al.*, 2019). Other components present in honeys also include flavonoids, antioxidant substances and unidentified plant-derived elements (phytochemical components) (Pashte *et al.*, 2020).

10. Medicinal property of honey

The antibacterial effect of honey, mostly against Gram-positive bacteria, both bacteriostatic and bactericidal effects have been reported, against many strains, many of which are pathogenic. Honey glucose oxidase produces the antibacterial agent hydrogen peroxide, while another enzyme, catalase breaks it down. Honey with a high catalase activity has a low antibacterial peroxide activity. Honey has both peroxide and non-peroxide antibacterial action, with different non-peroxide antibacterial substances involved: acidic, basic or neutral (Sharma *et al.*, 2023). Antimicrobial effect of honey is thus due to different substances e.g. aromatic acids and compounds with different chemical properties and depends on the botanical origin of honey. The high sugar concentration of honey, and also the low honey pH is also responsible for the antibacterial activity. Most experiments report on the stop of bacterial growth after a certain time of honey action.

The higher the concentration the longer is the period of growth inhibition. Complete inhibition of growth is important for controlling infections. Honey has also antiviral activity Rubella, Herpes virus (Kontogiannis *et al.*, 2022). Honey has also fungicide activity against different dermatophytes. Honey has been shown to have a prebiotic effect, i.e. its ingestion stimulates the growth of healthy specific Bifidus and *Lactobacillus* bacteria in the gut. Sourwood, alfalfa, sage and clover honeys have been shown to have prebiotic activity. The prebiotic activity of chestnut honey is bigger than that of the acacia, honey. Oligosaccharides from honeydew honey have prebiotic activity. Theoretically, honeydew honeys, containing more oligosaccharides should have a stronger prebiotic activity than blossom honeys (Mustar and Ibrahim, 2022).

10.1. Antibacterial activity

The antibacterial properties of honey include, the release of low lifes of hydrogen peroxide, some honey have an additional phytochemical antibacterial compound. The antibacterial property of honey is also due to osmotic effect of its high sugar content as it has osmolarity sufficient to inhibit the microbial growth (Obey *et al*., 2022). Hydrogen peroxide was responsible for the antibacterial activity of honey since both the antibacterial activity of honey and hydrogen peroxide was destroyed by light. Albaridi (2019) reported that hydrogen peroxidase which is produced by the glucose oxidase of honey could be the inhibitory substance against bacteria. However, it is known that honey as well as bacteria produces a catalase that eliminates hydrogen peroxide.

But although catalase is active with a high concentration of hydrogen peroxide, it is of low activity with physiological levels (Mustafa *et al*., 2022). Lavie found an additional group of light-sensitive, heat-stable antibacterial factors in honey which inhibited the growth of *Bacillus subtilis*, *Bacillus alvei, Escherichia coli, Pseudomonas pyocyanes, Salmonella typhi* and *Staphylococcus aureus* (Albaridi, 2019). A comparison was made by Cortopassi–Laurino and Gelli between the physicochemical properties and antibacterial activity of honey produced by Africanized honey bees (*Aphis mellifera*) and Melliponinae (stingless bees) in Brazil. For both types of honey at a concentration of 5-25%, *Bacillus stearothermophilus* was found to be the most susceptible and *Escherichia coli* the least susceptible of the seven bacterial isolates tested (the other five being, *Bacillus subtilis*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*).

Melipona subnitida honey produced by *Mimosa bimucronata* and *Plebia* sp. honey produced by *Borreria*/*Mimosa* exhibited the greatest antibacterial activities (Albaridi, 2019). Antibacterial activities of the two honey samples, produced by the honeybee (*Aphis mellifera*), were assayed using standard well diffusion method. Both honey samples were tested at four concentrations (5%, 25%, 50% and 100% w/v) against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Bacillus subtilis* and *Escherichia coli*. There are many reports of bactericidal as well as bacteriostatic activity of honey and the antibacterial properties of honey may be particularly useful against bacteria, which have developed resistance to many antibiotics (Mustafa *et al*., 2022).

10.2. Antifungal activity

The synergistic action of starch on the antifungal activity of honey, a comparative method of adding honey with and without starch to culture media was used. *Candida albicans* has been used to determine the minimum inhibitory concentration (MIC) of five varieties of honey (Conti *et al*., 2018). The antifungal action of three single samples of South African honey (wasbessie, blue gum and fynbos) against *Candida albicans* and found honey to inhibit the growth of *Candida albicans*, while the control, blue gum and fynbos honey produced only partial inhibition (Pavlin *et al*., 2023).

10.3. Antiviral activity

Honey had good anti-Rubella activity, while thyme did not. These results may justify the continuing use of honey in traditional medicines from different ethnic communities worldwide and in some modem medications such as cough syrups (Solayman, 2023).

10.4. Antioxidant activity

Honey contains a variety of phytochemicals (as well as other substances such as organic acids, vitamins, and enzymes) that may serve as sources of dietary antioxidants (Lewoyehu and Amare, 2019). The amount and type of these antioxidant compounds depend largely upon the floral source/variety of honey. In general, darker honeys have been shown to be higher in antioxidant content than lighter honeys. Researchers at the University of Illinois Champaign/Urbana examined the antioxidant content (using an assessment technique known as Oxygen Radical Absorbance Capacity or ORAC) of 14 unifloral honeys compared to a sugar analog. ORAC values for the honeys ranged from 3.0 μ mol TE/g for acacia honey to 17.0 μ mol TE/g for Illinois buckwheat, honey. The sugar analog displayed no antioxidant activity (Mumtaz *et al*., 2020).

