Received: 25 October 2022 / Accepted: 12 February 2023 / Published online: 28 February 2023

DOI 10.34689/SH.2023.25.1.030

UDC 615.035.1

REVIEW OF ANTIMICROBIAL PROPERTIES OF HONEY CHEMICAL CONSTITUENTS - PART I

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Summary

Introduction. From the perspective of biochemistry, honey is the multi-component solution with the unique healing properties. The application of medical honey preparations in clinical medicine, particularly for skin disorders and wound healing, might be attributed to the antimicrobial activity of honey.

Objective. The current review's objective is to describe the data that currently exists for the antibacterial properties of certain phytochemicals found in honey.

Search strategy: The following databases were searched for sources: Pubmed, ResearchGate, Cyberleninka, and eLibrary. Research on humans and animals, primary studies (descriptive and analytical studies, clinical trials), secondary studies (systematic reviews and meta-analyses), instructional manuals, clinical guidelines and protocols, and full-text publications in both Russian and English were the inclusion criteria.

Results and Conclusion. The antibacterial properties of honey can be explained by some physical and chemical parameters such as its high osmolarity, acidity (pH 3.4-6.1), hydrogen peroxide activity, high concentration of sugar. There is the growing evidence that the antimicrobial characteristics of honey are strongly associated with the content of the different minor components including bee defensin-1, flavonoids, and polyphenols. Methylglyoxal contained in Manuka honey of New Zealand origin is one of the most investigated phytochemicals in that light. However, the antibacterial activity of other honey constituents against the Gram-positive and Gram-negative microorganisms is the meaningful aim of multiple studies.

Keywords: *honey, antibacterial, 3-phenyllactic acid, p-coumaric acid, phloretin.*

Резюме

АНТИМИКРОБНЫЕ СВОЙСТВА ХИМИЧЕСКИХ КОМПОНЕНТОВ МЕДА - ЧАСТЬ I. ОБЗОР ЛИТЕРАТУРЫ

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Введение. С точки зрения биохимии мед представляет собой многокомпонентный раствор с уникальными целебными свойствами. Применение медицинских препаратов меда в клинической медицине, особенно при кожных заболеваниях и заживлении ран, можно объяснить антимикробной активностью меда.

Цель настоящего обзора — описать имеющиеся в настоящее время данные об антибактериальных свойствах некоторых фитохимических веществ, содержащихся в меде.

Стратегия поиска. Поиск источников проводился в следующих базах данных: Pubmed, ResearchGate, Cyberleninka, eLibrary. Включены исследования на людях и животных, первичные исследования (описательные и аналитические исследования, клинические испытания), вторичные исследования (систематические обзоры и метаанализы), методические пособия, клинические руководства и протоколы, а также полнотекстовые публикации на русском и английском языках.

Результаты и заключение. Антибактериальные свойства меда можно объяснить некоторыми физико-химическими показателями, такими как его высокая осмолярность, кислотность (pH 3,4-6,1), активность перекиси водорода, высокое содержание сахара. Появляется все больше доказательств того, что антимикробные свойства меда тесно связаны с содержанием различных второстепенных компонентов, включая пчелиный дефенсин-1, флавоноиды и полифенолы. Метилглиоксаль, содержащийся в меде манука новозеландского происхождения, является одним из наиболее изученных фитохимических веществ. Однако антибактериальная активность других компонентов меда в отношении грамположительных и грамотрицательных микроорганизмов является значимой целью многочисленных исследований.

Ключевые слова: *мед, антибактериальный, флавоноиды, фенольные кислоты.*

Түйіндеме

БАЛДЫҢ ХИМИЯЛЫҚ ҚҰРАМАНДАРЫНЫҢ МИКРОБҚА ҚАРСЫ ҚАСИЕТТЕРІНЕ ӘДЕБИЕТ ШОЛУ - І БӨЛІМ

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Кіріспе. Биохимия тұрғысынан бал – бірегей емдік қасиеті бар көп компонентті ерітінді. Балдың емдік препараттарының клиникалық медицинада, әсіресе тері ауруларында және жараларды емдеуде қолданылуын балдың микробқа қарсы белсенділігімен түсіндіруге болады.

Бұл шолудың **мақсаты** - балдағы кейбір фитохимиялық заттардың бактерияға қарсы қасиеттері туралы қазіргі уақытта қолда бар деректерді сипаттау.

