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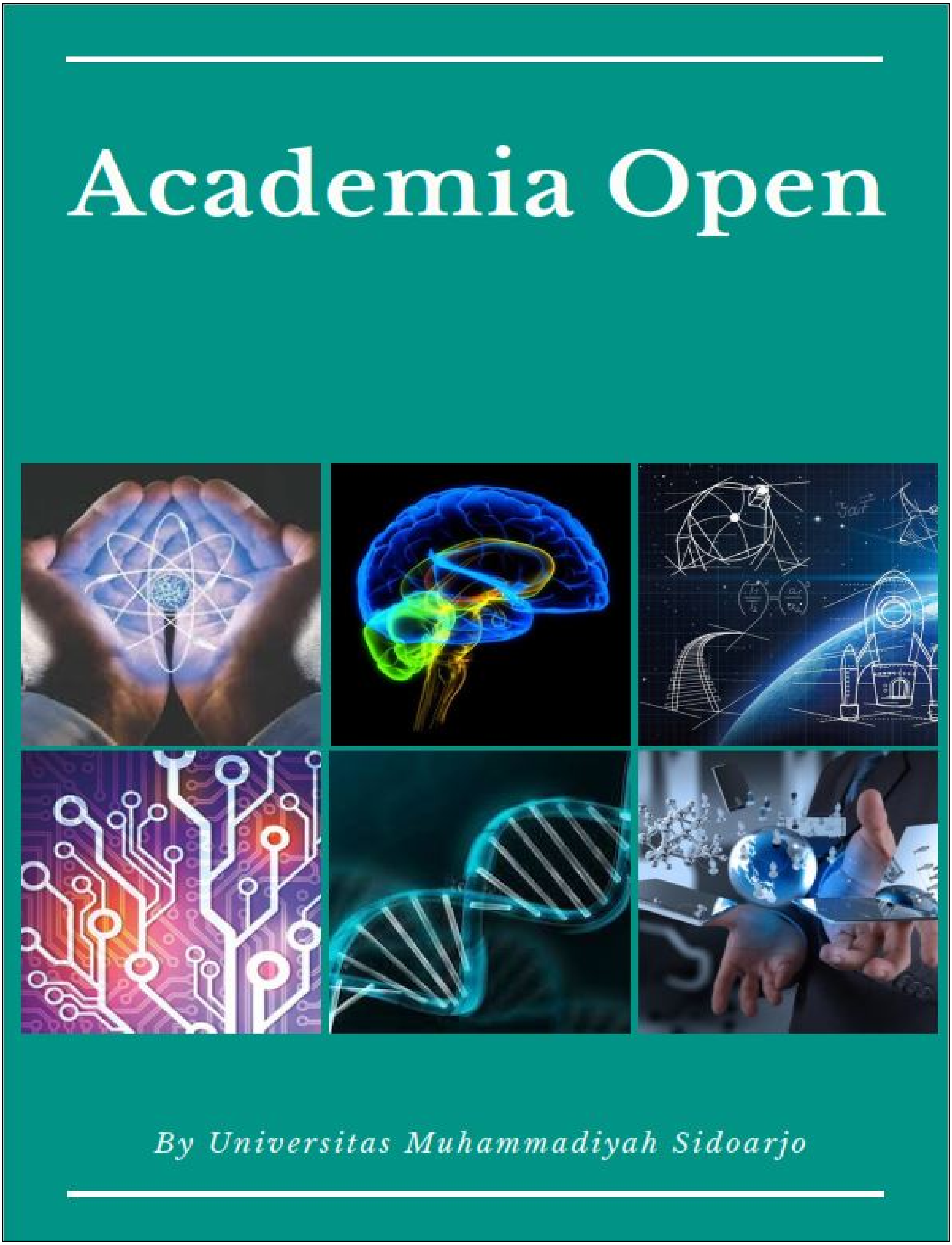

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Honey Enhances Antibiotic Effectiveness Against Urinary Tract Infections

Madu Meningkatkan Efektivitas Antibiotik Terhadap Infeksi Saluran Kemih

Lamyaa Gh. Fejer, lamyaagh@uomustansiriyah.edu.iq, (1)
Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq, Iraq

Ghaidaa S. Hameed, ghaidaahameed@uomustansiriyah.edu.iq, (0)
Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq, Iraq

Mayssam Hussein Mohammed Ali, mayssam.hussein@uomustansiriyah.edu.iq, (0)
Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq, Iraq