Free radicals and reactive oxygen species (ROS) have been implicated in contributing to the processes of aging and disease. Humans protect themselves from these damaging compounds, in part, by absorbing antioxidants from high-antioxidant foods. This report describes the effects of consuming 1.5 g/kg body weight of corn syrup or buckwheat honey on the antioxidant and reducing capacities of plasma in healthy human adults. It can be speculated that these compounds may augment defenses against oxidative stress and that they might be able to protect humans from oxidative stress. Given that the average sweetener intake by humans is estimated to be in excess of 70 kg per year, the substitution of honey in some foods for traditional sweeteners could result in an enhanced antioxidant defense system in healthy adults (Nweze *et al*., 2020). Antioxidant properties shown by volatile oil of propolis (VOP) from India were investigated by spectrophotometric methods and a photochemi-luminescence method and it was found that from IC50 values it could be concluded that the efficiency of scavenging ABTS radicals by the VOP was more pronounced as compared to scavenging other radicals (Oršolić *et al*., 2020).

11. Other medicinal uses of honey

11.1. Honey as antibiotics

Manuka honey has potent antibacterial properties, making it especially beneficial for preventing and treating wound infections by drug-resistant bacteria, according to physician Robert Frykberg of the Veterans Affairs Medical Center in Phoenix, Ariz.

11.2. Antidiabetic activity

Frykberg noted that the FDA-approved manuka honey product, Medihoney, has proven beneficial for healing foot ulcers in diabetic patients. Diabetics with foot ulcers that do not heal sometimes require foot amputation.

11.3. Arthritis

Take one part honey to two parts of lukewarm water and add a small teaspoon of cinnamon powder, make a paste and massage it on the itching part of the body. It is noticed that the pain recedes within a minute or two. Or for arthritis patients daily morning and night have one cup of hot water with two spoons of honey and one small teaspoon of cinnamon powder. If drunk regularly even chronic arthritis can be cured. In recent research done at the Coppen Hagen University, it was found that when the doctors treated their patients with a mixture of one tablespoon honey and half teaspoon cinnamon powder before breakfast, they found that within a week out of the 200 people so treated practically 73 patients were totally relieved of pain and within a month, mostly all the patients who could not walk or move around because of arthritis started walking without pain.

11.4. Heart diseases

Make a paste of honey and cinnamon powder, apply on bread or chapatti instead of jelly and jam and eat it regularly for breakfast. It reduces cholesterol in the arteries and saves the patient from a heart attack. Also, those who have already had an attack, if they do this process daily, are kept miles away from the next attack, regular use of the above process relieves loss of breath and strengthens the heart beat in America and Canada, various nursing homes have treated patients successfully and have found that due to the increasing age the arteries and veins, which lose their flexibility and get clogged, are revitalized.

11.5. Cancer

Recent research in Japan and Australia has revealed that advanced cancer of the stomach and bones have been cured successfully. Patients suffering from these kinds of cancer should daily take one tablespoon of honey with one teaspoon of cinnamon powder for one month 3 times a day.

Conclusion

Honey is one of the oldest known medicines that have continued to be used up to present times in folk medicine. Its use has been "rediscovered" in later times by the medical profession, especially for dressing wounds. The numerous reports of the effectiveness of honey in wound management, including reports of several randomized controlled trials, have recently been reviewed, rapid clearance of infection from the treated wounds being a commonly recorded observation. In almost all of these reports honey is referred to generically, there being no indication given of any awareness of the variability that generally is found in natural products. Yet the ancient physicians were aware of differences in the therapeutic value of the honeys available to them: Aristotle (384-322 BC), discussing differences in honeys, referred to pale honey being "good as a salve for sore eyes and wounds"; and Dioscorides (50 AD) stated that a pale-yellow honey from Attica was the best, being "good for all rotten and hollow ulcers".

Any honey can be expected to suppress infection in wounds because of its high sugar content, but dressings of sugar on a wound have to be changed more frequently than honey dressings do to maintain an osmolarity that is inhibitory to bacteria, as honey has additional antibacterial components. Since microbiological studies have shown more than one hundredfold difference in the potency of the antibacterial activity of various honeys, the best results would be expected if a honey with a high level of antibacterial activity were used in the management of infected wounds. Other therapeutic properties of honey besides its antibacterial activity are also likely to vary. An anti-inflammatory action and a stimulatory effect on angiogenesis and on the growth of granulation tissue and epithelial cells have been observed clinically and in histological studies. The components responsible for these effects have not been identified, but the anti-inflammatory action may be due to antioxidants, the level of which varies in honey. The stimulation of tissue growth may be a trophic effect, as nutrification of wounds is known to hasten the healing process: the level of the wide range of micronutrients that occur in honey also varies. Until research is carried out to ascertain the components of honey responsible for all of its therapeutic effects, it will not be possible to fully standardize honey to obtain optimal effectiveness in wound management. However, where an antiseptic wound dressing is required then standardization for this effect is possible. Several brands of honey with standardized levels of antibacterial activity are commercially available in Australia and New Zealand, but even where these are not available it is possible to assay the level of antibacterial activity of locally available honey by a simple procedure in a microbiology laboratory.