Іздеу стратегиясы. Дереккөздер келесі мәліметтер базасында іздестірілді: Pubmed, ResearchGate, Cyberleninka, eLibrary. Адам мен жануарларды зерттеу, бастапқы зерттеулер (сипаттамалық және аналитикалық зерттеулер, клиникалық сынақтар), қосымша зерттеулер (жүйелі шолулар және мета-талдаулар), әдістемелік нұсқаулықтар, клиникалық нұсқаулар мен хаттамалар, орыс және ағылшын тілдеріндегі толық мәтінді басылымдарды қамтиды.

Нәтижелер мен қорытынды. Балдың бактерияға қарсы қасиеттерін оның жоғары осмолярлығы, қышқылдығы (pH 3,4-6,1), сутегі асқын тотығының белсенділігі, қанттың жоғары болуы сияқты кейбір физикалық және химиялық көрсеткіштермен түсіндіруге болады. Балдың микробқа қарсы қасиеттері әртүрлі кішігірім компоненттердің, соның ішінде ара дефенсин-1, флавоноидтар мен полифенолдардың мазмұнымен тығыз байланысты екендігі туралы деректер өсуде. Жаңа Зеландиядан шыққан манука балында кездесетін метилглиоксал ең көп зерттелген фитохимиялық заттардың бірі болып табылады. Дегенмен, балдың басқа компоненттерінің грам-позитивті және грам-теріс микроорганизмдерге қарсы бактерияға қарсы белсенділігі көптеген зерттеулердің маңызды мақсаты болып табылады.

Түйін сөздер: *бал, бактерияға қарсы, флавоноидтар, фенол қышқылдары.*

Bibliographic citation:

Kassym L.T., Kussainova A.A., Adilgozhina S.M., Kozhakhmetova D.K., Zhokebaeva M.S., Zhagiparova Zh.A., Derbisalina G.A. Review of antimicrobial properties of honey chemical constituents - part I // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2023, (Vol.25) 1, pp. 262-270. *doi 10.34689/SH.2023.25.1.030*

Касым Л.Т., Кусаинова А.А., Адильгожина С.М., Кожахметова Д.К., Жокебаева М.С., Жагипарова Ж.А., Дербисалина Г.А. Антимикробные свойства химических компонентов меда - часть I. Обзор литературы // Наука и Здравоохранение. 2023. 1(Т.25). С. 262-270. *doi 10.34689/SH.2023.25.1.030*

Касым Л.Т., Кусаинова А.А., Адильгожина С.М., Кожахметова Д.К., Жокебаева М.С., Жагипарова Ж.А., Дербисалина Г.А. Балдың химиялық құрамандарының микробқа қарсы қасиеттеріне әдебиет шолу - I бөлім // Ғылым және Денсаулық сақтау. 2023. 1 (Т.25). Б. 262-270. *doi 10.34689/SH.2023.25.1.030*

Introduction

The medical and cosmetical use of honey had been well described since ancient times. Different forms of honey were used as healing remedies or beauty products for skin and scalp care. The cosmetic use of honey was described in manuscripts of Greek and Roman philosophers, and collections of religious texts and writings [14]. Traditionally, different honey products are utilized for several medical problems such as acute cough or pain reduction in pediatric otolaryngology or diet modifications in patients with cardiovascular or neurological disorders [49]. However, the overwhelming number of honey use practices are defined in dermatology and wound healing areas [29]. Probably this pattern of medical use of honey is predetermined by its potential efficacy and close link between honey application and reduction of wounds. Reduction of edema, inflammation, postoperative adhesion, and pain; stimulation of regeneration, promotion of collagen synthesis and vascularization, facilitation of debridement and greater wound contraction, wound deodorization are the most investigated and most reported wound healing properties of honey [7]. Even minimal inhibitory concentration of standardized honeys (below 11%) are efficient against various pathogens found in infected wounds [39]. Also honey and its products demonstrated immunomodulatory properties acting as stimulant for pro-inflammatory and anti-inflammatory cytokine secretion in skin immune cells [36].

