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REVIEW OF ANTIMICROBIAL PROPERTIES OF HONEY CHEMICAL CONSTITUENTS - PART II

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Summary

Introduction. Honey and its elements have a notable role in treating wounds and different skin infections due to their antibacterial properties. However, an examination of the phytochemicals in honey and how they contribute to its antimicrobial effectiveness and mode of operation has been carried out.

Objective. The aim of this present review is to outline the existing information on the antibacterial characteristics of specific phytochemicals discovered in honey.

Materials and methods. To find sources for this research, several databases such as Pubmed, ResearchGate, Cyberleninka, and eLibrary were explored. The criteria for inclusion were human and animal research, primary studies (including 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.

Results and Conclusion. Many studies have aimed to determine the effectiveness of various components found in honey against both Gram-positive and Gram-negative microorganisms. Honey has become a popular antibacterial agent due to the growing concern of antimicrobial resistance. For example, some E. coli bacteria have developed resistance to certain types of antimicrobial drugs, such as third-generation cephalosporins, fluoroquinolones, and aminoglycosides. Therefore, investigating the antibacterial properties of the chemical components found in honey may be useful in addressing the issue of antimicrobial resistance.

Keywords: *honey, phenolic acids, antibacterial, antimicrobial, E. Coli, therapy.*

Резюме

АНТИМИКРОБНЫЕ СВОЙСТВА ХИМИЧЕСКИХ КОМПОНЕНТОВ МЕДА - ЧАСТЬ II. ОБЗОР ЛИТЕРАТУРЫ.

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Введение. Мед и его элементы играют заметную роль в лечении ран и различных кожных инфекций благодаря своим антибактериальным свойствам. Тем не менее, необходимо дальнейшее исследование фитохимических веществ в меде и его противомикробных свойств и механизмов действия.

Целью настоящего обзора является обобщение имеющейся информации об антибактериальных свойствах конкретных фитохимических веществ, обнаруженных в меде.

Материалы и методы. Для поиска релевантных источников были изучены несколько баз данных, таких как Pubmed, ResearchGate, Cyberleninka и eLibrary. Критериями включения были исследования на людях и животных, первичные исследования (включая описательные и аналитические исследования, клинические испытания), вторичные исследования (систематические обзоры и метаанализы), учебные пособия, клинические руководства и протоколы, а также полнотекстовые публикации на английском и русском языках.

Результаты и заключение. Многие исследования были направлены на определение эффективности различных компонентов, содержащихся в меде, против грамположительных и грамотрицательных микроорганизмов. Мед становится популярным антибактериальным средством из-за растущей обеспокоенности по поводу устойчивости к противомикробным препаратам. Например, некоторые штаммы *E. coli* выработали устойчивость к определенным типам противомикробных препаратов, таким как цефалоспорины третьего поколения, фторхинолоны и аминогликозиды. Поэтому изучение антибактериальных свойств химических компонентов, содержащихся в меде, может быть полезным для решения проблемы устойчивости к противомикробным препаратам.

Ключевые слова: *мед, фенольные кислоты, антибактериальное, антимикробное, кишечная палочка, терапия.*

Түйіндеме

БАЛДЫҢ ХИМИЯЛЫҚ ҚҰРАМАНДАРЫНЫҢ МИКРОБҚА ҚАРСЫ ҚАСИЕТТЕРІНЕ ӘДЕБИЕТ ШОЛУ - II БӨЛІМ

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Кіріспе. Бал және оның элементтері бактерияға қарсы қасиеттеріне байланысты жараларды және әртүрлі тері инфекцияларын емдеуде маңызды рөл атқарады. Дегенмен, балдағы фитохимиялық заттар мен оның микробқа қарсы қасиеттері мен әсер ету механизмдері туралы қосымша зерттеулер қажет.

Бұл шолудың **мақсаты** - осы шолу балдағы белгілі фитохимиялық заттардың бактерияға қарсы қасиеттері туралы қолда бар ақпараттың қысқаша мазмұны болып табылады.

Материалдар мен тәсілдер. Тиісті дереккөздерді табу үшін Pubmed, ResearchGate, Cyberleninka және eLibrary сияқты бірнеше дерекқорлар іздестірілді. Зерттеуге енгізу критерийлері: адам мен жануарларды зерттеу, бастапқы зерттеулер (оның ішінде сипаттамалық және аналитикалық зерттеулер, клиникалық сынақтар), қосымша зерттеулер (жүйелі шолулар және мета-талдаулар), оқуға арналған нұсқаулықтар, клиникалық нұсқаулар мен хаттамалар, ағылшын және орыс тілдеріндегі толық мәтінді жарияланымдар болды.