References

Abbas, M., Shah, I., Nawaz, M. A., Pervez, S., Hussain, Y., Niaz, K. & Khan, F. (2021). Honey Against Cancer. in Jafari, S. M., Nabavi, S. M. & Silva, A. S. (eds.), *Nutraceuticals and Cancer Signaling: Clinical Aspects and Mode of Action*. Cham: Springer International Publishing, pp. 401-418.

Abselami, A., Tahani, A., Sindic, M., Fauconnier, M.-L., Bruneau, E. & Elbachiri, A. (2018). Physicochemical properties of some honeys produced from different flora of Eastern Morocco. *Journal of Materials and Environmental Science*, 9 (3), 879-886. doi: 10.26872/jmes.2018.9.3.97.

Ahmad, I., Qais, F. A., Samreen, Abulreesh, H. H., Ahmad, S. & Rumbaugh, K. P. (2019). Antibacterial Drug Discovery: Perspective Insights. in Ahmad, I., Ahmad, S. & Rumbaugh, K. P. (eds.), *Antibacterial Drug Discovery to Combat MDR: Natural Compounds, Nanotechnology and Novel Synthetic Sources*. Singapore: Springer Singapore, pp. 1-21.

Al-Kafaween, M. A., Alwahsh, M., Mohd Hilmi, A. B. & Abulebdah, D. H. (2023). Physicochemical characteristics and bioactive compounds of different types of honey and their biological and therapeutic properties: a comprehensive review. *Antibiotics*, 12 (2), 337. doi: 10.3390/antibiotics12020337.

Albaridi, N. A. (2019). Antibacterial Potency of Honey. *International Journal of Microbiology*, 2019, 1-10. doi: 10.1155/2019/2464507.

Almasaudi, S. (2021). The antibacterial activities of honey. *Saudi Journal of Biological Sciences*, 28 (4), 2188-2196. doi: 10.1016/j.sjbs.2020.10.017.

Alp, H. (2018). Effects of Propolis on Immune System. *ANADOLU Journal of Aegean Agricultural Research Institute*, 28 (2), 99-104.

Aly, A. A., Maraei, R. W., Abd-Allah, M. M. & Safwat, G. (2021). Evaluation of physical, biochemical properties and cell viability of gamma irradiated honey. *Journal of Food Measurement and Characterization*, 15 (5), 4794-4804. doi: 10.1007/s11694-021-01046-x.

Atanasov, A. G., Zotchev, S. B. & Dirsch, V. M. (2021). Natural products in drug discovery: advances and opportunities. *Nature reviews Drug discovery*, 20 (3), 200-216. doi: 10.1038/s41573-020-00114-z.

Ayad, R., Amessis-Ouchemoukh, N., Ouchemoukh, S., Madani, K. & Boulekbache-Makhlouf, L. (2021). Pollen profiles, physicochemical characteristics, and antioxidant activities of two honey samples from Jijel City (Algeria). *The Annals of the University Dunarea de Jos of Galati. Fascicle VI-Food Technology*, 45 (2), 147-167. doi: 10.35219/foodtechnology.202L2.10.

Baltz, R. H. (2019). Natural product drug discovery in the genomic era: realities, conjectures, misconceptions, and opportunities. *Journal of Industrial Microbiology and Biotechnology*, 46 (3-4), 281-299. doi: 10.1007/s10295-018-2115-4.

Bernardini, S., Tiezzi, A., Laghezza Masci, V. & Ovidi, E. (2018). Natural products for human health: an historical overview of the drug discovery approaches. *Natural product research*, 32 (16), 1926-1950. doi: 10.1080/14786419.2017.1356838.

Beyraghdar Kashkooli, A., Farmanpour-Kalalagh, K. & Babaei, A. (2022). Yeast synthetic biology for production of artemisinin as an antimalarial drug. in, *Synthetic Biology of Yeasts: Tools and Applications*. : Springer, pp. 157-180.

Bonometti, E., Giordana, A., Operti, L., Rabezzana, R., Turco, F. & Volpi, G. (2022). Characterization of unifloral Italian (Piedmont region) honeys by headspace solid phase microextraction coupled to gas chromatography–mass spectrometry. *JSFA Reports*, 2 (7), 341-350. doi: 10.1002/jsf2.67.

Boukraâ, L. (2023). *Honey in traditional and modern medicine*. : CRC Press, pp. 474.

Brudzynski, K. (2020). A current perspective on hydrogen peroxide production in honey. A review. *Food chemistry*, 332, 127229. doi: 10.1016/j.foodchem.2020.127229

Bucekova, M., Jardekova, L., Juricova, V., Bugarova, V., Di Marco, G., Gismondi, A., Leonardi, D., Farkasovska, J., Godocikova, J. & Laho, M. (2019). Antibacterial activity of different blossom honeys: New findings. *Molecules*, 24 (8), 1573. doi: 10.3390/molecules24081573.

Bugarova, V., Godocikova, J., Bucekova, M., Brodschneider, R. & Majtan, J. (2021). Effects of the carbohydrate sources nectar, sucrose and invert sugar on antibacterial activity of honey and bee-processed syrups. *Antibiotics*, 10 (8), 985. doi: 10.3390/antibiotics10080985.

