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Review

Towards a Better Understanding of Nutritional and Therapeutic Effects of Honey and Their Applications in Apitherapy

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Abstract: The nutritional and therapeutic aspects of natural products have gained more interest in recent years, owing to the importance that has been given to health and well-being. In this regard, honey represents an organic product whose high level of biologically active compounds and valuable nutrients have been extensively studied in order to prove its ability to provide an enhancement in health status. The use of honey in the process of healing or preventing certain diseases has been practiced throughout history and is now known as apitherapy. The aim of this review is to expand the knowledge and understanding towards the physicochemical characteristics of honey and the action of its main bioactive compounds towards health-beneficial properties (antioxidant, antimicrobial, antifungal, antiviral, etc.) for apitherapeutic purposes. Notwithstanding all the assets, the usage of honey for medical purposes encounters some limi-tations regarding the factors that may affect the therapeutic potential of honey in apitherapy that will be pointed out in this overview.

Keywords: honey; chemical composition; human health; nutritional value; therapeutic effects; apitherapy

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Citation: Cucu, A.-A.; Baci, G.-M.; Moise, A.R.; Dezsi, Ş.; Marc, B.D.; Stângaciu, Ş.; Dezmirean, D.S. Towards a Better Understanding of Nutritional and Therapeutic Effects of Honey and Their Applications in Apitherapy. *Appl. Sci.* **2021**, *11*, 4190. https://doi.org/10.3390/app11094190

Received: 19 April 2021
Accepted: 28 April 2021
Published: 5 May 2021

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1. Introduction

An interest in natural and quality products which have both nutritional and health benefits has manifested in the last few decades, largely due to the increased perception of the significance that well-being has on human life, especially in the wake of the COVID-19 pandemic. In light of this, the concept of "functional food", which has a variety of relevant high nutritional value components, as well as a positive impact on human physical and psychological health status [1], has gained attention. Functional food refers to all food products that have in their composition substances that confer physical health benefits, beyond the nutritional ones, and that are able to treat or prevent diseases [2].

Since honey contains a broad range of nutritional and bioactive properties owing to its high content of proteins, amino acids, simple sugars, flavonoids and phenolic acids [3,4], it can be considered as a health-supporting and functional food [5], gaining recent interest in research fields as a potential curative product. Therefore, its consumption has an upward trend because of the existing link between nutrition and health, which states that a well-balanced nutrition reduces the risk of developing certain diseases [6,7]. The key role played by food consumption in human health is also highlighted by recent studies that indicated a certain connection between different disorders and nourishment, with the most common being related to diabetes, cancer, cardiovascular and neuro-degenerative diseases or musculoskeletal disorders [8–15]. In order to keep their health balanced, consumers have become more aware of their preferences in terms of food, with honey becoming considered more than a natural sweetener with high–calorie content, but rather a product that may enhance health [16]. Thus, several studies have highlighted the focus of consumers towards products that improve well-being and that are organic-certified, sustainable, contain nutritional and medicinal properties, and environmentally friendly [17–20].

Honey can be defined as a sweet, natural and non-processed product [21], produced by honeybees from the nectar of plants or from secretions of living parts of plants which the bees collect [22,23]. The process of honey-making is a complex one due to the intense work that bees undertake after collecting the nectar. Using the enzymes of their stomach through regurgitation and their wings for humidity reduction, the bees transform the nectar in honey by breaking down sugars and by storing it in beeswax honeycombs for maturation [24,25]. Over recent years, the chemical composition of honey has been widely studied and it was revealed to contain more than 200 compounds, from which the most important are sugars (fructose and glucose). Other constituents include minerals, proteins, free amino acids, enzymes, vitamins, followed by phenolic acids; flavonoids are also present in honey composition, conferring its therapeutic effects [26]. According to some studies [9,27,28], phenolic acids and flavonoids are thought to be responsible for the health properties of honey on human health, including, but not limited to antimicrobial, anti-inflammatory, antimutagenic, antitumor, antiviral and antioxidative activity.

Honey composition depends on the botanical and geographical origin of plants [29–31], along with the environmental conditions as climate during harvest and the ability of the beekeeper to process, pack and store the honey in appropriate conditions [32,33]. The therapeutic benefits of natural foods such as honey is not a recent discovery, but rather dates back to when humankind considered some food products as having both nutritional and health benefits [2]. This is confirmed by ancient writings that reveal how bee products were used as remedies to several illnesses or for beauty purposes [34]. Historical finds and rock paintings from ancient times (the Spider Cave in Spain and ancient Egyptian temples) [6] highlight the importance that honey and other bee products had for many civilisations (Egyptians, Greeks, Romans, Chinese, Islamic, among others) in terms of prevention and treatment of a variety of diseases [35]. The term "apitherapy" derives from "apis" meaning "bee", and therapy" meaning "treatment" [36]. Despite the fact that the term was mainly used for bee venom therapy [37], thanks to several studies carried out in the last years, all bee products are now considered as having important and healing qualities, and therefore, regarded as part of an alternative and complementary medicine, namely, apitherapy. The findings reveal that honey was used especially as facilitators to wound healing [38], treating skin condition diseases [39], alleviating gastrointestinal disorders [9], and also for embalming the deceased (ancient Egypt) [25], promoting virility and longevity (ancient Greece), or regulating the body secretions or the fever [25]. The composition of different types of honey has been widely investigated [13,30,40–46], bringing into attention the potential that natural products can have on the health status of individuals. Despite all of the evidence, the use of honey in current medicine, as a complementary therapy, is continuously manifesting distrust towards both medical specialists and potential patients. Therefore, the need to clarify the potential therapeutic effects of honey, as manifest in human health via apitherapy, represents a necessity. Given the importance of natural products as promising remedies against severe diseases and ongoing contemporary disorders, the goal of this review is to identify the mechanism of action that honey has in healing or preventing different diseases. Thus, we have gathered and compared data from the relevant literature, in order to have a better understanding of whether, and how, honey could be considered a natural remedy, as well as the quality parameters that honey needs to respect for the use in apitherapy. The main databases used for this review article were Web of Science, Science Direct and Google Scholar, where the composition of honey has been meticulously covered. Our research gathered 250 articles using relevant keywords and focusing mainly on the research progress in honey composition and its applicability for human health over the last 5 years. This research highlighted honey's biological and molecular mechanisms in order to understand the importance that these constituents have on its therapeutic properties.

2. Nutritional Properties of Honey Corresponding to Its General and Specific Chemical Composition

Honey can be classified by taking in consideration the source of raw material and botanical origin. Concerning the source of raw material, according to Terzo et al. (2020) [47] we can distinguish between Honeydew, produced from secretions of living parts of plants or insect's sweet exudates [48], and Blossom honey, which is produced from the nectar of flowers. As for botanical origin, we can refer to monofloral honeys and Polyfloral honeys depending on the source of nectar collected by the bees. Considering the variety of honey sources, it is worth noting that the therapeutic properties of honey are influenced by its main constituents that are strongly related to the plants from which the pollen is taken [49], thus the large spectrum of utilisation in different medical disorders.

The complex and unique composition of honey, gathering a large number of different compounds, is shaped by various factors that are mainly related to botanical and geographical origin, while some other external variables related to climate conditions, the whole honey production process or storage can influence its chemical composition [50,51]. Moreover, soil characteristics and bee species origin can also shape the molecular parameters of honey's food matrix [52]. In order to understand their mechanism of action and their importance as fundamental constituents of honey, we have described the main compounds, outlining their chemical structures.