Extended systematic review including numerous comparative studies which were aimed to find the impact of honey on wound healing was performed by Jull et al. in 2015. The authors found that the use of honey dressings promotes markedly the healing of burns in comparison with conventional dressings. Also, they reported the similar reduction in the overall risk of adverse events with honey relative to silver sulfadiazine. Honey healed infected post-operative wounds more quickly than antiseptic washes; healed pressure ulcers more quickly than saline soaks; and healed Fournier's gangrene more quickly than EUSOL (Edinburgh University solution of lime) soaks [28]. The use of honey in clinical dermatology is not limited with wound healing only. Anti-inflammatory and antioxidant properties of honey might be utilized for the treatment of chronic inflammatory skin conditions and some cutaneous infections. For instance, the series of studies with the use of honey from UAE conducted by Al-Waili demonstrated efficacy of honey constituents for the treatment of atopic dermatitis, psoriasis, diaper dermatitis, fungal infections, seborrheic dermatitis and dandruff, and recurrent herpes simplex [3-6]. Braithwaite et al. conducted the randomized controlled trial revealing the efficiency of topical 90% medical-grade kanuka honey in treatment of rosacea [12]. Alangari et al. (2017) reported the significant improvement of atopic dermatitis lesions in 14 patients after one-week course with manuka honey application. Additionally, authors found that manuka honey significantly downregulated chemoattractant of eosinophils to the site of inflammation in a dose-dependent manner [1]. Also, kanuka honey was successfully used for the treatment of premalignant skin condition – actinic keratosis in 66 years old male patient [38]. Furthermore, there is a range of *in vitro* and *in vivo* studies which demonstrate the anti-carcinogenic activity of honey constituents. The inhibition of proliferation and induction of apoptosis in melanoma cell lines were shown for manuka and acacia honeys [21,46]. However, there is a lack of secondary studies summarizing the antimicrobial properties of some honey phenolic acids and flavonoids. Thus, aim of current review is to describe the existing evidence of the antibacterial characteristics of the selected honey phytochemicals

Search strategy. Both the Pubmed (https://www.ncbi.nlm.nih.gov) and ResearchGate (https://researchgate.net) databases were thoroughly searched for English-language literature. For the search and collecting of publications in Russian and Kazakh, two scientific electronic libraries - eLibrary (https://elibrary.ru) and cyberleninka (https://cyberleninka.ru/) - were also employed.

The following terms were retrieved using MeSH (NLM controlled vocabulary thesaurus) in accordance with the purpose of the literature review, and a search strategy was created using the AND/OR/NOT logical operators:

1) honey;
2) phenolic acids;
3) flavonoids;
4) 3-phenyllactic acid;
5) p-coumaric acid;
6) phloretin;
7) antibacterial, antimicrobial.

Full-text publications in English and Russian, animal and human trials, primary data (descriptive and analytical studies, randomized and non-randomized clinical trials), secondary data (systematic reviews and meta-analyses), instructional methodological manuals, clinical guidelines, protocols, and recommendations were the aspects we looked for when including data in our search. In addition to materials available in digital format, the review includes information from the available printed versions of chapters of textbooks and monographs. The initial search and selection of articles was performed independently by two co-authors (L.K. and A.K.). Subsequentially, we screened for titles and abstracts and excluded all articles that did not meet the inclusion criteria. Finally, we selected 50 publications in English which were analyzed for the present literature review.

Results and Discussion

Honey's constituents and their healing properties

Chemically, honey is a multicomponent solution with unique properties. Honey major principles include as follows highly concentrated sugars such as fructose (~38.2%), glucose (~31.3%) and sucrose (1%), and water (17%). These elements are approximately consistent among the honeys of different origin. The minor components are highly variable; their qualitative and quantitative features vary regarding to geographical area and floral source. Numerous minor compounds include proteins and amino acids (up to 0.5%), organic acids and vitamins (including A, B2, B6 and C), enzymes (including diastase, invertase, glucose oxidase, and catalase), carotenoid derivatives, minerals, flavonoids, and polyphenols [35]. Some effects on skin are documented or presumed for honey compounds. For instance, the moisturizing and humectant properties are related to the high sugar content in honey whereas nourishing phenomenon might be explained by the presence of some vitamins and minerals [14]. The multiple studies conducted with some standardized honeys identified minimum inhibitory concentration (MIC) values for a range of species of microbes found in infected wounds: *Staphylococcus aureus (S. aureus)*, various coagulase-negative *Staphylococci*, various species of *Streptococci*, various species of *Enterococci, Pseudomonas aeruginosa, Escherichia coli (E. coli), Klebsiella oxytoca*, and a spectrum of anaerobes. And interestingly, in all reports, MIC measurements were defined to be less than 11%. It means that even heavily diluted honey may save its potent antimicrobial properties enough to inhibit the growth of pathogens [39]. Antimicrobial effects of honey can be attributed to numerous physical and chemical characteristics (Figure 1) [2]. Firstly, high osmolarity of honey inhibits bacterial growth in wound. However, the high content of sugars is not enough for antibacterial function. The low acidity (pH 3.4-6.1) is another factor of antimicrobial activity of honey. Thirdly, hydrogen peroxide produced by honeybee in the process of glucose oxidation is also known as the antimicrobial agent [37,13].