Cabezas-Cruz, A., Tonk, M., Bleackley, M. R., Valdés, J. J., Barrero, R. A., Hernández-Jarguín, A., Moutailler, S., Vilcinskas, A., Richard-Forget, F. & Anderson, M. A. (2019). Antibacterial and antifungal activity of defensins from the Australian paralysis tick, Ixodes holocyclus. *Ticks and tick-borne diseases*, 10 (6), 101269. doi: 10.1016/j.ttbdis.2019.101269.

Carreck, N. L. (2018). Special issue: honey. *Journal of Apicultural Research*, 57(1), 1-4. doi: 10.1080/00218839.2017.1412565.

Cheung, Y., Meenu, M., Yu, X. & Xu, B. (2019). Phenolic acids and flavonoids profiles of commercial honey from different floral sources and geographic sources. *International Journal of Food Properties*, 22 (1), 290-308. doi: 10.1080/10942912.2019.1579835.

Chikhaoui M., E Hajjouji H., Belghiti A., Badri W., Mouslim J. (2023) Antibacterial activity of honey on some antibiotic-resistant strains, systematic review, *AJMAP*, 9, 165-183, https://doi.org/10.48347/IMIST.PRSM/ajmap-v9i1.30042

Chin, N. L. & Sowndhararajan, K. (2020). A review on analytical methods for honey classification, identification and authentication. *Honey Analysis—New Advances and Challenges*, doi: 10.5772/intechopen.90232, 1-33. doi: 10.5772/intechopen.90232.

Cianciosi D., Forbes-Hernández T. Y., Afrin, S., Gasparrini, M., Reboredo-Rodriguez, P., Manna, P. P., Zhang, J., Bravo Lamas, L., Martínez Flórez, S. & Agudo Toyos, P. (2018). Phenolic compounds in honey and their associated health benefits: A review. *Molecules*, 23(9), 2322. doi: 10.3390/molecules23092322.

Combarros-Fuertes, P., Fresno, J. M., Estevinho, M. M., Sousa-Pimenta, M., Tornadijo, M. E. & Estevinho, L. M. (2020). Honey: another alternative in the fight against antibiotic-resistant bacteria? *Antibiotics*, 9 (11), 774. doi: 10.3390/antibiotics9110774.

Conti, M. E., Canepari, S., Finoia, M. G., Mele, G. & Astolfi, M. L. (2018). Characterization of Italian multifloral honeys on the basis of their mineral content and some typical quality parameters. *Journal of Food Composition and Analysis*, 74, 102-113. doi: 10.1016/j.jfca.2018.09.002.

da Rosa, C., Bueno, I. L., Quaresma, A. C. M. & Longato, G. B. (2022). Healing potential of propolis in skin wounds evidenced by clinical studies. *Pharmaceuticals*, 15 (9), 1143. doi: 10.3390/ph15091143.

da Silva Cruz, L. F., Lemos, P. V. F., Santos, T. d. S., Tavares, P. P. L. G., Nascimento, R. Q., Almeida, L. M. R., de Souza, C. O. & Druzian, J. I. (2023). Storage conditions significantly influence the stability of stingless bee (Melipona scutellaris) honey. *Journal of Apicultural Research*, 62 (3), 530-541. doi: 10.1080/00218839.2021.1950971.

Deyrup, S. T., Stagnitti, N. C., Perpetua, M. J. & Wong-Deyrup, S. W. (2021). Drug discovery insights from medicinal beetles in traditional chinese medicine. *Biomolecules & therapeutics*, 29 (2), 105. doi: 10.4062/biomolther.2020.229.

Farkasovska, J., Bugarova, V., Godocikova, J., Majtan, V. & Majtan, J. (2019). The role of hydrogen peroxide in the antibacterial activity of different floral honeys. *European Food Research and Technology*, 245, 2739-2744. doi: 10.1007/s00217-019-03393-y.

Gambo, S., Ali, M., Diso, S. & Abubakar, N. (2018). Antibacterial activity of honey against Staphylococcus aureus and Pseudomonas aeruginosa isolated from infected wound. *Arch Phar & Pharmacol Res*, 1 (2), 2018. doi: 10.33552/APPR.2018.01.000506.

Gao, X., Ding, J., Liao, C., Xu, J., Liu, X. & Lu, W. (2021). Defensins: The natural peptide antibiotic. *Advanced drug delivery reviews*, 179, 114008. doi: 10.1016/j.addr.2021.114008.

Garlapati, D., Charankumar, B., Ramu, K., Madeswaran, P. & Ramana Murthy, M. (2019). A review on the applications and recent advances in environmental DNA (eDNA) metagenomics. *Reviews in Environmental Science and Bio/Technology*, 18, 389-411. doi: 10.1007/s11157-019-09501-4.

Gercek, Y. C., Celik, S. & Bayram, S. (2021). Screening of plant pollen sources, polyphenolic compounds, fatty acids and antioxidant/antimicrobial activity from bee pollen. *Molecules*, 27 (1), 117. doi: 10.3390/molecules27010117.

Green, K. J., Lawag, I. L., Locher, C. & Hammer, K. A. (2022). Correlation of the antibacterial activity of commercial manuka and Leptospermum honeys from Australia and New Zealand with methylglyoxal content and other physicochemical characteristics. *Plos one*, 17 (7), e0272376. doi: 10.1371/journal.pone.0272376.