2.1. General Chemical Composition of Honey

2.1.1. Carbohydrates

The main carbohydrates found in honey are represented by sugars, containing 95% of the dry matter [53], and are responsible for its nutritional value. They are produced by honey bees through the enzyme invertase process, when sucrose is transformed from the collected nectar in different sugar elements [53,54] in order to bring the honey to maturity. The carbohydrates are divided into three important groups that are found in all types of honey, namely: monosaccharides, disaccharides and trisaccharides [53,55].

Monosaccharides, specifically fructose and glucose, represent 75% of the total sugars found in honey structure [32]. Disaccharides are composed by maltose, sucrose, turanose, maltulose, laminaribiose, isomaltose, nigerose, kojibiose, gentiobiose, and B-trehalose, whereas trisaccharides comprises: maltotriose, erlose, melezitose, centose 3-a5, l-kestose, isomaltosylglucose, isomaltotriose, panose, isopanose, and theanderose [56]. Furthermore, when further reviewing the composition of honey's sugars, we can also find fructo-oligosaccharides, which are an important source of prebiotics with great importance for the digestive system [57]. The most notable disaccharides are maltose and sucrose, while in terms of trisaccharides, melezitose is most commonly found in the composition of Honeydew honeys. Seraglio et al. (2019) [58] analysed samples of Honeydew honeys from Spain, Turkey, Poland, and Romania, and found they presented a melezitose concentration ranging from 0.1 to 3.2 $g/100\ g^{-1}$. Studies have revealed that the type and the concentration of sugars are the most efficient to indicate the difference between monofloral honeys [59]. For most honey types, a higher concentration of sugars is represented by fructose, (in this case we can mention Acacia honey, which has the highest amount of fructose) [60], however there are other honey varieties such as Rape, Dandelion or Blue Curls honeys, where glucose is the carbohydrate found in the greatest proportion [53]. Moreover, in their study Pauliuc et al. (2020a) [21] identified some Romanian honey samples of which the highest fructose content was identified in thyme honey (36.77%), while the highest glucose content was related to Rape honey (31.78%). Honey sugar's concentration is influenced principally by the type of flowers used by honeybees when gathering nectar, and can be affected by several external factors, with storage time and conditions being the most significant [61]. Therefore, the sugar content is considered one of the main indicators of honey's adulteration, as we later highlight.

2.1.2. Lipids

The quantity of lipids compounds present in honey is small (0.04%), comprising glycerides, sterols, and phospholipids, followed by various fatty acids including palmitic, oleic, lauric, miristic, stearic and linoleic [53]. As the lipid content of honey is essentially composed from free fatty acids, their importance for health is significant, as they play an important role in the composition of cells membranes, dictating the growth and development of the human body [62]. Even if some studies have revealed the presence of these fatty acids in pollen [63,64] there is still limited research regarding their presence in honey. However, Jarukas et al. (2021) [62], have compared the presence of fatty acids in some bee products (bee bread, bee pollen, propolis and honey), with the results showing that the quantity of fatty acids present in honey was lower than in the other three bee products.

2.1.3. Proteins

The content of protein in honey (0.5%) has been attributed to both bees and plants and it related to the enzymes and free amino acids contained in the bee's salivary glands or in the nectar and pollen of floral sources [53]. Therefore, we can distinguish between proteins originating from bees and the proteins that come from floral sources. Honey proteins that originated from bees consists of enzymes secreted from the salivary and hypopharyngeal glands of worker bees [61] during ripening, the most well-known being invertase (α-glucosidase), amylase (diastase) and glucose oxidase. Along with these enzymes, the protein content of honey is also represented by individual amino acids (around 20 aminoacids), of which proline is taught to be the most important [60] along with antimicrobial proteins such as bee-Defensine-1 and royal jelly protein [65]. Invertase is important for the sugar stability matrix, diastase is a parameter of honey freshness [66], while glucose oxidase has the role of producing hydrogen peroxide (H_2O_2), which is responsible for the antimicrobial properties of honey [55]. Proline amino acid con-centration in honey varies from 50% to 85%, and results from the salivary secretions of honeybees [9]. Besides the fact that its main role is to protect membranes and proteins from stress conditions, and therefore its role in antioxidant activity, proline is also used to evaluate the degree of honey maturation, which is an indicator of quality [59].

Several studies have analysed the protein content of various honey samples. Anand et al. (2018) [67], revealed that the protein content of the tested samples (5 types of Australian honey) varied from 900 to 2200 μg/g. Among these, *Agastache rugosa* honey had the highest protein content, while Manuka honey the lowest. A recent study [42] reviewed the chemical composition and quality parameters of Eucalyptus honey, underlining that the amount of protein found in European Eucalyptus honeys (0.9–1.24 mg/g honey), is higher compared to other honey varieties such as Orange (0.58–0.66 mg/g honey), Chestnut (0.59–0.71 mg/g honey) or Acacia (0.1 mg/g honey). Moreover, Azevedo et al. (2017) [68], observed during a comparative proteomic profiling that the content of protein in honey Blossom (0.016 g/100 g^{-1}) is lower than in Honeydew honey (0.042 g/100 g^{-1}), from the same botanical species of *Mimosa scabrella Bentham*. This latter observation can be a turning point for the assessment of the protein profile for the differentiation between various honey types.

2.1.4. Vitamins

In terms of vitamins contained in honey composition, it can be said that their main provenance is derived from the botanical origin of the pollen, nectar, and the insects' sweet exudates during the collecting period of bees [53,60]. The small concentration of vitamins includes B-complex vitamins especially [60]: thiamine (B1), riboflavin (B2), nicotinic acid (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B8 or H), and folic acid (B9), but also small amounts of tocopherol (E), anti-haemorrhagic vitamin (K), ascorbic acid (C) [47]. Even if the proportion of vitamin C in honey cannot be compared with the amount found in citrus, it is still the main vitamin found in nearly all types of honey, whose antioxidant properties have been largely studied. Karabagis et al. (2020) [43] noted a large amount of vitamin C in the content of Dryomelo honey from Greece (19.12–29.83 mg/100 g), which was lower than the content of the heather honeys of Portugal (35.66 mg/100 g) [69]. The presence of vitamin C in honeys is unstable because of its vulnerability towards chemical and enzymatic oxidation [60], and therefore its processing and storage can cause a reduction of the vitamin content [51]. Although vitamin C can rapidly oxidise, this reaction can cause the apparition of some molecules that can affect the antimicrobial activity of some antibiotics [70].

2.1.5. Minerals

In order to manifest in honey's composition, minerals have to pass through a lengthy process. Originated mainly from soil, minerals are incorporated into the plants through the roots, arriving to their last stage with the aid of honey bees that collect the raw material for the honey-making process [71]. However, minerals may also appear due to environmental pollution or beekeeping extraction methods in particular [72]. The main mineral elements found in honey are: potassium (K), sodium (Na), calcium (Ca) and magnesium (Mg), followed by iron (Fe), cop-per (Cu), manganese (Mn), chlorine (Cl) [53]. Only small quantities of boron (B), phosphorus (P), sulfur (S), silicon (Si), Barium (Ba), and nickel (Ni) can be found in honey. All of these minerals are important for the human diet, as they play a key role in the metabolic functions of the human body [58] by maintaining normal physiological responses, influencing the circulatory and reproductive systems acting as catalysts in various biochemical reactions [59].

The mineral content of honey is different in Blossom honeys (0.1–0.2%) than in Honeydew varieties (1%) [41]. One of the representative minerals in honey is K, standing for 80% of the total [72], followed by P, Ca, Mg, Na, Fe. Studies reported data regarding the existence of K as the main mineral present in honey samples from Turkey [73], Serbia [74] or Morocco [13].