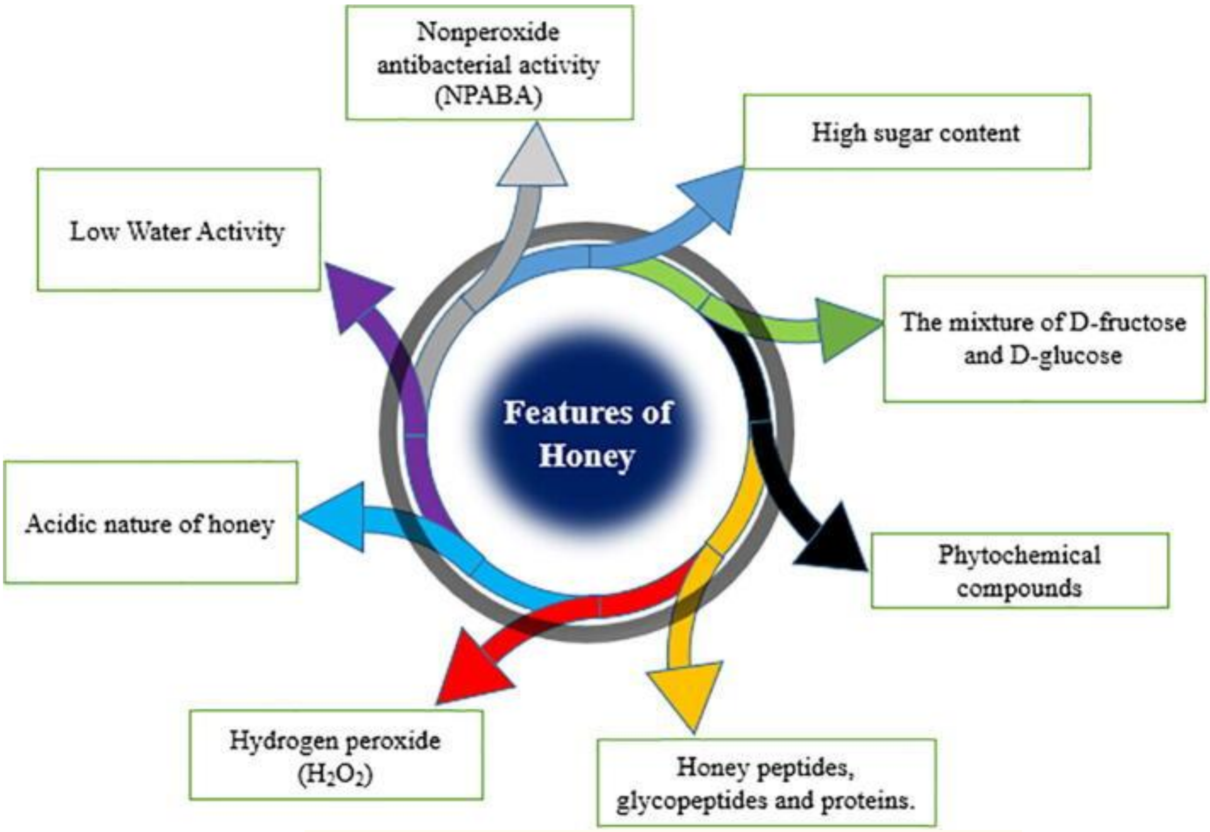

Figure 1. The parameters that contribute to the antimicrobial potential of honey.
(Adapted from "The antibacterial activities of honey," by Almasaudi, 2021, *Saudi journal of biological sciences*, 28(4), p. 2189. doi:10.1016/j.sjbs.2020.10.017)