Gül, A. & Pehlivan, T. (2018). Antioxidant activities of some monofloral honey types produced across Turkey. *Saudi Journal of Biological Sciences*, 25 (6), 1056-1065. doi: 10.1016/j.sjbs.2018.02.011.
Gupta, D., Chauhan, H., Gupta, S. & Gupta, R. (2019). Effect of colony collapse disorder on honeybees. *Journal of Computational and Theoretical Nanoscience*, 16 (10), 4149-4152. doi: 10.1166/jctn.2019.8494.
Hauer, B. (2020). Embracing nature's catalysts: a viewpoint on the future of biocatalysis. *Acs Catalysis*, 10 (15), 8418-8427. doi: 10.1021/acscatal.0c01708.
Howard, J. & Zimmerman, M. (2020). *Encyclopedia of Insects*. : Wide Eyed Editions, pp. 160.
Hussain, M. B. (2018). Role of honey in topical and systemic bacterial infections. *The Journal of Alternative and Complementary Medicine*, 24 (1), 15-24. doi: 10.1089/acm.2017.0017.
Jassam, R. A. K. M., Saranraj, P. & Hasan, M. S. (2021). *Antibacterial Activity of Natural and Commercial Honey*. : Amazon Digital Services LLC - Kdp, pp. 90.
Johnston, M., McBride, M., Dahiya, D., Owusu-Apenten, R. & Nigam, P. S. (2018). Antibacterial activity of Manuka honey and its components: An overview. *AIMS microbiology*, 4 (4), 655. doi: 10.3934/microbiol.2018.4.655.
Kamo, T., Kusumoto, Y., Tokuoka, Y., Okubo, S., Hayakawa, H., Yoshiyama, M., Kimura, K. & Konuma, A. (2018). A DNA barcoding method for identifying and quantifying the composition of pollen species collected by European honeybees, Apis mellifera (Hymenoptera: Apidae). *Applied entomology and zoology*, 53, 353-361. doi: 10.1007/s13355-018-0565-9.
Khatabi, L., Dakkach, M., Bouziane, H. & Allouch, M. (2023). Physicochemical properties, antioxidant, and antibacterial activity of Argania Spinosa honey produced only in Morocco: Application in the care of surgical wounds. Moroccan Journal of Chemistry, 11 (04), 1038-1056. doi: 10.48317/IMIST.PRSM/morjchem-v11i04.36132.
Konteatis, Z. (2021). What makes a good fragment in fragment-based drug discovery? *Expert Opinion on Drug Discovery*, 16 (7), 723-726. doi: 10.1080/17460441.2021.1905629.
Kontogiannis, T., Dimitriou, T. G., Didaras, N. A. & Mossialos, D. (2022). Antiviral activity of bee products. *Current Pharmaceutical Design*, 28 (35), 2867-2878. doi: 10.2174/1381612828666220928110103.
Kuropatnicki, A. K., Kłósek, M. & Kucharzewski, M. (2018). Honey as medicine: historical perspectives. *Journal of Apicultural Research*, 57 (1), 113-118. doi: 10.1080/00218839.2017.1411182.
Lalchhandama, K. (2021). History of penicillin. *WikiJournal of Medicine*, 8 (1), 1-16. doi: 10.3316/informit.644471542314939.
Lewkowski, O., Mureșan, C. I., Dobritzsch, D., Fuszard, M. & Erler, S. (2019). The Effect of Diet on the Composition and Stability of Proteins Secreted by Honey Bees in Honey. *Insects*, 10 (9), 282. doi: 10.3390/insects10090282.
Lewoyehu, M. & Amare, M. (2019). Comparative evaluation of analytical methods for determining the antioxidant activities of honey: A review. *Cogent Food & Agriculture*, 5 (1), 1685059. doi: 10.1080/23311932.2019.1685059.
Li, M., Pare, P. W., Zhang, J., Kang, T., Zhang, Z., Yang, D., Wang, K. & Xing, H. (2018). Antioxidant Capacity Connection with Phenolic and Flavonoid Content in Chinese Medicinal Herbs. *Records of Natural Products*, 12 (3). doi: 10.25135/rnp.24.17.08.138.
Lima, W. G., da Silva Santos, F. R., de Faria, V. O., de Souza, N. A., de Souza-Costa, L. P., de Assis, D. C. S., da Cruz Nizer, W. S., Ferreira, J. M. S., de Paiva, M. C. & Brito, J. C. M. (2023). Production of a phenolic-rich extract of aroeira honey and characterization of its antimicrobial, antitumoral and antioxidant activities. *Revista Colombiana de Ciencias Químico-Farmacéuticas*, 52 (1). doi: 10.15446/rcciquifa.v52n1.109396.
Liu, S., Lang, D., Meng, G., Hu, J., Tang, M. & Zhou, X. (2022). Tracing the origin of honey products based on metagenomics and machine learning. *Food chemistry*, 371, 131066. doi: 10.1016/j.foodchem.2021.131066.

Machado, A. M., Miguel, M. G., Vilas-Boas, M. & Figueiredo, A. C. (2020). Honey volatile as a fingerprint for botanical origin—a review on their occurrence on monofloral honeys. *Molecules*, 25 (2), 374. doi: 10.3390/molecules25020374.

Mădaş, M. N., Mărghitaş, L. A., Dezmirean, D. S., Bobiş, O., Abbas, O., Danthine, S., Francis, F., Haubruge, E. & Nguyen, B. K. (2020). Labeling regulations and quality control of honey origin: A review. *Food Reviews International*, 36 (3), 215-240. doi: 10.1080/87559129.2019.1636063.