Since minerals can indicate the botanical origin of a specific honey, several studies have aimed to classify honey's botanically origin by taking into consideration their trace elements profile. Even if almost all minerals are part of honey's chemical structure worldwide, Cl has been detected only in honey samples from Spain [75]. Moreover, Karabagias et al. (2018b) [76] analysed different varieties of honey samples from different parts of Cyprus, Greece and Egypt. They identified a vast range of trace elements, the major found in the three areas were P and Ca. While P was significant for the Greece region, Ca was found in higher proportions in Egyptian honey samples.

Fe is another important element for the human physiological processes. Its concentration has been revealed in honey samples from Serbia, with Acacia having the highest content of Fe (mean value 1.24 mg/kg). Similar results were reported for Croatian honeys [77], where the highest Fe concentration was observed for rapeseed honey (mean value 3.14 mg/kg), whereas for Romanian honey samples were observed higher ranges of Fe (11.35–54.78 mg/kg) [21,78]. Some studies have been reported the presence of heavy metals, such as Pb and Cd or toxic elements (Cr and As) in Honeydew honey samples, but their manifestation was determined by environmental contamination, fertiliser treatments, or incorrect procedures during processing and honey storage [58]. However, European Commission Regulations [79] established the maximum level of Cd and Pb in honeys (0.1 mg/kg). Cadmium was detected, among others, for Croatian [77], Iranian [80] and Romanian [78] honeys samples: 0.239–2.53 μg/kg, 1.36–125.88 μg/kg and 0.5–11.60 μg/kg, respectively. Due to the low concentration in minerals, honey cannot be considered a reliable source of these nutrients.

2.2. Specific Chemical Composition on Honey

2.2.1. Phenolic Compounds

Phenolic compounds are bioactive substances that can be found in honey, and it has been demonstrated that they play an essential role in honey's antioxidative, anti-inflammatory and antibacterial properties, among others [73,81], thus possessing beneficial effects for human health. These compounds are secondarily metabolised by plants in order to gain protection against biotic and abiotic stress and oxidative damage and are subsequently transferred into honey via nectar. Therefore, their composition is dependent mainly on the botanical source, the geographic origin, climate conditions, season [82] or even the floral preference of each bee species at the time of collecting food (nectar or exudate) [83]. However, there are some other external factors which they are subjected to that can have a considerable influence on the composition of these bioactive compounds, with the analytical methods used for their quantification, particularly high-performance liquid chromatography (HPLC), being the most relevant [42].

Phenolic compounds can be classified into different classes according to their chemical structure: phenolic acids, including phenolic esters, and flavonoids [84]. The most important phenolic acids found in honey are hydroxybenzoic acids (gallic acid, benzoic acid, vanillic acid) and hydroxycinnamic acids (caffeic acid, p-coumaric acid, ferulic acid and cinnamic acid), each one having a different chemical structure [85].

In addition to the phenolic acids found in honey, flavonoids can be sub-divided into other groups depending on their structural complexity. In this regard, we can discuss flavonols (such as myricitin, galangin, quercetin, rutin and kaempferol), flavones (such as chrysin, tectochrysin, luteolin and apigenin), flavanols (such as cate-chin), flavanones (such as hesperetin, naringenin, pinocembrin and pinobanksin), isoflavones, anthocyanins and chalcones [53].

Various authors have studied the profile of phenolic compounds in honey. Pauliuc et al. (2020b) [86] analysed the total phenolic content (TPC) of various Romanian honey samples: Raspberry, Mint, Thyme, Rape, Sunflower and Polyfloral, and noticed that the TPC varied between 18.91 mg GAE·100 g^{-1} for Thyme honey, and 23.71 mg GAE·100 g^{-1} for Mint honey. Some phenolic compounds were described as possible tool markers classification and authentication for different honey types, monofloral honeys in particular [87]. Among them, gallic acid (361.81 µg 100 g^{-1}), was reported as the most frequent phenolic compound found in mononfloral honeys [88]. Moreover, studies showed that quercetin could be attributed for sunflower honey [61], while other research [27] revealed that quercetin is related to Romanian Rape honey. Conversely, rutein was observed in greatest proportion in Chinese Acacia honey (3825 µg/100 g^{-1}) [89].

2.2.2. Volatile Compounds

Monofloral honeys acquire particular volatile compounds from the flower's nectar such as different aromas, fragrances or even pharmacological properties, which transform it into a highly demanded product by consumers [90].

To date, the most relevant volatile aromatic compounds identified in different honey types are aldehydes, ketones, acids, alcohols, esters, linear hydrocarbons, and cyclic compounds [52], which exhibit a great importance in terms of contribution to the quality of aroma and fragrance found in honey [91]. These volatile compounds are taught to be related to the other substances present in the floral source [48], therefore, their chemical volatile composition is of great importance in indicating honey's botanical source [92].

An increasing interest in volatile substances is underlined throughout studies that have described the volatile profile of different monofloral honeys, trying to find a correlation between the presence of some volatile substances and the botanical origin of flowers and plants. Demir et al. (2021) [93] indicate the presence of both isovaleric acid and 2-aminoacetophenone in the chemical composition of several chestnut honey samples from Turkey. Moreover, some authors have indicated the presence of methyl anthranilate and sinensal isomers only in citrus honey samples, although cis-linalool oxide, nonanol, and decanal were related to Acacia honey [60]. As for Honeydew, Gerhardt et al. (2018) [94] proposed 3-hydroxy-2-butanone, trans-2- pentenal, and 3-methylbutanol as indicators of Honeydew honeys, after analysing various samples of European honeydews. Another finding was reported by Pita-Calvo et al. (2016) [95] where the presence of several volatile compounds (3-hydroxy-2-butanone, 2,3-butanediol, 1-hydroxy 2-propanone and 1-(2-furanyl)-ethanone) was used to distinguish Honeydew honey from Blossom honey.

It is important to mention that volatile compounds status can change according to some actions involved in honey storage and/or processing. In this regard, knowledge of reactions that may occur during the storage period is essential in order to avoid a negative impact on honey's sensory properties.

3. Physicochemical Properties of Honey

3.1. Colour

The colour of honey is a particularly important parameter, possessing a great impact on product price and consumer's choice. It has been stated that the colour of honey is related to its flavour [96,97], with dark honeys bring more intense in terms of taste. In addition, dark tones of honey have been associated with a higher phenolic and mineral concentration [75,98]. With this said, we can easily assume that the dark coloured honeys have a higher antioxidant activity than the light coloured honeys [99]; even if honey's colour is mainly influenced by the botanical origin of flowers [5], it can undergo colour changes during storage owing to non-enzymatic browning reactions, particularly the Maillard reaction [100], where different compounds such as furfural and 5-HMF are formed [32], contributing to the honey-browning process. Pauliuc et al. (2020a) [21] analysed 45 samples of honey from different regions of Romania and reported values between 29.4 and 74.3 mm Pfund, with the colour varying from white (Rape honey), extra light amber (sunflower honey, thyme and Polyfloral) and light amber (Mint and Raspberry honey). Additionally, some authors have reported that colour associated with other physicochemical parameters can act as indicators for differentiation between mixed flora honeys, or even between Honeydew and Blossom honey. In this regard, Szabo et al. (2016) [101] indicated that the average of Lightness (L) value was 51.34 mm Pfund in chestnut honeys and 34.7 mm Pfund in mixed flower honeys. Moreover, the colour parameters of the honey analysed by Oroian et al. (2017) [100] showed that the highest values of Lightness (L*-translucent) were for Acacia and Tilia honeys, while the lowest values (L*-dark) were determined for Honeydew honeys. Similar results were found for Spanish [102], Serbian [41] and Greek honeydews [43].