Some honey-specific compounds may demonstrate bacteriostatic and bactericidal properties. For example, bee-derived defensin-1 was defined as the effective antibacterial peptide against some Gram-positive and Gram-negative species including pathogens grown in biofilms [54]. But in some cases, the antibacterial capacity of honey is not related to sugar concentration or the amount of hydrogen peroxide production. Manuka honey is well-described for the levels of phenolic acids, flavonoids and other constituents which contribute widely to its' antibacterial activity. The main antibacterial compound of Manuka honey is methylglyoxal (MGO) [27]. The remarkably abundant compound of MGO correlates greatly with antibacterial activity of Manuka honey and is used commercially as so-called Unique Manuka Factor (UMF) [23]. Thus, the polyphenolic composition (non-peroxide antibacterial compounds) of honey and other bioactive compounds may explain the antimicrobial functions of honey. Viana et al. reported that the antimicrobial activity of Aroeira honey against *E. coli* and *S. aureus* might be explained by the presence of different non-peroxide agents including phenolic acids and flavonoids [56]. Cianciosi et al. (2018) described the chemical structure, functions, anti-inflammatory and antiproliferative properties of wide spectrum of phenolic compounds such as *p*-coumaric acid contained in Manuka, Acacia, Tualang, and other honeys [17]. Kum et al. demonstrated that phloretin, a polyphenol found in some types of honey, suppresses the growth of *Propionibacterium acnes, Propionibacterium granulosum*, and *Staphylococcus epidermidis* with different MIC levels. Additionally, a clinical trial conducted in 30 volunteers showed the reduction of acne vulgaris severity after 4-week treatment course of phloretin [31]. Recently, Scepankova et al. (2021) described the multiple biomedical effects of honey which may contribute significantly to the treatment of wounds (Figure 2). Particularly, antimicrobial, anti-inflammatory, and antioxidative properties of honey are strongly associated with the phenolic compounds [50].