Maione, C., Barbosa Jr, F. & Barbosa, R. M. (2019). Predicting the botanical and geographical origin of honey with multivariate data analysis and machine learning techniques: A review. *Computers and Electronics in Agriculture*, 157, 436-446. doi: 10.1016/j.compag.2019.01.020.

Maitip, J., Mookhploy, W., Khorndork, S. & Chantawannakul, P. (2021). Comparative study of antimicrobial properties of bee venom extracts and melittins of honey bees. *Antibiotics*, 10 (12), 1503. doi: 10.3390/antibiotics10121503.

Mamedova, M. & Alimzhanova, M. B. (2023). Determination of Biomarkers in Multifloral Honey by Vacuum-Assisted Headspace Solid-Phase Microextraction. *Food Analytical Methods*, doi: 10.1007/s12161-023-02499-0, 1-11. doi: 10.1007/s12161-023-02499-0.

Mărgăoan, R., Topal, E., Balkanska, R., Yücel, B., Oravecz, T., Cornea-Cipcigan, M. & Vodnar, D. C. (2021). Monofloral honeys as a potential source of natural antioxidants, minerals and medicine. *Antioxidants*, 10 (7), 1023. doi: 10.3390/antiox10071023.

Martinotti, S., Bucekova, M., Majtan, J. & Ranzato, E. (2019). Honey: an effective regenerative medicine product in wound management. *Current Medicinal Chemistry*, 26 (27), 5230-5240. doi: 10.2174/0929867325666180510141824.

Mateo, F., Tarazona, A. & Mateo, E. M. (2021). Comparative study of several machine learning algorithms for classification of unifloral honeys. *Foods*, 10 (7), 1543. doi: 10.3390/foods10071543.

McArdle, C., Coyle, S. & Santos, D. (2023). The impact of wound pH on the antibacterial properties of Medical Grade Honey when applied to bacterial isolates present in common foot and ankle wounds. An in vitro study. *Journal of Foot and Ankle Research*, 16 (1), 66. doi: 10.1186/s13047-023-00653-9.

Mehanned, S. & Dehbi, A. (2022). Physico-chemical study and quality control of some types of Moroccan honey. Moroccan Journal of Chemistry, 10 (4), 10-14 (2022) 2822-2829. doi: 10.48317/IMIST.PRSM/morjchem-v10i4.34435.

Milburn, O. (2020). A taste of honey: Early medieval Chinese writings about sweeteners. *Early Medieval China*, 2020 (26), 43-66. doi: 10.1080/15299104.2020.1780740.

Mohamadzade Namin, S., Ghosh, S. & Jung, C. (2023). Honey Quality Control: Review of Methodologies for Determining Entomological Origin. *Molecules*, 28 (10), 4232. doi: 10.3390/molecules28104232.

Moumeh, B., Dolores Garrido, M., Diaz, P., Peñaranda, I. & Linares, M. B. (2020). Chemical analysis and sensory evaluation of honey produced by honeybee colonies fed with different sugar pastes. *Food Science & Nutrition*, 8 (11), 5823-5831. doi: 10.1002/fsn3.1843.

Mumtaz, P. T., Bashir, S. M., Rather, M. A., Dar, K. B., Taban, Q., Sajood, S., Ali, A., Rather, Z. A., Amin, I. & Dar, M. A. (2020). Antiproliferative and Apoptotic Activities of Natural Honey. in Rehman, M. U. & Majid, S. (eds.), *Therapeutic Applications of Honey and its Phytochemicals : Vol.1*. Singapore: Springer Singapore, pp. 345-360.

Mustafa, G., Iqbal, A., Javid, A., Manzoor, M., Aslam, S., Ali, A., Azam, S. M., Khalid, M., Farooq, M. & Al Naggar, Y. (2022). Antibacterial properties of Apis dorsata honey against some bacterial pathogens. *Saudi Journal of Biological Sciences*, 29 (2), 730-734. doi: 10.1016/j.sjbs.2021.09.059.

Mustar, S. & Ibrahim, N. (2022). A sweeter pill to swallow: a review of honey bees and honey as a source of probiotic and prebiotic products. *Foods*, 11 (14), 2102. doi: 10.3390/foods11142102.

Nalbantsoy, A., Sarıkahya, N. B., Özverel, C. S., Barlas, A. B., Kırcı, D., Akgün, İ. H., Yalçın, T., Düven, G., Kışla, D. & Demirci, B. (2022). Chemical composition and biological activities of Cypriot propolis. *Journal of Apicultural Research*, 61 (2), 233-245. doi: 10.1080/00218839.2021.1977028.

Newman, D. J. & Cragg, G. M. (2020). Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *Journal of natural products*, 83 (3), 770-803. doi: 10.1021/acs.jnatprod.9b01285.

Nong, Y., Maloh, J., Natarelli, N., Gunt, H. B., Tristani, E. & Sivamani, R. K. (2023). A review of the use of beeswax in skincare. *Journal of Cosmetic Dermatology*, 22 (8), 2166-2173. doi: 10.1111/jocd.15718.

Nweze, A., Olovo, C. V., Nweze, E. I., John, O. O. & Paul, C. (2020). Therapeutic properties of honey. *Honey Anal. New Adv. Chall*, 332, 1-21. doi: 10.5772/intechopen.86416.