3.2. Moisture and Water Content

Water is one of the principal constituents found in honey, the proportion of which is determined by several factors including geographical and floral origin of the collected nectar, pedoclimatic conditions, season of harvesting, and maturation degree. The most influential of these being the manipulation by beekeepers during harvest, extraction, processing, as well as storage conditions [53]. An important study [103] reported the moisture content for mint and thyme honey samples of Tunisia, which ranged between the value of 19.8% (mint) and 18.16% for thyme honey. These results are similar to the values reported for Romanian samples [86] which revealed a moisture content between 17.36% (thyme honey) and 17.77% (mint honey). All honey samples had moisture contents in the limits established by the European legislation (maximum 20%) [104]. On the contrary, some studies have found honey samples that did not fulfil the limits imposed by the European Union, as seen in the case of Italian citrus honey, where the water content was established at 20.56% [105]. When honey samples do not meet the criteria of maximum 20% moisture, they can become susceptible to deterioration, as the yeast and different bacteria found originally in honey can ferment [74]. Water activity (aw) depends on carbohydrate composition (glucose/fructose content), but also on environmental conditions [100], as it is used to predict moisture exchange with the environment, thus the low water activity values present in honey, ranging from 0.562 to 0.62 [106]. Even if at the European level no limits were established for the water activity standards, it is well-known that, depending on the quantity of water present in honey's composition, the growth/limitation of different microbial organisms that may appear throughout the fermentation process can be influenced [107]. As a consequence, the so-called osmotic pressure that determines the loss of water inside the bacteria is produced, which causes the cells to dehydrate and thus being unable to grow and proliferate [108]. Colour, crystallisation, flavour, viscosity, density [53] or solubility and conservation [32] can also be affected by water content. As honey has a tendency to absorb airborne humidity, beekeepers should pay special attention during honey processing in order to avoid extra moisture content and thus bacterial activity.

3.3. Organic Acids, Acidity and pH

Even if organic acids are present in honey's composition in small quantities (less than 0.6%), their importance is still critical for some of its physicochemical parameters such as flavour, colour and preservation [53,109]. Depending on the amount of acids contained within it, honey has the ability to prevent microorganisms developing [110–112], and thus the presence of acids as an indicator for honey's authenticity and quality [113–115]. Literature shows that plants can be considered the foremost source of organic acids present in honey [116,117] other than the enzymes secreted by the bees during the honey process making [61]. In this sense, organic acids are often used to determine the botanical origins of honey [32,109]. Many authors have identified the profile of organic acids in various honey samples through analytical methods such as high-performance liquid chromatography, enzymatic determination, or capillary zone electrophoresis with direct ultraviolet detection [88,112,118–120], leading to up to 32 compounds. The most common organic acids present in honey's composition are acetic, butyric, citric, formic, fumaric, glyoxylic, propionic, lactic, maleic, malic, gluconic, pyroglutamic, oxalic and succinic acids among others [53,60,61]. Gluconic acid is considered the main organic acid present in honey's composition, its proportion representing 70–90% of the total [42,110,112]. Apart from gluconic acid, citric or malic acids are also part of honey's composition [32,120] their concentration being an indicator of discrimination among Blossom and Honeydew honey [43,118,121], the latter suggesting a higher concentration of these organic acids [50,102,122]. The presence of organic acids in correlation with other compounds such as esters, lactones and inorganic ions, determines the free acidity of honey [54]. This parameter, when determined, can evaluate the freshness of honey and the degree of possible fermentation [43,123]. The recommended value for free acidity, as imposed by the European regulations, is 50 mEq/kg [86]. If values are higher, it is an indication of incipient sugar fermentation, leading to the presence of acetic acid, formed by alcohol hydrolysis [61,103,123]. The pH is another parameter for the determination of acidity, and its value can vary according to the honey extraction and storage conditions [59,86]. Honey pH should be situated between 3.2 and 4.5 in order to avoid microorganism contamination [124]. Various honey samples from different geographical regions have been analysed in order to determine their acidity. For Acacia honey, the pH reported had similar values in Romania [123], Italy [105] and Serbia [74], respectively 3.94, 3.92 and 3.99. Moreover, the pH for thyme honey in Romania had much the same values as in Tunisian samples [86].

3.4. Ash Content and Electrical Conductivity

The ash content in honey directly correlates with its mineral content, which as seen previously, can be influenced by the same class of determinants that are related to all honey compounds. Its values range, according to [61], is between 0.02 and 0.3%. For the time being, the determination of the ash content in honey has been replaced by another physicochemical parameter, namely electrical conductivity, due to its ability to detect smallest changes in mineral levels [58]. In addition, electrical conductivity (EC) can be used for the classification of various types of honey in accordance with their botanical origin and purity, describing the amount of minerals and other trace elements contained in honey's composition [43,46].

In-line with the European regulations, honey's electrical conductivity should not exceed 0.8 mS/cm [104]. Studies from Turkey related that for chestnut honey, values of electrical conductivity ranged between 559.30 and 714.06 µS/cm [93], respectively. These values of are in conformity with previous studies made in Portugal [69].

It has been stated that an electrical conductivity of less than 0.8 mS/cm is associated to Blossom honey, contrary to what a higher value could indicate in Honeydew honey [46]. Studies from Greece [43], Italy [105], Romania [100], Serbia [41], and Spain [102] have shown that Honeydew honeys have electrical conductivity values higher than Blossom honeys.

In order to understand the liaison between the various compounds aforementioned and the therapeutic properties that they can induce in honey, a continuous investigation of the botanic origin of plants is still needed.

4. Therapeutic Effects of Honey

The structural characteristics along with other heterogeneous compounds that can be found in honey's composition, are indicated to be a rich source of biologically active substances [53] that are essential for its specific and distinct therapeutic properties. Honey's therapeutic properties have drawn a great deal of attention recently, and therefore its applicability using in-vitro and in-vivo models has been widely investigated, as we review below. However, these biologically active compounds can vary depending on several factors. Therefore, in order to validate honey as an effective drug in medical practice and apitherapy in particular, it is required to have laboratory analyses that can certify the quality of its compounds.

4.1. Antioxidant Effects

The positive therapeutic effects of honey are mainly associated with its antioxidant capacity [125]. This property is related to the inhibition of free radicals that are responsible for the oxidative reactions inside the human body [126] that can damage the cells and cause various disorders [127].

The chemical compounds found in honey, such as phenolic compounds, organic acids, amino acids, carotenoids, proteins, Maillard reaction products or enzymes (glucose oxidase, catalase) are considered crucial contributors to this property [53,128]. Therefore, these antioxidant elements found in honey are thought to be nutritional supplements against oxidative stress [129], improving the formation of stable molecules and neutralising the negative mechanism of the reactive oxygen and nitrogen species [9]. In this regard, several honey varieties, including Buckwheat honey and Manuka honey, have demonstrated strong capacities to prevent oxidative damage [130,131].

Nevertheless, the phenolic compounds are the most representative antioxidants [126], as several authors have proven a high correlation between the phenolic content and this biological property. For instance, Boussaid et al. (2018) [103] observed some positive correlations between the antioxidant activities and the total polyphenol ($r = 0.945$, $p < 0.01$), total flavonoids ($r = 0.866$, $p < 0.01$), and between total flavonoids and total polyphenols ($r = 0.957$, $p < 0.01$). These results are in agreement with those reported for Brazilian honey samples [88] that reveal the connection found between antioxidant activity and the content of phenolic compounds is very strong.