Orooba Al-Hammood, orooba.alhammood@nahrainuniv.edu.iq, (0)
Department of Forensic Sciences Collage of Sciences, Al-Nahrain University, Baghdad, Iraq, Iraq

(1) Corresponding author

Abstract

Background: Urinary tract infections (UTIs) are prevalent across all ages and genders and pose significant treatment challenges, often requiring alternative therapeutic approaches due to increasing antibiotic resistance. **Specific Background:** The study examines the impact of antibiotics and honey on bacterial UTIs, revealing 17 cases, primarily caused by Staphylococcus aureus and Klebsiella pneumoniae. **Knowledge Gap:** The study evaluates the effectiveness of honey in combining antibiotics with anise and spring flower honey, focusing on its potential to enhance antimicrobial effects in UTIs. **Results:** Biochemical analysis and VITEK diagnostics revealed significant bacterial growth. Antibiotic susceptibility tests showed varied effectiveness, with spring flower honey enhancing the activity of nitrofurantoin (35%), trimethoprim (17.6%), trimethoprim-sulfamethoxazole (23.5%), tetracycline, and norfloxacin (35.2%). Anise honey also demonstrated notable synergistic effects, particularly with norfloxacin (47%) and tetracycline (41%). **Novelty:** This study highlights the potential of combining honey with antibiotics to combat UTIs, offering new insights into alternative treatment strategies and demonstrating significant synergy with specific antibiotics. **Implications:** The findings suggest that incorporating honey into UTI treatments could improve therapeutic outcomes and help mitigate the growing issue of antibiotic resistance. Further research is needed to identify active compounds in honey and optimize their use with antibiotics.

Highlights:

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1. Enhanced Efficacy: Honey boosts antibiotic effectiveness against UTIs.
2. Resistance Solution: Combines honey to counteract antibiotic resistance.
3. Honey Variability: Different honeys show varied synergistic effects.

Keywords: Urinary Tract Infection, Antibiotics, Honey, Synergistic Effect, Antibiotic Resistance

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Introduction

Urinary tract infection (UTI) can refer as the term describe any infection involving any part of the urinary tract system [1] .it may occur in men, pregnant women, and patients with immune suppression or urinary tract abnormalities[2], However, it seems that UTI is more common among female and when an old female diagnosed as UTI it might often be regarded as a harmless and banal condition while in male, in contrast, the suggestion is that it should be carefully assessed and followed up the right treat methods [3].

Previous studies have shown that many species of bacteria can cause UTI eg. E. coli, enterococci, and coagulase-negative staphylococci [4]. Klebsiella, Staphylococci, Enterobacter, Proteus, Pseudomonas, and Enterococci species are more often isolated from inpatient hospitals, and Corynebacterium urealyticum has been recognized as an important nosocomial pathogen, identified as anaerobic organisms are rarely pathogens in the urinary tract [5]. Antibiotics are the most significant class of pharmaceuticals and one of the twentieth century's most influential medical inventions. New forms of antibiotic resistance can easily cross international boundaries and spread between continents. Many forms of resistance spread with remarkable speed [6,15,20], according to experts we are approaching a 'post-antibiotic era'. From the past decade, a driver and ongoing evolution of resistance mechanisms is likely to be the never-ending competition for resources among microorganisms, including the natural production of secondary metabolites similar to many of the antibiotics used today as pharmaceuticals [16,18,19].