Obey, J. K., Ngeiywa, M. M., Lehesvaara, M., Kauhanen, J., von Wright, A. & Tikkanen-Kaukanen, C. (2022). Antimicrobial activity of commercial organic honeys against clinical isolates of human pathogenic bacteria. *Organic Agriculture*, 12 (2), 267-277. doi: 10.1007/s13165-022-00389-z.

Oršolić, N., Kunštić, M., Kukolj, M., Odeh, D. & Ančić, D. (2020). Natural phenolic acid, product of the honey bee, for the control of oxidative stress, peritoneal angiogenesis, and tumor growth in mice. *Molecules*, 25 (23), 5583. doi: 10.3390/molecules25235583.

Osterman, J., Aizen, M. A., Biesmeijer, J. C., Bosch, J., Howlett, B. G., Inouye, D. W., Jung, C., Martins, D. J., Medel, R. & Pauw, A. (2021). Global trends in the number and diversity of managed pollinator species. *Agriculture, Ecosystems & Environment*, 322, 107653. doi: 10.1016/j.agee.2021.107653.

Özkök, A., Keskin, M., Tanuğur Samancı, A. E., Yorulmaz Önder, E. & Takma, Ç. (2021). Determination of antioxidant activity and phenolic compounds for basic standardization of Turkish propolis. *Applied Biological Chemistry*, 64 (1), 1-10. doi: 10.1186/s13765-021-00608-3.

Pascual-Mate, A., Oses, S. M., Fernandez-Muino, M. A. & Sancho, M. T. (2018). Methods of analysis of honey. *Journal of Apicultural Research*, 57 (1), 38-74. doi: 10.1080/00218839.2017.1411178.

Pashte, V. V., Pashte, S. V. & Said, P. P. (2020). Nutraceutical properties of natural honey to fight health issues: A comprehensive review. *Journal of Pharmacognosy and Phytochemistry*, 9 (5), 234-242. doi: 10.22271/PHYTO.2020.V9.I5D.12220.

Pavlin, A., Kočar, D., Imperl, J., Kolar, M., Marolt, G. & Petrova, P. (2023). Honey Origin Authentication via Mineral Profiling Combined with Chemometric Approaches. *Foods*, 12 (15), 2826. doi: 10.3390/foods12152826.

Pluta, P. & Sokol, R. (2020). Changes in the expression of antimicrobial peptide genes in honey bees (Apis mellifera) under the influence of various pathogens. *Annals of Parasitology*, 66 (4). doi: 10.17420/ap6604.286.

Qamar, W. & Rehman, M. U. (2020). Brief History and Traditional Uses of Honey. in Rehman, M. U. & Majid, S. (eds.), *Therapeutic Applications of Honey and its Phytochemicals : Vol.1*. Singapore: Springer Singapore, pp. 1-10.

Quraisiah, A., Fazalda, A., Alfizah, H. & Azlina, M. (2020). In vitro Study of Anti-Helicobacter pylori Activity of Honey: A Systematic Review. *Sains Malaysiana*, 49 (2), 411-420. doi: 10.17576/jsm-2020-4902-20.

Rahman, M., Fatima, N. & Alam, N.-E.-. (2023). Aroma Compounds. in, Honey. : John Wiley & Sons, pp. 137-151.

Rahman, M. A., Hossain, M. M. & Barman, D. N. (2023). Organic Acids in Honey. in, *Honey*. : , pp. 102-112.

Ramalingam, K. (2021). Evaluation of the Pharmacological Properties of Piscine Venoms from both Lionfish (Pterois) and Stonefish (Synanceja). *Current Enzyme Inhibition*, 17 (1), 9-15. doi: 10.2174/1573408016999201231204746.

Rane, M., Deshmukh, K., Mulik, P., Mulani, N. & Patwardhan, R. (2021). Resolving a mechanism of honey antibacterial action: Polyphenol/H. *Indian J. Applied & Pure Bio. Vol*, 36 (1), 1-10.

Rodriguez-Herrera, R., Puc, L. E. C., Sobrevilla, J. M. V., Luque, D., Cardona-Felix, C. S., Aguilar-González, C. N. & Flores-Gallegos, A. C. (2019). Enzymes in the pharmaceutical industry for β-lactam antibiotic production. in, *Enzymes in food biotechnology*. : Elsevier, pp. 627-643.

Sandhya, K. & Pai, S. (2022). A Review on Honey Contemplating Ayurvedic Emphasis Viz-A-Viz Source and Availability. *RGUHS Journal of AYUSH Sciences*, 9 (2), 1-7. doi: 10.26463/rjas.9_2_4.

Saravanan, M., Mohanapriya, G., Laha, R. & Sathishkumar, R. (2019). DNA barcoding detects floral origin of Indian honey samples. *Genome*, 62 (5), 341-348. doi: 10.1139/gen-2018-0058.

Schmidt, C., Eichelberger, K. & Rohm, H. (2021). New Zealand mānuka honey-A review on specific properties and possibilities to distinguish mānuka from kānuka honey. *LWT*, 136, 110311. doi: 10.1016/j.lwt.2020.110311.

Shah, A. & Smith, D. L. (2020). Flavonoids in agriculture: Chemistry and roles in, biotic and abiotic stress responses, and microbial associations. *Agronomy*, 10 (8), 1209. doi: 10.3390/agronomy10081209.

Shanahan, M. & Spivak, M. (2021). Resin use by stingless bees: A review. *Insects*, 12 (8), 719. doi: 10.3390/insects12080719.