Нәтижелер мен қорытынды. Көптеген зерттеулер балдың құрамындағы әртүрлі компоненттердің грам-оң және грам-теріс микроорганизмдерге қарсы тиімділігін анықтауға бағытталған. Микробқа қарсы тұрақтылық туралы алаңдаушылықтың артуына байланысты бал танымал бактерияға қарсы агентке айналуда. Мысалы, кейбір *E. coli* штамдарына қарсы препараттардың кейбір түрлеріне, мысалы, үшінші ұрпақ цефалоспориндеріне, фторхинолондарға және аминогликозидтерге төзімділігін дамытты. Сондықтан балдың құрамындағы химиялық компоненттердің бактерияға қарсы қасиеттерін зерттеу микробқа қарсы тұрақтылық мәселесін шешуде пайдалы болуы мүмкін.

Түйін сөздер: *бал, фенол қышқылдары, бактерияға қарсы, микробқа қарсы, E. coli, терапия.*

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Introduction

In the light of growing concern of antimicrobial resistance, the search for alternative antibacterial agents is a global biomedical issue. Infections caused by antibiotic-resistant strains are linked directly to the impaired quality of life, generalized bacterial infections and sepsis, the growing rates of recurrent infections, high frequency of failures in treatment strategies, increased risk of complications, worsening of disease course, and death [16]. According to 2019 Antibiotic Resistance Threats Report, more than 2.8 million people get the antibiotic-resistant infections annually in USA, and at least 35,000 patients die as a result [3]. In comparison, more than 2 million infections occurred in the United States in 2013, and the number of AMR-related deaths was 23,000 [1]. Recently, two new AMR indicators were included to The Sustainable Development Goals (SDGs) monitoring groupwork: the frequencies of bloodstream infections caused by methicillin-resistant Staphylococcus aureus (MRSA); and E. coli resistant to third generation cephalosporins (3GC). In 2019, the median rate observed for MRSA was 12.11% (IQR 6.4–26.4) (data provided by 25 countries) and that for E. coli resistant to third generation cephalosporins was 36.0% (IQR 15.2–63.0) (according to data from 49 countries) [2].

Gram-negative skin infections attract great concern due to the development multidrug resistance whereas there is a strong deficiency of antibacterial agents to treat them [49]. In condition of severely limited options of therapy Gram-negative bacteraemia is strongly associated with mortality in burn patients [35]. E. coli is recognized as the most common Gram-negative bacterial pathogen, being burden of both clinical medicine and public health. The current literature demonstrates the wide range of antibacterial substances to which E. coli became resistant: penicillins, first, second and third generation cephalosporins, aztreonam, cefamandole, cefoperazone, carbapenems, colistin, and polymyxin B [44]. According Allocati N. et al. (2013) the antibiotic resistance of E. coli ranges heavily regarding the country and the group of antibiotics. For instance, the resistance of E. coli to the third-generation cephalosporines varied from 3.0 R% in Bosnia and Herzegovina to 42.0 R% in Turkey. The prevalence of multidrug resistant E. coli was from 0.8 R% in Iceland to 23.0 R% in Turkey [6].

The group of alternative topical treatments for wound infections includes allopurinol, dimethyl sulphoxide, silver sulfadiazine, silver zinc allantoinate cream, povidone-iodine hydrocolloid, and silver-impregnated charcoal dressings [42]. In parallel about 20 commercially available medical grade honey and honey ointments for topical application are available now [47]. The investigation of the potential benefits of honey constituents against antibiotic resistant strains of pathogens is the current agenda of multiple studies.

Materials and Methods

The approach used for conducting the search involved searching extensively through two databases, Pubmed and ResearchGate, for literature written in English. To collect publications in Russian and Kazakh, two scientific electronic libraries, eLibrary and cyberleninka, were also utilized.

The aim of the literature review was taken into account while using MeSH, which is a controlled vocabulary thesaurus managed by NLM, to retrieve specific terms. Based on this, a search strategy was developed using logical operators such as AND, OR, and NOT. The key words "honey", "phenolic acids", "antibacterial / antimicrobial", "*E. Coli*", "therapy".

To find relevant information for our search, we looked for complete texts in both English and Russian languages, conducted animal and human trials, and collected primary data such as analytical and descriptive studies, randomized and non-randomized clinical trials, as well as secondary data such as meta-analyses and systematic reviews. We also considered instructional methodological manuals, clinical guidelines, protocols, and recommendations. Along with digital materials, we also included information from printed versions of textbooks and monographs. Initially, two co-authors (L.K. and A.K.) independently searched and selected articles based on the inclusion criteria. We then screened titles and abstracts and excluded articles that did not meet the criteria, ultimately selecting 48 English publications for analysis in this literature review.