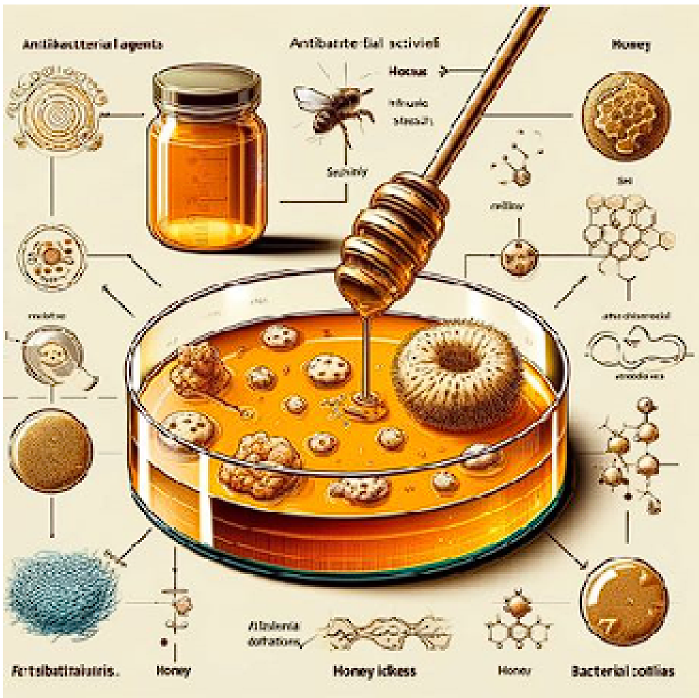

Figure 1. *The antibacterial activity of Honey from Chat GPT*

Honey has had a valued place in traditional medicine for centuries. It was used to overcome liver, cardiovascular, and gastrointestinal problems and treat some types of infectious diseases.

The antimicrobial activity of this product is highly complex. The generation of hydrogen peroxide, bee defensin-1, high osmolarity, and low value of pH seems to be crucial for its antimicrobial potential. The antimicrobial activity of honey is highly complex and remains not fully recognized. To date, it has been established that several components of this product play a crucial role in its antimicrobial properties and appoints that hypothesized its activity a highly attractive property given the global antibiotic resistance crisis. Compared to neat honey, which is a sticky and viscous liquid, honey-based medicinal products might be more convenient to use, and they also offer a more targeted therapeutical use [17]. Floral Origin: The specific flowers from which the honey is derived can influence its antibacterial potency.

Different floral sources contribute various bioactive compounds that can enhance the antimicrobial activity of the honey. For instance, kinds of honey from certain floral origins are more effective against specific bacterial strains due to their unique compositions (Frontiers)(Chat GPT). There is need for alternative strategies to treat infections, particularly by reducing or avoiding the use of our most potent antibiotics for superficial infections, has never been greater. Applying antibiotics with honey yielded better antimicrobial potential and synergistic effects were noted against biofilms. In medicine, honey has been used to treat surface wounds, burns, and inflammation, and has a synergistic effect when applied with antibiotics. Tissue repair is enhanced by the low pH of honey (3.5–4) which causes a reduction in protease activity on the wound site, elevating oxygen release from hemoglobin, and stimulating fibroblast and macrophage activity. Furthermore, H2O2 has antiseptic effects, and it disinfects the wound site and stimulates the production of vascular endothelial growth factor. The use of honey will clean wounds or burn areas from free radicals and reduce scarring and contractures. The anti-inflammatory and antibacterial potential of honey will keep the injured area moist and as such prevent it from deterioration and fibrosis. Honey can promote fast healing and reduce scarring and is very convenient for plastic surgery. [14]

Dressings and wound gels, licensed by regulatory authorities in many countries, are currently available for clinical Liu et al. (2018) have demonstrated a strong synergy between manuka honey and rifampicin, oxacillin, and clindamycin in inhibiting the growth of planktonic cells and preventing biofilm formation by different S. aureus strains [including methicillin-resistant S. aureus (MRSA)][7].

This study aim of study aims to detect the synergism effect of selected antibiotics with two types of honey produced in local farms in Iraq- Baghdad.

Methods

Material :

Two types of honey were chosen from the local market to estimate the antibacterial activity and the synergism effect with honey these types of honey are (anise honey,

spring flowers honey) as shown in Table 1

Type of honey	Company	Origin
Anise honey	Local market	Iraq
Spring flowers honey	Local market	Iraq

Table 1. *the honey used in the experiments*

study scanned three main laboratories of the largest hospitals in Baghdad city (Teaching laboratories in City Medicine/ Baghdad, The Main Lab of Baghdad Teaching Hospital /Medicine City-Baghdad, and Al-Kindey Teaching Hospital /Baghdad) For 3 months period the urine samples collecting for patients who advise by a physician to make general urine examination.

METHODS :

Seventeen isolates for Urinary Tract Infections (UTI) from one hundred samples of urine were identified as positive for bacterial infections who asked for urgent medical intervention after confirmation tests as a reference for UTI infection and these isolates were used in the study.

pH measure for honey

The acidity for the different types of honey used in the study is measured in an electrical pH meter by immersing the column of the meter in honey for 5 min at room temperature (25 ºC) and the reading was recorded. the experiment was done in triplicate and the average was recorded as the true pH number for the honey [8].

Antibacterial sensitivity test

Antimicrobial drug susceptibility of the isolates was tested by the Kirby-Bauer technique and results were interpreted according to the Clinical Laboratory Standards Institute-CLSI Guideline (2017) [9]. The antimicrobial susceptibility testing for nitrofurantoin 300 mcg, tetracycline 30 mcg, norfloxacin 10 mcg, trimethoprim, and trimethoprim-sulfamethoxazole.