Sharma, A., Pant, K., Brar, D. S., Thakur, A. & Nanda, V. (2023). A review on Api-products: Current scenario of potential contaminants and their food safety concerns. *Food Control*, 145, 109499. doi: 10.1016/j.foodcont.2022.109499.

Solayman, M. (2023) Minerals and Trace Elements. in, *Honey*. : , pp. 80-101.

Srećković, N. Z., Mihailović, V. B. & Katanić, S. J. S. (2019). Physico-chemical, antioxidant and antimicrobial properties of three different types of honey from central Serbia. *Kragujevac Journal of Science*, doi: 10.5937/KgJSci1941053S (41), 53-68. doi: 10.5937/KgJSci1941053S.

Straumite, E., Bartule, M., Valdovska, A., Kruma, Z. & Galoburda, R. (2022). Physical and microbiological characteristics and antioxidant activity of honey bee pollen. *Applied Sciences*, 12 (6), 3039. doi: 10.3390/app12063039.

Tedesco, R., Scalabrin, E., Malagnini, V., Strojnik, L., Ogrinc, N. & Capodaglio, G. (2022). Characterization of botanical origin of Italian honey by carbohydrate composition and volatile organic compounds (VOCs). *Foods*, 11 (16), 2441. doi: 10.3390/foods11162441.

Thakur, M., Gupta, N., Devi, D., Bajiya, M. R., Sharma, R. & Sharma, D. (2022) Variations in physicochemical characteristics of honey: A review. *The Pharma Innovation Journal*, 11 (7), 337-348.

Thapa, R., Aryal, S. & Jung, C. (2018). Beekeeping and honey hunting in Nepal: Current status and future perspectives. *Asian beekeeping in the 21st century*, doi: 10.1007/978-981-10-8222-1_5, 111-127. doi: 10.1007/978-981-10-8222-1_5.

Thomford, N. E., Senthebane, D. A., Rowe, A., Munro, D., Seele, P., Maroyi, A. & Dzobo, K. (2018). Natural products for drug discovery in the 21st century: innovations for novel drug discovery. *International journal of molecular sciences*, 19 (6), 1578. doi: 10.3390/ijms19061578.

Tian, X. R., Tang, H. F., Tian, X. L., Hu, J. J., Huang, L. L. & Gustafson, K. R. (2018). Review of bioactive secondary metabolites from marine bryozoans in the progress of new drugs discovery. *Future medicinal chemistry*, 10 (12), 1497-1514. doi: 10.4155/fmc-2018-0012.

Ullah, A., Aldakheel, F. M., Anjum, S. I., Raza, G., Khan, S. A. & Tlak Gajger, I. (2023). Pharmacological properties and therapeutic potential of honey bee venom. *Saudi Pharmaceutical Journal*, 31 (1), 96-109. doi: 10.1016/j.jsps.2022.11.008.

Vazhacharickal, P. J. (2021). A review on health benefits and biological action of honey, propolis and royal jelly. *J. Med. Plants Stud*, 9 (5), 1-13.

Vilas-Boas, M., Lopes, M., Nunes, L., Pereyra, A., Kunert, C., Beckh, G., Çelemli, O., Sorkun, K., Georgé, S. & Paulo, L. (2023). Assessing the performance of analytical methods for propolis–A collaborative trial by the international honey commission. *Journal of Apicultural Research*, 62 (3), 542-555. doi: 10.1080/00218839.2022.2053320.

Wang, X., Chen, Y., Hu, Y., Zhou, J., Chen, L. & Lu, X. (2022). Systematic review of the characteristic markers in honey of various botanical, geographic, and entomological origins. *ACS Food Science & Technology*, 2 (2), 206-220. doi: 10.1021/acsfoodscitech.1c00422.

Wu, Y., Liu, Q., Weiss, B., Kaltenpoth, M. & Kadowaki, T. (2020). Honey bee suppresses the parasitic mite Vitellogenin by antimicrobial peptide. *Frontiers in Microbiology*, 11, 1037. doi: 10.3389/fmicb.2020.01037.

Wyndham Lewis, S. (2021). Eva Crane: Honey, 'A Comprehensive Survey'. *Bee World*, 98 (3), 105-105. doi: 10.1080/0005772X.2020.1865626.

Yang, Q., Zhang, A.-h., Miao, J.-h., Sun, H., Han, Y., Yan, G.-l., Wu, F.-f. & Wang, X.-j. (2019). Metabolomics biotechnology, applications, and future trends: a systematic review. *RSC advances*, 9 (64), 37245-37257. doi: 10.1039/C9RA06697G.

Yilmaz, A. C. & Aygin, D. (2020). Honey dressing in wound treatment: a systematic review. *Complementary therapies in medicine*, 51, 102388. doi: 10.1016/j.ctim.2020.102388.

Zafar, M., Latafat, T., Zehra, A. & Farooqui, Y. (2020). Therapeutic properties of honey: a review of literature. *Res. Rev. A J. Pharmacol.*, 10, 41-49.

Żebracka, A., Winiarska-Mieczan, A., Nowakowicz-Dębek, B., Banach, M., Drabik, A., Pulit-Prociak, J. & Chmielowiec-Korzeniowska, A. (2022). Assessment of the microbiological quality and bactericidal properties of flavoured honey. *Med. Weter*, 78 (11), 556-562.

(2024) ; http://www.jmaterenvironsci.com