Since the phenolic content of honey derives mainly from the nectar of the plants that bees feed on [46], we can infer that the antioxidant capacity of honey depends strongly on the botanical origin of plants [35,89,132]. Further evidence shows that the antioxidant capacity is also correlated with the honey colour intensity stating those darker-coloured honey possesses higher antioxidant properties and therefore a higher phenolic content [29,133]. However, other factors including environmental and seasonal conditions, processing methods, packaging and storage conditions, can influence the antioxidant ability of honey and contribute to its changes [53,60].

Considerable studies regarding the antioxidant activity of various types of honey have been carried out worldwide, as illustrated in Table 1.

Table 1. Antioxidant effect of honey.

Geographical Origin	Honey Type	Analytical Method/Unit	Values/Unit	Reference
China	*Amorpha fruticosa* L. honey	DPPH (IC_{50})	100.41 ± 15.35 mg/mL	[59]
Romania	Thyme Mint Raspberry Sunflower Polyflower	DPPH assay	67.3% 74.03% 79.05% 68.03% 70.7%	[21]
	Heather			[134]
	Honeydew	DPPH assay FRAP assay DPPH assay (IC_{50})	4.39 mmol Trolox/g 10.92 µmol Fe^{2+}/g 3.93 ± 0.6%	[135]
Iran	Saffron Sunflower	DPPH assay FRAP assay	82.4 ± 7.4% 1247.5 ± 13.5 µM 45.77 ± 2.16% 309.7 ± 24.1 µM	[29]
Serbia	Acacia honey Polyforal honey Forest honey	ABTS assay DPPH assay	26.72 ± 0.99 mg Trolox/kg honey 8.36 ± 0.42 mg Trolox/kg honey 37.02 ± 0.86 mg Trolox/kg honey 11.97 ± 0.35 mg Trolox/kg honey 594.77 ± 38.30 mg Trolox/kg honey 260.77 ± 0.45 mg Trolox/kg honey	[136]
Brazil	*Eucalyptus* spp. Polyfloral	ORAC assay DPPH assay (EC_{50}) FRAP assay	3.41–18.48 µmol ET/g honey 25.4–105.3 mg/mL honey 0.4–2.11 µmol ET/g honey 2.8–10.10.68 µmol ET/g honey 37.6–139.07 mg/mL honey 0.5–1.76 µmol ET/g honey	[88]
Turkey	23 monofloral honey samples	(a) TPC assay (b) DPPH assay (c) FRAP assay (d) β-Karoten assay	(a) 470.70 ± 7.43 and 34.37 ± 0.44 mg/100 g GAE (b) 29.07 ± 1.42 mg/mL (c) 0.0022–0.0091 mg/100 g honey (d) 32.09 and 94.87% OE	[137]
	Acacia Astragalus Heather Rhododendron	DPPH assay (EC_{50}) FRAP assay	152.40 ± 62.004 mg/mL 0.64 ± 0.34 µmol $FeSO_4 7H_2O$/g 123.56 ± 25.12 mg/mL 0.66 ± 0.74 µmol $FeSO_4 7H_2O$/g 27.84 ± 13.20 mg/mL 1.42 ± 0.28 µmol $FeSO_4 7H_2O$/g 78.06 ± 28.65 mg/mL 0.67 ± 0.22 µmol $FeSO_4 7H_2O$/g	[98]
Italy (Sicily)	Dill *Eucalyptus globes* Ferula	DPPH assay FRAP assay	114.2–238.4 µmol ET/100 g 159.3–173.6 mg AAE/100 g 180.6–194.3 µmol ET/100 g 62.8–75.2 mg AAE/100 g 114.2–150.4 µmol ET/100 g 93.7–110.2 mg AAE/100 g	[138]
India	*Sesamum indicum*	DPPH assay (EC_{50}) FRAP assay	39.5 ± 0.4 mg/mL honey $2.75 \times 10^6 \pm 4.8$ µmol Fe(II)/L	[139]

DPPH, 1,1-diphenyl-2-picrylhydrazyl radical assay; FRAP, Ferric Reducing Antioxidant Power; ORAC, Oxygen Radical Absorption Capacity; β-Karoten assay, croton or β-carotene bleaching; ABTS, Radical cation (2,2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid)).

The methods used for the measurement of honey's antioxidant capacity, such as 1,1-diphenyl-2picrylhydrazil (DPPH), Oxygen Radical Absorbance Capacity (ORAC), Ferric Reducing Antioxidant Power (FRAP), Radical cation (2,2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid)) (ABTS) or the croton or β-carotene bleaching [140] are also summarised

(Table 1). Because of the diversity of assays employed and geographical origins, the outcome showed high variability in the antioxidant activities of the analysed samples, underlining once again the dependence on the botanical source.

As shown in Table 1, Heather honey had different values in the study from Romania, compared to the study in Turkey [98], the latter reporting the highest DPPH radical scavenging activity, while Dezmirean et al. (2015) [134] observed a higher value of the FRAP assay. Analysing the same honey type (in 30 samples), Moise et al. (2013) [141] noticed an average antioxidant activity of 56% by using a DPPH test.

Conversely, Chiș et al. (2016) [135] and Pauliuc et al. (2020a) [21] examined other Romanian honey samples that overall exhibit lower antioxidant activity when compared to Brazilian Eucalyptus and Polyfloral honeys. Both Can et al. (2015) [98] and Srećković et al. (2019) [136] determined the antioxidant activity for Acacia from the DPPH assay in a study on honey samples from Turkey and Serbia, respectively. Contrary to the antioxidant activities of Acacia honey in Turkey, Serbian Acacia honey exhibited lower antioxidant activity. Sicilian honeys (Dill, Eucalyptus Globes and Ferula) as described by Attanzio et al. (2016) [138] are characterised by an antioxidant activity higher than the values identified in *Amorpha fruticosa L.* honey from China [59], but not lower than the average of monofloral honey samples from Turkey [137]. As for Iranian honeys, [29] it was reported that saffron honey had the highest percentage inhibition, whereas the lowest was found in Polyfloral honey.

Based on current knowledge, honey, because of its high content of antioxidants can protect the human body from the damaging effects of free radicals and thus helps to prevent the onset of some chronic diseases (cancer, cardiovascular diseases, diabetes, obesity etc.) [50,142].

4.2. Antibacterial Effects

Another popular and complex biological property of honey with high therapeutic value (as manifest in in-vivo and in-vitro studies) is its antibacterial ability. Factors influencing this derive mainly from the botanical source of the plants, bee metabolism [111], bee species [143] and the climatic, processing and storage conditions that honey is submitted to [51,58]. All of these factors have a critical importance for the inhibition of the structure and growth of microorganisms, influencing the physicochemical composition of honey and the mechanism of action of different bioactive compounds.

In general, the antibacterial and antimicrobial activity of honey is related to the inhibition of microbial growth throughout different processes [39]. One process is associated to the enzymatic action, namely hydrogen peroxide (H_2O_2), and the other is related to the action of different compounds, such as the high content of sugars, viscosity, osmotic pressure and low pH [26], water activity or protein content [106,144]. In addition, polyphenols, phenolic acids, flavonoids, together with antioxidants, lysozyme, methylglyoxal, and bee peptides (especially the peptide Defensin-1) [134,145] are other vital components of this property.

The H_2O_2 is shaped by the oxidation of glucose throughout the action of the enzyme glucose oxidase during honey maturation [42] and then hydrolysed by catalase to water and oxygen [146]. Its main function is to prevent the spoilage of honey caused by microorganism's action [53] by producing minimum inhibitory concentrations in bacteria (10–1000 μg/mL) [51,146] and thus damaging the bacterial cell walls [147].