The Muller Hinton Agar plates (Prepare as mentioned on the pack of Lab UK) were inoculated with 50µl of bacterial suspension (bacterial suspension equal to 0.5 Mc Ferland) and distributed on the media after that they were left for 10 minutes to be absorbed and dry on the media. The antibiotic disks used in the study were placed with pathogenic isolates (Staphylococcus aureus, E.coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Proteus SPP.) and incubated at 37 ºC for 24 hours then recorded the diameter of inhibition zone to see either sensitive, intermediates or resistance ability to a different drug.

Study of synergism effect between antibiotic disks and honey

The synergism effect has been done as mentioned in [11]. Fifty microliters (µl) of bacterial suspension that is equal to 0.5 McFarland and gives approximately about 1.5 *108 of the bacterial colony and let for 10 minutes.

The honey about 50 µl was added to the antibiotic disks separately for each kind of honey (two kinds). In the centre of the agar, it had made about a 5-millimeter pore made by a cork borer. For control was honey only put in the centre pore. the inhibition zone was measured in millimetres by using of vernier clipper then the increased inhibition fold was calculated as the mentioned formula [10] according to the following equation:

$$increasingfold = \frac{a-b}{a} \times 100 \text{ ....Eq 1}$$

Figure 2.

where :

a. represents the inhibition zone of the antibiotic disk alone

b. represents the inhibition zone of the antibiotic disk with honey

1. Two kinds of honey are used in the study from the local market

2. Anise honey is the local name for the honey for the bees that use anise stars in feeding Pimpinella anisum.

3. Spring honey is a local name for the honey harvested in spring for bees to feed on different kinds of spring flowers

Result and Discussion

Result

From the clinical samples of 100 patients (urine) include (male, and female) of young and old ages; only 17 samples had positive results for bacterial growth improving the bacterial infection with a ratio of 17%, and the bacteria that were identified as the reason for the UTI are S. aureus (7 isolates) 41.17% is the most known isolates between bacterial infection, K. pneumoniae (4 isolates) 23.52%, followed by P. aeruginosa, E.coli, and proteus spp. (2 isolates for each) 11.76% without identifying if it’s a chronic or acute infection.

The antibiotic susceptibility for the isolates shows different abilities to act towards the antibiotic depending on the bacterial isolates themselves, antibiotics used, and strains of the same bacterial isolates, as seen in Fig 2,3Fig 4.