Results and Discussion

Evidence of antimicrobial activities of honey

The antibacterial activity of honey was documented in numerous research papers. The constituents of honey have different activities against multiple microorganisms including pathogens resistant to conventional antibiotics. Exposure with Manuka honey demonstrated its efficacy against *S. aureus*, *Salmonella typhimurium*, *E. coli*, *Pseudomonas aeruginosa* and *Bacillus subtillis* [29,30,15]. Some *in vivo* studies showed that honey also may inhibit the growth and reproduction of MRSA and vancomycin-resistant enterococci (VRE) [31,18]. Furthermore, honey constituents are capable to suppress the bacterial activity in biofilms. Biofilms are the structures formed from microbes and their products composing together the extracellular polymeric substance matrix (Pubmed, Mesh). *Lu J. et al.* (2014) found that manuka honey may inhibit the biofilm development even at low concentrations. The biomass of matrix might be killed by manuka honey constituents due to its bacteriocidic properties. Authors suggested that this type of antimicrobial activity of manuka honey could be used for the treatment of chronic wounds and ulcers [30]. Besides in vivo studies some experiments in animals were also conducted. For instance, different concentrations of Manuka honey or its combination with methylglyoxal (MGO) were investigated regarding to their biofilm suppression activity in sheep frontal sinuses. It was revealed that the abovementioned substrates are efficacious for treatment of biofilm associated sinusitis in animal models [45]. Clinical studies on honey efficiency for skin infections and wounds are limited by some case reports only. Further high-quality research in clinical settings might be arranged for getting some robust clinical data and enhanced evidence on honey's efficiency and safety issues in humans [12]. However, the systematic review based on the analysis of 26 studies showed that the use of honey dressings might be beneficial for the quicker re-epithelization of burns. Also honey dressings appeared to be an effective option for the prevention of local infections in postoperative wounds [23].

The synergistic effect of honey phytochemicals

Since ancient times, honey has been considered as a natural substance with a wide range of therapeutic effects. The flavonoids and polyphenolic compounds contained in the honey can play an important role for human health due to their high antioxidant and anti-inflammatory effects [9]. Moreover, a number of authors noted about the antidiabetic activity of honey, which is associated with decline of the concentration of glucose, fructosamine and glycosylated hemoglobin in the blood serum [7]. Honey also has a protective effect for the cardiovascular system, where it mainly prevents oxidation of low-density lipoproteins [8]. However, the most important effect of honey is presented with its high antibacterial activity. The synergistic work of honey components allows it to combat actively with various types of microorganisms, including multidrug-resistant bacteria [20]. The effectiveness of honey against microorganisms depends on the type of its botanical origin, the health of the bee, its origin and processing methods [14]. Nowadays, the most studied and used one in medical practice is New Zealand manuka honey. It is obtained from nectar collected bees (*Apis mellifera*) feeding on the manuka tree (*Leptospermum scoparium*) growing in Australia and New Zealand. Manuka honey is used in the pharmaceutical industry to treat different diseases, superficial and chronic wounds, and burns [22]. Antibacterial effect of honey is still unclear. Some authors believe that several components which identified in honey contribute its antimicrobial activity, such as high sugar content, low water activity, low pH, and the formation of hydrogen peroxide during dilution. Among numerous phytochemicals methylglyoxal (MGO) has been identified as the dominant antimicrobial component of manuka honey [28]. Based on this fact, some researchers studied the combining effects of honey with antibiotics on antimicrobial activity *in vitro* [38]. Karayil S. et al. (1998) were the first who reported about the synergistic effect of honey and antibiotics. In their report researchers studied several bacterial strains of *Pseudomonas* and *Klebsiella* species isolated from various samples to test the antibacterial effect of Indian honey *in vitro* on the principle of Minimum Inhibitory Concentration (MIC) and its synergy with 3 antibiotics – gentamicin, amikacin, ceftazidime. The ratio of honey and antibiotics in the study was 1:1. A synergistic effect was observed in case of *Pseudomonas aeruginosa,* but not against *Klebsiella* species [24]. In another study, the authors evaluated the antimicrobial effect of honey on organisms isolated from infected burns in comparison with some antibiotics. In addition, they evaluated the effects that occur when bee honey is added to antibiotic discs. According to the results of the study, the antimicrobial effect of honey was significantly higher than ciprofloxacin, sulbactam/ampicillin, ceftriaxone, and vancomycin. Honey also had a greater inhibitory effect on isolated gram-negative bacteria (*P. aeruginosa, Enterobacter spp., Klebsiella*) and on methicillin-resistant *S. aureus* compared to the used antibiotics [4]. Other authors have tried to determine the effect of manuka honey on oxacillin resistance in methicillin-resistant *S. aureus* (MRSA). As a result, the researchers found that manuka honey and oxacillin interacted synergistically, inhibiting MRSA [21]. A little later, these researchers continued to search for additional synergistic combinations of antibiotics and manuka honey which might be helpful in treatment of wounds. They tested 15 antibiotics with and without subinhibitory concentrations of manuka honey against both of MRSA and *P. aeruginosa*. The most significant results were in the combination of tetracycline and manuka honey, which demonstrated increased activity against MRSA and *P. aeruginosa*. Rifampicin and manuka honey showed an enhanced effect against MRSA when they were tested using disk diffusion assay and E-strip, but no synergism was observed using broth dilution assay. Similarly, the combination of imipenem and manuka honey was synergistic with respect to MRSA, but not with *P. aeruginosa*, which suggests a species-specific effect [22]. In a recent study, *Hayes G. et al.* (2018) demonstrated that manuka honey and its component MGO, separately increase the sensitivity of *S. aureus* to linezolid in agar diffusion and in microdilution assays. Linezolid is effective antibiotic against many Gram-positive bacteria, especially *S. aureus*, and acts by inhibiting bacterial protein synthesis. The authors showed that MGO increased intracellular accumulation of linezolid in bacterial cells. These data proved that manuka honey and its active ingredient MGO could be used as an antibiotic supplement [19].