Conversely, methylglyoxal is formed non-enzymatically from nectar dihydroxyacetone [39,51] and it is found mainly in Manuka honey, where it is predominantly responsible for Manuka honey's antibacterial properties [148,149]. This is achieved through its mechanism of action: inducing alterations in the structure of bacteria, and therefore preventing it to damage the cell membranes [150].

The bee Defensin-1 is an antibacterial peptide secreted by the bees [151], added into honey at the beginning of its processing [51]. It has been reported to be effective against both Gram-positive and Gram-negative bacteria [152], especially in wound healing [153], while also exhibiting a large spectrum of anti-biofilm activity [154,155].

Studies that have evaluated the antibacterial potential of honey showed that the bioactive compounds found in honey's composition manifest in a direct correlation with the antimicrobial effects of honey [73,156,157]. Therefore, the antibacterial activity of honey may vary according to the geographical and botanical origin of the raw material [158–160], as the content of polyphenols can influence its beneficial health effects [144]. Literature reports that phenolic compounds have a well-structured antibacterial mechanism [28], as they are capable to diminish antibiotic resistance of infective bacteria and to prevent biofilm formation [161]. The outcomes indicated that the antimicrobial potential of several phenolic compounds present in various honey samples had a significant impact against microorganism inhibition. Wang et al. (2018) [162] reported through in-vitro and in-vivo analyses that quercetin has bacteriostatic effects against Gram-positive bacteria (*Staphylococcus aureus* in particular). Similar results were reported by Anand et al. (2019) [163], who demonstrated that the same kind of bacteria was susceptible to all analysed honey samples (concentrations ranging from 3.12 to 25% w/v) that contained a high amount of phenyl lactic acid and 4-hydroxybenzoic acid. Interestingly, the study of Majtan and al. (2020) [164] revealed how vitamin C supplementation can amplify the antimicrobial potential of honey against *Pseudomonas aeruginosa* and *Escherichia coli* in a dose-dependent manner, but also against *Staphylcoccus aureus* and *Enterococcus faecalis* at a higher concentration of vitamin C (100 mg/g honey).

However, the antimicrobial and antibacterial effects of honey are a result of the symbiosis of all these factors [143], especially between hydrogen peroxide and phenolic substances, since the presence of hydrogen peroxide alone is not considered sufficient to demonstrate antibacterial effects in honey [165]. Other studies have shown, similarly, that the content of H_2O_2 cannot necessary be correlated with the antibacterial activity, as some honey varieties with high antibacterial potential had a low content of H_2O_2 [81,166,167]. As a result, even if the presence of H_2O_2 is compulsory for antibacterial activity, some other compounds play a key role in increasing this healing potential [168]. Moreover, the bee Defensin-1 is reported to have the same synergistic antibacterial effect with H_2O_2 [65] as it cannot neutralise the presence of bacteria alone. A recent study revealed the antibiofilm activity of Eucalyptus honey depends on the combined action of osmotic activity, H_2O_2 and Def-1 [108].

The antibacterial mechanism of various honey types against the most common types of Gram-positive (*Bacillus cereus*, *Enterococcus faecalis*, *Listeria monocytogenes*, *Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella enterica Serovar Typhimurium*, *Salmonella enteritidis*, *Salmonella Typhi*, *Salmonella Typhimurium*) or yeast (*Candida albicans*) have been widely described in Table 2, along with the most recurrent methods to determine the minimum inhibitory concentrations (MIC), the minimum bactericidal concentration (MBC).

The results of antibacterial activities in honey samples investigated from different geographical areas and having different botanical origins have shown variable antibacterial effects against the tested bacteria in the presence of differing concentrations of honey. Among all tested bacteria, the most sensitive strains were *S. aureus, B. cereus ATCC 14579, L. monocytogenes ATCC 7644* (Gram-positive) reported in Bucekova et al. (2019) [81], Dezmirean et al. (2015) [134] and Cilia et al. (2020) [145], while the most resistant Gram-positive bacteria were *S. aureus ATCC 25923 and S. aureus CCM 4223* in Đogo Mračević et al. (2019) [41] and Cilia et al. (2020) [144].

Table 2. Antibacterial effect of honey.

Geographical Origin	Honey Type	Analytical Method/Unit	Sample	Values/Unit	Reference
Ukraine	*Brassica* spp. *Helianthus* spp. *Robinia* spp.	Microdilution method	(a) *S. aureus—CCM 4223* (b) *L. monocytogenes—ATCC 7644* (c) *Sal. enterica Serovar Typhimurium—CCM 3807* (d) *E. coli—ATCC 25922*	(a) 0.188–0.375g/mL MIC (b) 0.188g/mL MIC (c) 0.188–0.375g/mL MIC (d) 0.375g/mL MIC (a) 0.094–0.375g/mL MIC (b) 0.094–0.375g/mL MIC (c) 0.094–0.375g/mL MIC (d) 0.188–0.375g/mL MIC (a) 0.188–0.375g/mL MIC (b) 0.188–0.375g/mL MIC (c) 0.188–0.750g/mL MIC (d) 0.188–0.750g/mL MIC	[144]
Serbia	Linden Honeydew Acacia	Microdilution method	*E. coli—ATCC 25922* *S. aureus—ATCC 25923* *C. albicans—ATCC 10231*	46.1–92.2% MIC 0.01–39.7% MIC 0.01–44.8% MIC 5.0–40.3% MIC 39.7–67.7% MIC 0.01–12.2% MIC 68.1–70.0% MIC 21.8–63.0% MIC 0.01–13.8% MIC	[41]
Slovakia	Wildflower honeys (WH) Acacia honeys (AH) Rapeseed honeys (RH)	MIC method	*S. aureus—CCM4223* *P. aeruginosa—CCM1960*	WH > AH > RH MIC < 20%	[81]
China New Zealand	Buckwheat honey (BH) Manuka honey (MH)	Agar well-diffusion method Broth microdilution method	*S. aureus* *P. aeruginosa*	<5–60% *w/v* honey no inhibition for both samples 70–80% *w/v* honey BH>MH 90–100% *w/v* honey MH>BH (a) > (b) (22.5%) MICs for both honey samples	[169]
Iran	*Eucalyptus* spp.	Disc-diffusion method	*E. faecalis—ATCC 11700* *S. aureus—ATCC 25923* *E. coli—ATCC 25922* *P. aeruginosa—ATCC 27853*	12.0–15.0 mm IZ 10.0–11.0 mm of IZ 8.0–9.0 mm IZ <7.00 mm IZ	[157]
India	Sesamum indicum honey	Agar well-diffusion method	*E. coli* *S. Typhi* *S. Typhimurium*	15 mm MIC 12.5 mm MIC 12.5 mm MIC	[139]
Romania	Heather honey	Disc-diffusion	*S. aureus—ATCC 6538P* *B. cereus—ATCC 14579 P* *E. coli—ATCC 10536* *P. aeruginosa—ATCC 27853* *Sal. enteritidis ATCC—13076* *Sal. typhi—ATCC—14028*	9–11mm IZ 9–11 mm IZ 9–11 mm IZ 10–12 mm IZ 10–12 mm IZ 9–10 mm IZ	[134]

ATCC, American Type Culture Collection; IZ, Inhibition Zone; MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration.