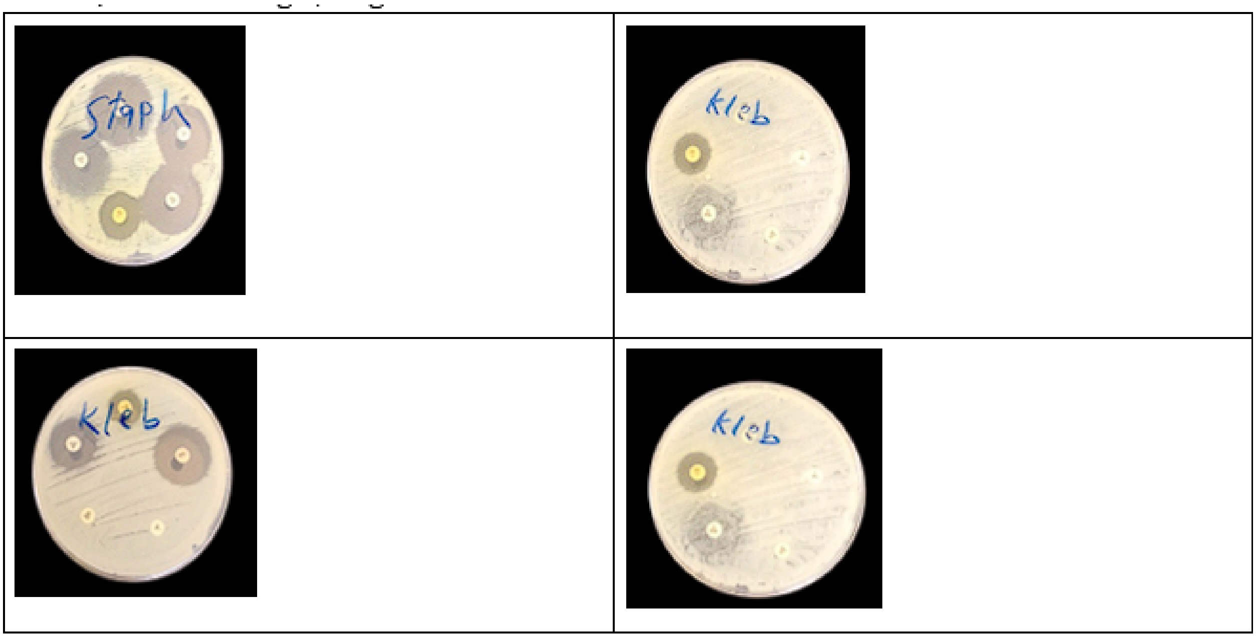

Figure 3. *Antibiotic susceptibility for bacterial isolates*

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Figure 4. *Antibacterial activity of spring flower honey with antibiotics*

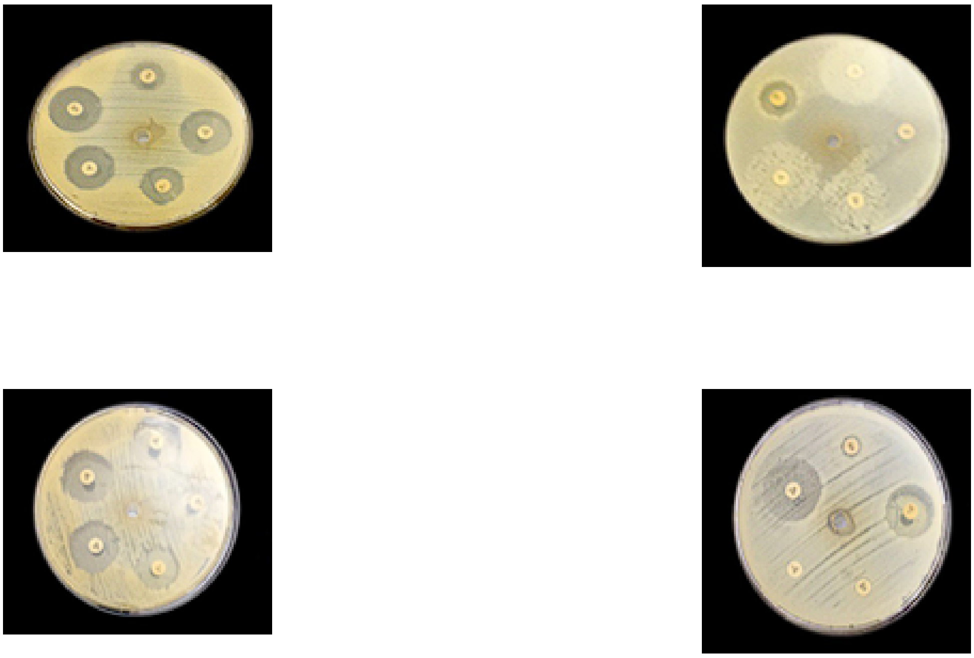

Figure 5. *Antibacterial activity of Anise honey with antibiotics*

The pH estimation of the two types of honey has shown different acidity degrees as seen in Table 2. which is 4.6 for anise honey and 3.84 for spring flower honey.

Honey	pH
1	Anise
2	Spring flower honey

Table 2. ***the pH estimation of the different kinds of honey***

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The increasing fold was calculated for the antibiotics and honey to estimate the (synergism, and antagonism) effects according to the formula of the increasing fold. The study showed different effects as seen in Fig 5,6,7,8 and 9

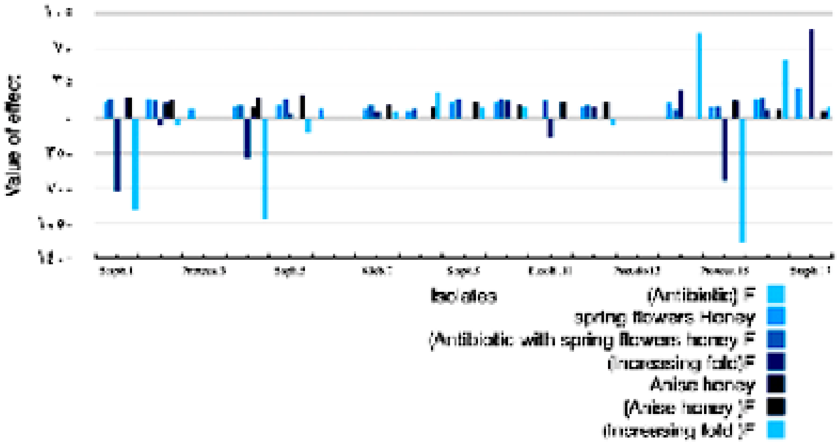

Figure 6. *Antibiotic susceptibility for (F), Spring flowers honey, Anise honey, increasing fold of F and honey*