Bacterial biofilms are the essential cause of chronic wound infections. Biofilms very poor respond to antibacterial therapy due to the fact that bacterial cells are protected in the biofilm, and it becomes more difficult to control and eradicate them [28]. In this regard, a number of researchers have developed new approaches to combat with biofilms in chronic wounds based on the interaction of honey and antibiotics. For example, *Campeau M.E.M. and Patel R.* (2014) found that manuka honey had a synergistic interaction with vancomycin against *S. aureus* biofilms and an additive interaction with gentamicin against *P. aeruginosa* biofilms [11]. *Merckoll P. et al.* (2009) showed that Norwegian honey eliminated biofilms due to its biocidal potential and was effective in treating wounds [39]. Another study reported about the synergism of Portuguese honey with phage therapy. The results of this study showed that the addition of a phage to a low concentration of honey, even in four times dilution, had the antibacterial activity against *E. coli.* Thus, the authors proved that Portuguese honey had excellent antibiofilm activity and could be utilized as the alternative therapeutic agent for wound infection associated with biofilm [43]. In several studies it was reported that bacterial biofilms of *Streptococcus pyogenes, Streptococcus mutans, Proteus mirabilis, P. aeruginosa, Enterobacter cloacae*, and *S. aureus* were removed by manuka honey [48,32,33].

There are very few studies in the literature which examined the synergistic effects of honey and antibiotics in clinical settings. *Mat Lazam N. et al.* (2013) investigated the effect of Tualang honey on improvement of the wound healing process in patients after tonsillectomy. In their prospective study, patients aged from 9 to 11 years were divided into two groups. The main group received treatment in the form of honey and sultamicillin, while the second group received treatment with antibiotic only. As a result, in the main group wound healing was significantly faster than in the control group. Thus, the authors concluded that Tualang honey had a positive effect on accelerating the healing process of wounds in patients after tonsillectomy [36]. There are also several clinical cases in which the use of honey dressings relieved the condition of patients with trophic ulcers of the lower extremities and feet [34,41]. Obviously, additional studies to determine the clinical efficacy of honey and antibacterial drugs *in vivo* are needed. In general, the use of honey in medical institutions has provided economic benefits by reducing direct costs compared to traditional methods of treatment and has decrease the use of antibacterial drugs, which often lead to antibiotic resistance [40].