Conversely, for Gram-negative bacteria, the most resistant were *E. coli, Sal. typhi ATCC 14028, P. aeruginosa ATCC 27853* and *P. aeruginosa CCM1960* related to Das et al. (2015) [139], Dezmirean et al. (2015) [134], Leyva-Jimenez et al. (2018) [157] and Bucekova et al. (2019) [81], whereas the most susceptible Gram-negative strains were manifested in the studies of Leyva-Jimenez et al. (2018) [157] (*E. coli ATCC 25922*) and Đogo Mračević et al. (2019) [41] (*E. coli ATCC 25922*).

Given the importance that antibiotic resistance of bacteria shows lately, honey can be considered an alternative antibacterial agent [170]. Furthermore, side effects of honey utilisation as complementary therapy should be still investigated within in-vivo studies [46].

4.3. Antifungal Effects

In addition to its antibacterial properties, honey also exhibits antifungal activity. Fungi are taught to be more pathogenic than bacteria, and therefore their resistance to antifungal drugs is more complex and requires new treatment approaches. Recently, the shift towards natural products and their promising antifungal effects has gained more attention, with honey being considered a viable solution in this regard [171].

As shown in the previous chapters, the large variance of therapeutic effects of honey is due to both its physicochemical characteristics and biological compounds. Several studies have reported that the high sugar content can act as an inhibitor of fungi growth through the osmotic pressure [172]. Moreover, the variety of other substances contained in honey, namely phenolic compounds, play a key role in its antifungal effects [173]. These compounds have the ability to denature proteins and therefore the membranes of cells through the alteration of their stability [174]. It is well-known that the phenolic composition of each honey type depends on the botanical and geographical origin of collected plants, and thus various honey types can have a different outcome when it comes to antibacterial and antifungal properties [175,176]. Indeed, Kalakattawi et al. (2019) [177] reported that the presence of gallic acid and quercetin in different Saudi honey samples proved to have antifungal effects by inhibiting *Candida albicans (C. albicans*) strains. Moreover, in this same study, the free acidity content was correlated with the highest *Candida* inhibition effect, thus highlighting the importance of acids in influencing the antifungal effect of honey.

Another study emphasised the antifungal activity of Manuka honey, stating that its chemical composition, mainly the presence of polyphenols such as gallic acid, caffeic acid, and quercetin, has a strong resistance to fungal strains [178]. These data were in accordance with other reports that have evaluated the antifungal activity of Manuka honey, where its main component, namely methylglyoxal, was predomenantly responsible for the high inhibition of fungal strains [148,172,177]. Fernandes (2020) [179] presented the results of various Portuguese honeys (Chestnut, Eucalyptus, Orange Blossom, Rosemary and Heather) against several pathogens (clinical isolates and reference strains of *Candida* species). It was concluded that among all honey samples, Portuguese heather honey had the higher phenolic and flavonoids content and thus exhibited the higher antifungal activity against the tested microorganisms. Furthermore, this variety of honey is considered to be a biofilm reducer for *Candida* species at concentrations that range between 50% and 75% (w/v). Further relevant academic work has suggested that the production of H_2O_2 is critical for the antifungal activity of honey, but still not sufficient, as its level in honey's composition was too low to manifest a potent activity against some pathogenic fungi [180]. This can lead us to the conclusion that there are other compounds that act may as enhancing factors for the observed antifungal activity. This notwithstanding, it was demonstrated that the inhibition degree on several pathogenic microorganisms depends on various honey concentrations, as observed in Tualang, Acacia and Kelulut honey against *C. albicans* and *Aspergillus niger* (5–25% v/v) [181]. In general, the outcomes suggest that the antifungal effects are intensified with an increased honey concentration [176,182]. It is important to note that recent advances in research showed how medical-grade honey could be considered a promising alternative for antifungal treatment against *Candida auris* and other *Candida* species [183].

4.4. Antiviral Effects

Even if the antiviral activity of honey has not been extensively studied, its mechanism of action is explained by the existence of various compounds (cooper, ascorbic acid, flavonoids, and H_2O_2) that are able to inhibit the viral growth through the interruption of viral transcription and replication [56].

The antiviral potential of honey can be related to some specific pathways including nitric oxide (NO), which is a molecule that has proved beneficial activities in viral infections [184] by both decelerating the spread of viral lesions and arresting their replication [185].

The available data suggest that flavonoids may have a significant contribution in the antiviral activity, due to their effectiveness against several viruses such as herpes simplex virus (HSV), Coxsackie B virus [186], syncytial virus, poliovirus, and Sindbis virus [60]. Among the flavonoids, quercetin exhibits a high therapeutic potential against viral infections, particularly against respiratory viruses such as influenza A virus strains, acting as an inhibitor for the viral infiltration into cells with half-maximal inhibitory concentration (IC50) [187]. Moreover, honey in combination with ginger and garlic has been described as having positive outcomes for antiviral activity [188]. Other studies have identified that various honey varieties (Manuka, Soba, Kanro, Acacia, and Renge) have antiviral effects towards influenza A virus, by using Madin–Darby canine kidney (MDCK) cell line [189]. The same study observed that MGO found in Manuka honey enhanced its abilities to stop the growth and reproduction of viruses, thus manifesting a higher sensitivity against influenza viruses than the other honey samples. The same Manuka compound was found to act in a combined effort with antiviral drugs [190].

Other comprehensive analyses have proven the efficacy of Manuka and Clover honey varieties in fighting against varicella-zoster virus (VZV) in human malignant melanoma cells [191], while Kanuka honey acted as a broad-spectrum antiviral agent for the treatment of herpes simplex virus, being able to replace the traditional treatment with acyclovir [192,193]. Regarding the Human Immunodeficiency Virus (HIV) Wan Yusuf et al. (2019) [194] have investigated the properties of Malaysian Tualang honey, showing its inhibitory effects on infected patients by reducing the viral load and improved the quality of life of these cases.

4.5. Other Honeys Properties Valuable for Apitherapy

In addition to the aforementioned biological activities, honey has some other important therapeutic effects proven by different in-vivo and in-vitro studies. For instance, honey exhibits anticancer effects against different carcinoma cells by means of different pathway mechanisms, such as inhibition of cell migration, cell arrest action and apoptotic induction [195,196]. The most representatives studies in this regard were focused on breast [197–199] and colon [40,200,201] cancer activity that different honey varieties exert, namely Acacia, Manuka, Tualang and Gelam honey types.

Moreover, honey has proven its ability to reduce the nephrotoxicity of cisplatin in patients with cancer that introduced into their diet 80 g of honey daily [202]. Additionally, Al-Ghamdi and Ansari (2021) [170], showed that Saudi honeys, including Sidr and Sumra varieties, exert immunomodulatory properties by measuring the interleukin 6 and nitric oxide levels in the PC-3 cells.

Promising results regarding the anti-inflammatory effects of honey were reported by Kamal et al. (2021) [46] who reviewed that Tualang and Gelam honeys can reduce the inflammatory cells in various related disorders.

The anti-diabetic activity of honey was demonstrated by its potential to reduce the concentration of sugars in blood that are caused by the lack or low amount of insulin production in the body [10]. Several studies in this direction [203–205] suggested the protective effects on diabetes by producing insulin signalling pathway mechanisms and thus assuring a better glycaemic control. Moreover, the consumption of honey was described to be beneficial for obesity-related derangements in both animal and human studies [206–208].

Research has revealed that honey has a protective effect for the cardiovascular system by preventing the oxidative stress process of blood vessels, improving the plasma lipid constituents and attenuating elevation of heart function marker [209–211].