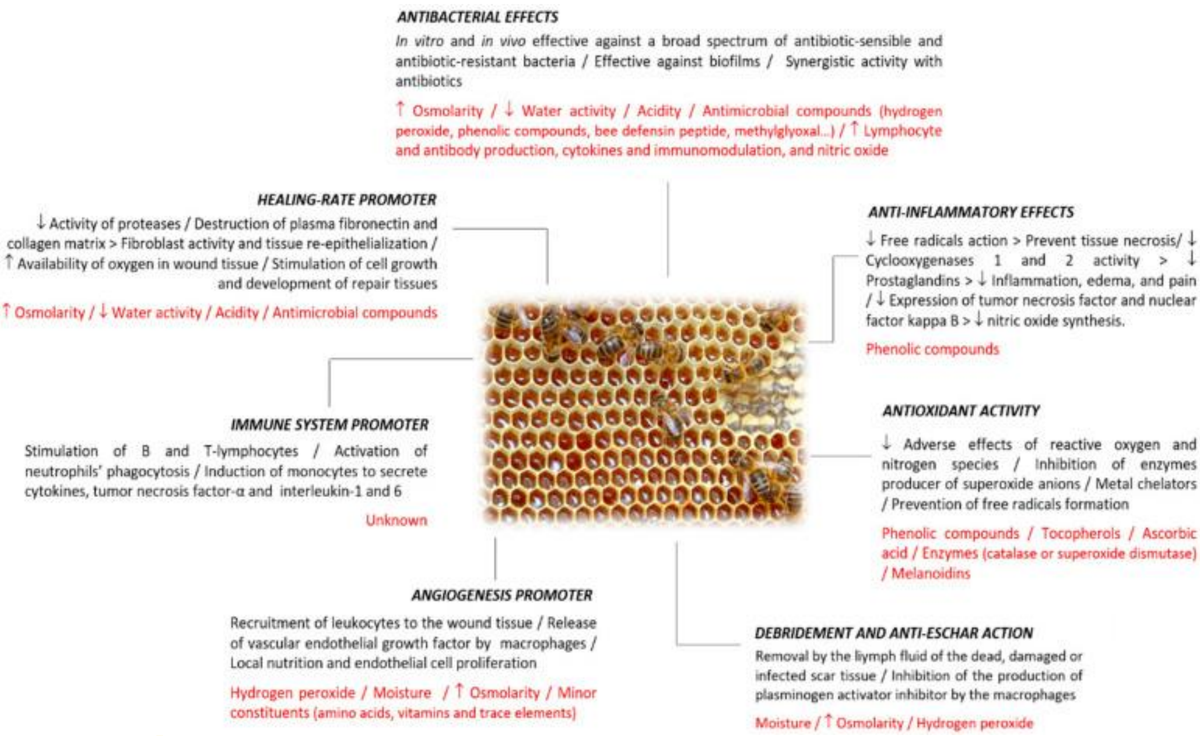

Figure 2. Wound healing mechanisms described for honey, different effects related to each mechanism, and the compound(s) or honey characteristics associated with the mechanism.
(Adapted from Scepankova H., Combarros-Fuertes P., Fresno J.M., Tornadijo M.E., Dias M.S., Pinto C.A., Saraiva J.A., Estevinho L.M. (2021). Role of Honey in Advanced Wound Care // *Molecules (Basel, Switzerland)*, *26*(16), 4784. https://doi.org/10.3390/molecules26164784)

The characteristics of 3-phenyllactic acid

3-phenyllactic acid (PLA) (2-hydroxy-3-phenylpropanoic acid or β-phenyllactic acid; (**Figure 3**) is an organic acid, which can be synthesized through the reduction of phenylpyruvic acid by lactate dehydrogenase of lactic acid bacteria (LAB) [64]. PLA was found widely in several types of honey, especially its concentration was high in heather and manuka honey [19]. Also, PLA has been found in fermentation products using LAB as a starter [56].

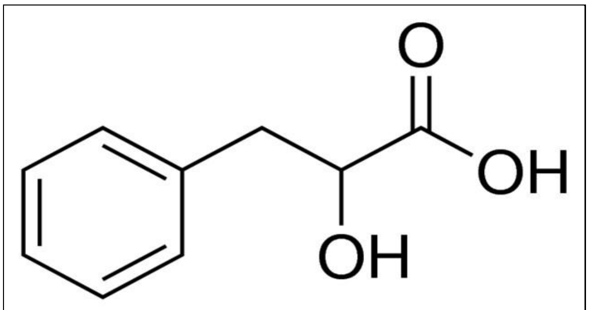

Figure 3. The skeletal formula of 3-phenyllactic acid.
(Adapted from https://www.chemsrc.com/en/cas/828-01-3_78162.html)

According to the current data, 3-phenyllactic acid has a wide spectrum of antimicrobial and antimycotic action [40]. Based on these effects, PLA is considered a good candidate for use as a chemical preservative in the food industry [63]. In the earliest studies of the antibacterial activity of PLA, its D-PLA isomer have higher antilisterial activity than its L-PLA isomer. The authors also proved that PLA is able to inhibit the growth of *Listeria monocytogene*s in the culture medium, milk, and cheese [18]. In addition, PLA can inhibit several Gram-positive bacteria such as *S. aureus, Enterococcuss faecalis*, *Bacillus cereus,* and some Gram-negative bacteria, namely *Salmonella enterica*, *E. coli*, *Providencia stuartii*, and *K. oxytoca* [42]. The mechanism of the antibacterial action of 3-phenyllactic acid is still being studied. Thus, Ning et al. (2017) using flow cytometry analysis stained with propidium iodide, showed that PLA can damage the integrity of the *L. monocytogenes* membrane, and the uptake of 1-N-phenylnaphthylamine indicated that PLA impairs the permeability of the *E. coli* outer membrane. Fluorescent analyzes have shown that PLA can interact with bacterial genomic DNA in an intercalation manner. This finding proposed dual antibacterial targets of PLA, namely membrane and genomic DNA [41].

Antifungal activity of PLA is also well described in the various studies. For instance, Schwenninger et al. (2008) demonstrated the inhibitory properties of PLA against some types of yeast, such as *Candida pulcherrima*, *Candida parapsilosis*, and *Rhodotorula mucilaginosa* [51]. In other studies, authors have proven the antifungal activity of PLA against a large type of mold isolated from bakery products, flour, and cereals [22,48]. However, the contribution of PLA to the inhibition of fungal growth on bread remains unclear. Gerez et al. (2009) suggested that antifungal activity of PLA depends on its acidity. The antifungal activity of the PLA increases at low pH, because in this way there is more undissociated acid that can migrate through the cytoplasmic membrane of the fungus [23].