Investigation of honey and its constituents against *E. coli*

There are several studies dedicated to the testing the hypothesis of antibacterial properties of honey compounds against *E. coli. Mavric E. et al.* (2008) reported the results of qualitative and quantitative analysis of Manuka honey constituents in terms of its antimicrobial potency against *E. coli* and *S. aureus.* Authors found that the most noticeable antibacterial activity was identified for methylglyoxal (MGO), which was expressed by a MIC (minimum inhibitory concentration) value of 1.1 mM for both bacteria. This finding allowed to conclude that MGO was determined as the most important bioactive substance in New Zealand Manuka honey [37]. Later, *Rabie E. et al.* (2016) demonstrated the ultrastructural mechanisms of action of MGO against *E. coli.* At concentration of 0.5 mM MGO, microbial structure was unimpaired. At concentration of 1 mM MGO E. coli had started to loss fimbriae and flagella. The abovementioned structured appeared stunted and fragile. At concentration of 2 mM MGO fimbriae and flagella were totally lost whereas *E. coli* became of rounded shape, and the bacterial membrane lost its integrity. The loss of fimbriae and flagella due to MGO exposure leads to the reduced adherence and motility of bacteria [46].

In 2007, *George N.M. and Cutting K.F.* conducted the *in-vitro* study of antibacterial properties of the standardized honey (Medihoney) against wide range of the multiresistant Gram-positive and Gram-negative microorganisms including ESBL (extended spectrum β-lactamases) producing strains of *E. coli*. They found that 8/10 ESBL producing strains of *Escherichia coli* (80%) were inhibited at 6% v/v. The remaining 2 strains (20%) were inhibited at 8% v/v. For comparison, concentrations of 14% v/v were required to inhibit 17/20 (85%) of test isolates of P. aeruginosa. The remaining 3 strains were inhibited at a lower concentration of 12% [17].

Lee J.H. et al. (2011) reported that low concentrations of acacia and polyfloral honeys, such as in honeyed water, may act as an efficient alternative for prevention and treatment of wounds infected with pathogenic E. coli O157:H7. The mechanism of action of 0.5% concentration of Korean honeys was explained with the reduced biofilm formation and the inhibited expression of quorum sensing genes and virulence genes in E. coli O157:H7. Authors presented glucose and fructose containing in the investigated honeys as the main antibacterial components [26]. *Kumar N.D. et al.* (2014) compared the antimicrobial potency of Manuka honey against E. coli (ATCC 25922) in comparison with the conventional endodontic disinfectants. It was demonstrated that 5.25% NaOCl, 2% CHX, 0.2% CHX, Net Manuka honey are bactericidal while Ca (OH)2, Honey 1:2 dilution, Honey 1:4 dilution are bacteriostatic based on the death rate constant values. Authors concluded that Manuka honey containing medications might be used as a potential root disinfectant [25].

The broth microdilution assay as a method for the investigation of the antibacterial properties of honey against *E. coli* was utilized in several studies. *Brudzynski K.* (2007) analyzed the antimicrobial characteristics of 42 samples of Canadian honeys against *E. coli* (ATCC 14948). Researcher measured the MIC_{50} and MIC_{90} in correlation with endogenous H_2O_2 concentrations. It was found that both MIC_{50} and MIC_{90} significantly inhibited the growth of *E. Coli*, and the activity was positively correlated with the H_2O_2 content [10]. *Lu J. et al.* (2013) used the broth microdilution assay for the determination of the antibacterial activity of the range of concentrations of clover honey and a suite of manuka and kanuka honeys against four bacteria including *E. coli.* Authors also investigated the contribution of hydrogen peroxide to the antimicrobial potency of honey. They found that the content of hydrogen peroxide was associated with the antibacterial activity of the manuka and kanuka honeys; and it was never essential for complete growth inhibition *E. coli* [29].

The disc and well diffusion assays are also popular methods for the investigation of antimicrobial properties against *E. coli. Akujobi C.O. et al.* (2010) reported that the high concentration of Nigerian honey was a strong predictor of its activity against *E. coli.* Also, they found that well diffusion assay was more accurate test than disc diffusion assay for the measurement of the antibacterial capacity of honey [5]. *Chau T.C. et al.* (2017) used disc diffusion assay and 96-well microliter plate assay for the comparison of the antibacterial properties of the Manuka honey extract and unfractioned honey against E. coli. They reported the higher antimicrobial capacity for unfractioned honey whereas the honey extract demonstrated antioxidant properties [13].

Conclusion

The antibacterial activity of several honey constituents against the Gram-positive and Gram-negative microorganisms is the meaningful aim of multiple studies. The emergence of honey as an antibacterial agent is in large part due the expanding problem of the antimicrobial resistance. *E. coli* isolates were recognized resistant to some antimicrobial groups including third generation cephalosporines, fluoroquinolones, and aminoglycosides. Thus, the determination of antibacterial properties of honey chemical constituents may help to address the issue of the antimicrobial resistance.

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