In addition, the neuro-protective activity of honey and its constituents against neurodegenerative disorders (Parkinson Alzheimer, multiple sclerosis, dementia, among others) was proven by numerous works [212,213]. Studies have shown that these disorders are correlated with the inflammation of nerve cells, and thus honey is well placed to prevent it through the protection from oxidative stress, as well as the improvement and regeneration of neurons [87]. Additionally, the consumption of honey can reduce the anxiety and enhance the memory performance [214].

Some specific research considers that honey may be an ideal remedy against gastrointestinal disorders, especially ulcers [131], as well as in respiratory [215] and allergic [216] dysfunctionalities.

Finally, the positive effects on reproductive system were outlined for different honey varieties, Tualang and Kelulut honey in particular [217,218]. Overall, the results from animal studies suggest that honey can be included in future analyses in order to see its potential as an alternative to hormone replacement therapy for postmenopausal women [46,219].

5. Authenticity, Processing and Adulteration for Apitherapy Use

Because of its importance in terms of nutritional value and therapeutic effects, honey can be submitted to various fraud modalities in order to increase its production at lower price [53,220]. Therefore, there is a need for an increased European quality control approach, using safety protocols and standards that can guarantee its quality so as to be available for the purpose of apitherapy.

The authenticity of honey can be assured by taking into consideration physicochemical properties and the obtaining, processing and storage conditions [32]. Moreover, other parameters can also affect the quality of honey, including the geographical origin of plants, harvesting period, correct labelling and the contaminant remnants [53,221]. Currently, there have been several recognised quality standards, as listed in both the European Council Directive 2001/110/EC [104] and the Codex Alimentarius Standard for Honey (2001) [222]. These quality standards refer to the maximum content of various parameters (water content, pH, electrical conductivity, 5-hydroxymethylfurfural (5-HMF) content, diastase activity, colour, reducing and non-reducing sugars) [33,124] suggested for consumption and market purposes [168], as described in previous sections. These parameters can reveal useful information regarding the raw material origin and thus finding discriminating marker compounds for various unifloral honey varieties [52] or chemical parameters for distinguishing Blossom honey from Honeydew honey [33,41,43,58,100,223] as has been previously reported.

Moreover, it is well-known that honey undertakes important composition changes during storage, due to the chemical reactions that occur in the presence of high temperature or long preservation conditions [9]. Among these reactions, 5-HMF and diastase [224] are considered key elements for the indication of honey freshness [88,225,226] or possible adulteration with inverted sugars [9]. Furthermore, the 5-HMF content in honey is established by the Codex Alimentarius Standard Commission (5-HMF in honey at 40 mg/kg and 80 mg/kg for tropical origin honeys).

Different methods are used for analysing the composition of honey and identifying its authenticity, including physicochemical parameters assay [51], using linear discriminant analysis (LDA) [227] or carbon isotope ratios and trace elements [228] and pollen analysis (melissopalynological analysis) [100,229]. Other modern assets available for honey authentication are the chemometric procedure [224,230], mass spectrometry [231,232], high-performance liquid chromatography (HPLC) [233,234], spectroscopy (UV visible), near-infrared (NIR) [114,225], gas chromatography coupled with mass spectrometry (GC-MS) [235,236] or nuclear magnetic resonance (NMR) [237,238]. However, in the majority of cases, when evaluating the authenticity and traceability of honey samples, combined analytical methods are employed by using various clustering and classification algorithms [22,220].

Regarding processing beekeepers perform several activities that include extraction by pressing and centrifugation, filtration or storage [239] in order to produce commercial honey. During these procedures, the production and characteristics of honey can be modified. Based on this, beekeepers should follow some rules of good apicultural practices during all honey processing phases, as suggested by Bogdanov et al. (2005) [240] or more recently by Bett (2017) [241]: personal hygiene and cleanness in the extraction room, equipment, instruments used, containers or surfaces that come into direct contact with honey; compatible materials for containers and processing equipment in order to avoid contamination (Cu, Fr, Zn or steel should be avoided as materials). An important aspect to consider regarding the beekeeper's management for assuring a high quality in honey is the avoidance to use drugs or chemicals that are banned or have restricted use at European level [242,243]. These antibiotics and drugs are used to treat the honeybee colony for various diseases or pest control [244]. Recently, Blaga et al. (2020) [245] have investigated the antifungal residues present in Romanian honey samples by using high-resolution mass spectrometry, where the most present was enilconazole, followed by metalaxyl, penconazole and propiconazole among others.

Another major source of contamination in honey are pesticides that are governed by regulation (EC) No. 396/2005 [246] in which values have been established for maximum residue levels (between 10 to 50 mg/kg in honey). The use of these products on the environment can affect both the bees and their products, and consequently can become a threat for consumer's health [244]. For instance, Basa Cesnik et al. (2019) [247] found the presence of amitraz, coumaphos, thymol and thiacloprid in conventional and organic honey samples from Slovenia, while for the studies carried on in Israel [248], the same residues were found in higher concentration. In the same study [248], an analysis was conducted on the trace element residues, underlining the presence of Cr, which had the highest mean concentration (65.1 μg/kg), followed by Zn (54.1 μg/kg) and Mn (43.4 μg/kg). For both studies, the quantified levels of residues were in accordance with the European regulation.

As for adulteration in honey, it should be noted that the common methods used for this purpose include artificial and over feeding of bees with sucrose, artificial addition of high fructose corn syrup (HFCS) and rice syrup, and mislabelling of botanical, entomological, and geographical origin [27,220]. In light of the current research, Yan et al. (2021) [249] detected the adulteration of Acacia honey with high fructose corn syrup (HFCS) by determining the α-Dicarbonyl compound (3,4-DDPS). Using ion-mobility mass spectrometry coupled with UHPLC-MS/MS, the authors indicated that the 3, 4-DDPS can be used to identify the adulteration of Acacia honey with a concentration of 20% HFCS. The results were in accordance with the studies performed by Geană et al. (2019) [123].

The use of these methods has the advantage to increase the apparent value of honey and decrease its production cost [120], providing the producers with economic gains [250]. However, the disadvantages cannot be ignored, namely the negative impact on the bioactive and curative properties of honey along with the toxic effects that can be observed in human health [248].

Hence, determining the quality parameters of honey and therefore its expected therapeutic properties requires performing qualified laboratory analyses that can suggest whether a honey variety can meet the required quality conditions for human consumption and apitherapy use. In addition, correct labelling can be viewed as a quality guarantee for consumers and as a sign of origin, authenticity and prestige for producers [250].

6. Conclusions

Honey has in recent years gained an enormous interest because of its nutritional and therapeutic properties. Its composition and, in particular, its biologically active compounds have been extensively studied and proved to be responsible for the nutritive profile and main therapeutic activities of honey.

The goal of this review was to provide a better understanding towards the mechanism of action that honey exhibits in healing or preventing certain disorders by bringing into attention its efficiency and potential applicability for medical use (apitherapy). Focusing on the recent published data, we have described the wide range of therapeutic effects exerted by honey, emphasising mainly its antioxidant, antibacterial, antifungal and antiviral properties. In addition, we have underlined the negative impact that contaminants and other substances used to adulterate this functional food may have on its bioactive and curative properties, as well as on human health. Therefore, in order to establish the quality parameters that honey needs to adhere to for human consumption and use in apitherapy, certified laboratory analyses are mandatory.

Even if apitherapy is still not supported by enough evidence-based medicinal clinical trials, it can be used as a promising supportive therapy for a variety of different diseases, not to mention its potential as a reliable source of energy. However, further preclinical and clinical investigations on the matter must be performed in order to assess the potential of honey as a novel drug agent for human health.

Author Contributions: All authors contribute equally at the manuscript preparation. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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