Moreover, PLA can also be used as a substitute for antibiotics in poultry and livestock feed. For example, Wang et al. (2009) described the positive effects of this additives on the immune system of laying hens, which increased production performance and egg quality [59]. In another study, PLA improved growth rates and reduced the yellowing of the meat of feed chickens [58].

The characteristics of *p*-coumaric acid

p-Coumaric acid (*p*-Hydroxycinnamic acid, (Figure 4) is the representative of phenolic acids mainly found in dried fruits, berries, nuts, herbs, and olive oil. The daily intake of phenolic acids around 200 mg/day might be covered by the consumption of abovementioned food products or dietary supplements as green tea or grape extracts [32]. According to Dimitrova et al. (2007) the mean content of *p*-coumaric acid in honey ranges from 0.22 to 3.39 mg/kg [19].

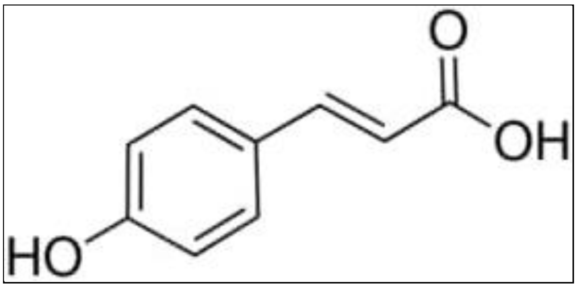

Figure 4. The skeletal formula of p-Coumaric acid.
(Adapted from https://www.chemsrc.com/en/cas/7400-08-0_946915.html)

p-Coumaric acid is well-known with the multiple biological activities. Generally, phenolic acids are a group of natural antioxidants with medical and cosmetic effects. They may act as direct antioxidants; but there is the evidence of the indirect way of activity by stimulation of endogenous protective enzymes and signaling pathways [55]. These mechanisms make *p*-coumaric acid useful in reducing the oxidative stress in skin cells [52,45]. From the perspective of anti-age activity *p*-coumaric may act also as the effective photo-protective factor. The antimelanogenic effect of *p*-coumaric acid might be explained with the structural similarity to L-tyrosine [11].

Another potential clinical use of *p*-coumaric acid is associated with its' anti-inflammatory properties. *p*-Coumaric acid reduces TNF-α expression in the synovial tissue of adjuvant-induced arthritic rats [47]. Furthermore, *p*-coumaric acid demonstrates several anticancer effects including slowing the cycle progression of cancer cells and promotion of apoptotic mechanisms in malignancies [26,25].

p-Coumaric acid also shows antimicrobial activity explained with several mechanisms of action. Firstly, phenolic acids damage the bacterial cell wall by affecting the rigidity and alternating the dynamics of phospholipid bilayer membrane [44]. This process linked directly to the increase of membrane permeability and leakage of cytoplasmic compounds. In addition to the loss of the barrier function of cell wall *p*-coumaric is able to affect the DNA of microbes. Lou et al. (2012) reported the efficiency of *p*-coumaric acid in inhibition of growth of gram-positive and gram-negative bacteria. Besides the descripted mechanism of bacterial wall damage, they found that the minimal inhibitory concentration values ranging from 10 to 80 mg/ml were able to bind to the phosphate anion in DNA double helix and intercalate the groove in DNA double helix [34].

The characteristics of phloretin

Phloretin (Dihydronaringenin, 3-(4-Hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl) propan-1-one, (Figure 5), a natural dihydrochalcone flavonoid which widely distributed in the leaves, bark, and fruit of apple trees [15]. The production of flavonoids in apples is associated with the protection of the plant from environmental influences, such as ultraviolet radiation [65]. Phloretin is a polyphenol without the heterocyclic C ring and the a-b double bond. This structure makes it a very flexible molecule, which is able to bind efficiently with biological macromolecules [9]. These interactions and block/activation of intracellular signaling pathways give rise to great pharmacological activities of phloretin, such us antibacterial, antiviral, antifungal, anti-inflammatory, antioxidant, and anticancer [33,16].

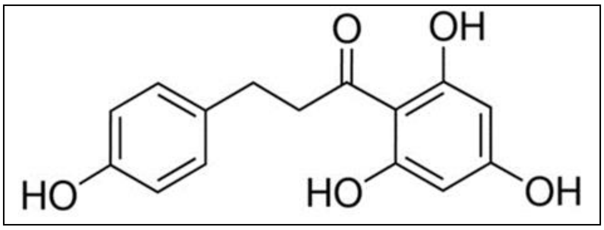

Figure 5. The skeletal formula of phloretin.
(Adapted from https://www.chemsrc.com/en/cas/60-82-2_947033.html)

Recently, phloretin has attracted increasing attention due to its immunoregulatory functions. Specifically, phloretin has been found to decrease the levels of inflammatory cytokine induced by TLR2/1 and TLR4 agonists, Pam3CSK4 and LPS, respectively, in bone marrow–derived dendritic cells and RAW264.7 macrophages [30]. In some studies, authors found that phloretin could suppress autoantibody production, which plays essential role in the pathogenesis of collagen-induced arthritis in an animal model [60]. Wu et al. (2020) discovered a new therapeutic role of phloretin, which consisted in the reduce the symptoms of atopic dermatitis and other immunopathological effects in mouse models [62].

Flavonoids also can play a substantial role in the processes of melanogenesis because of their antioxidant properties having the ability to chelate copper ions, a main metal in the active site of tyrosinase. Moreover, flavonoids have structures equivalent to tyrosine and are oxidized by tyrosinase; thus, they can act as substrate analog inhibitors against melanogenesis [20]. Research intending to recognize the possible mechanisms underlying the inhibitory effect of phloretin on tyrosinase confirmed that this polyphenol is both a substrate and an inhibitor of tyrosinase [15]. Anunciato Casarini et al. (2020) suggested that phloretin can be used as a skin-whitening product. However, there are no studies confirming the depigmentation effect of phloretin after topical application [8].

According to the literature phloretin has been widely investigated for its anti-cancer activities. For instance, phloretin considerably decrease the volume and weight of xenograft tumors in hard combined immunodeficiency mice inoculated with human hepatocellular carcinoma cells [61]. Additional evidence of *in vivo* anti-tumor effects of phloretin were described that topical application of this substance significantly reduced the multiplicity of papillomas in 7,12, -dimethylbenz(a)anthracene-initiated and TPA-promoted mouse skin [53]. In healthy participants, topical application of an antioxidant mixture containing vitamin C, ferrulic acid and phloretin repressed ultraviolet (UV) radiation in skin

[43]. Whereas exposure to UV radiation is a main cause of skin cancer, this study reveals the potential of phloretin to inhibit UV-induced skin carcinogenesis.

The antibacterial and anti-inflammatory effects of phloretin have been well considered in a number of modern studies. For example, Birru et al. (2021) investigated the activity of phloretin to inhibit bacterial growth and inflammation caused by the main pathogens associated with chronic obstructive pulmonary disease (COPD). This polyphenol demonstrated bacteriostatic and anti-biofilm activity against *Haemophilus influenzae* (NTHi), *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and to a lesser extent, *P. aeruginosa*. *In vitro*, phloretin inhibited NTHi adherence to respiratory epithelial cell line and exhibited anti-inflammatory activity in macrophages and human bronchial epithelial cells derived from normal and COPD-affected lungs [10]. In another study, the results revealed that phloretin had better antibacterial activity against *Cutibacterium acnes* than the standard anti-acne agent benzoyl peroxide used as a control. In addition, authors showed that phloretin is safer for humans than triclosan and benzoyl peroxide, which are commonly used in the treatment of acne [30].

Conclusion. Pure honey and its constituents are valuable and promising treatment option of natural origin. The antimicrobial resistance is the growing concern of clinical medicine and public health areas. The investigation of potential antibacterial properties of the honey may contribute markedly to the discovery of new therapeutic variants for some cutaneous infections, chronic inflammatory skin disorders, chronic wounds, burns, and ulcers. Several honey constituents such as methylglyoxal or bee-defensin-1 are well established as active substrates with healing characteristics. However, there is a wide range of honey components which demonstrated good antimicrobial or immunomodulatory activities in preliminary studies. The further laboratory investigation of their potential therapeutic roles is necessary to perform.

Author Contributions. *All the authors took peer part in writing the article.*

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

Funding: *This research received no external funding.*

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