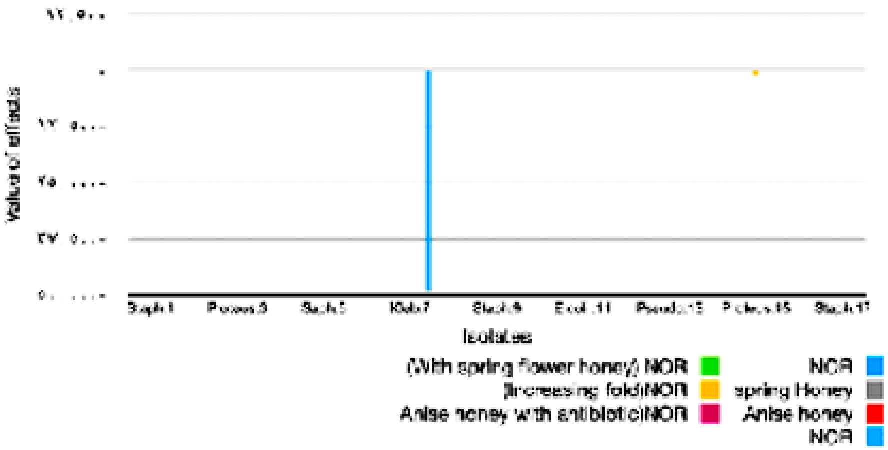

Figure 7. *Antibiotic susceptibility for (NOR), Spring flowers honey, Anise honey, increasing fold of NOR and honey*

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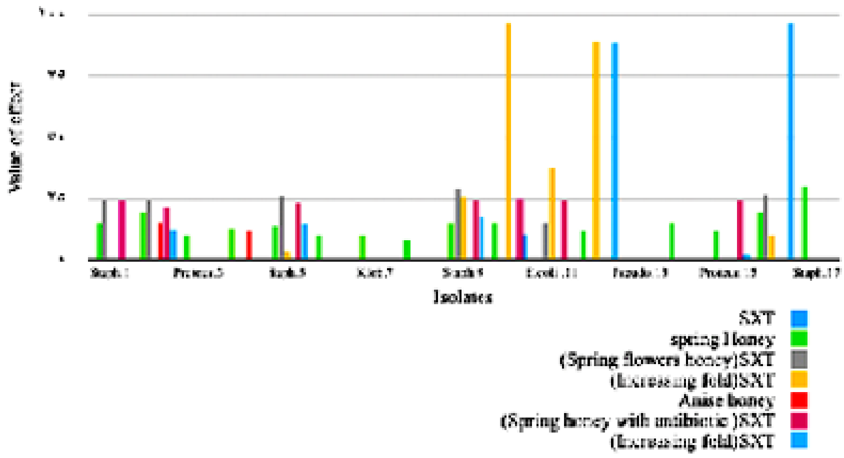

Figure 8. *Antibiotic susceptibility for (SXT), Spring flowers honey, Anise honey, increasing fold of SXT and honey*

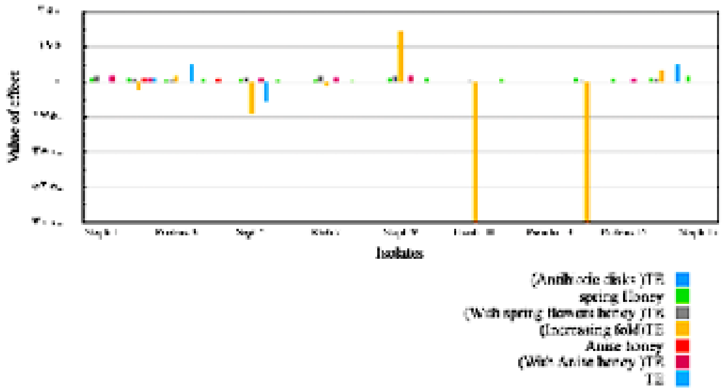

Figure 9. *Antibiotic susceptibility for (TE), Spring flowers honey, Anise honey, increasing fold of TE and honey*

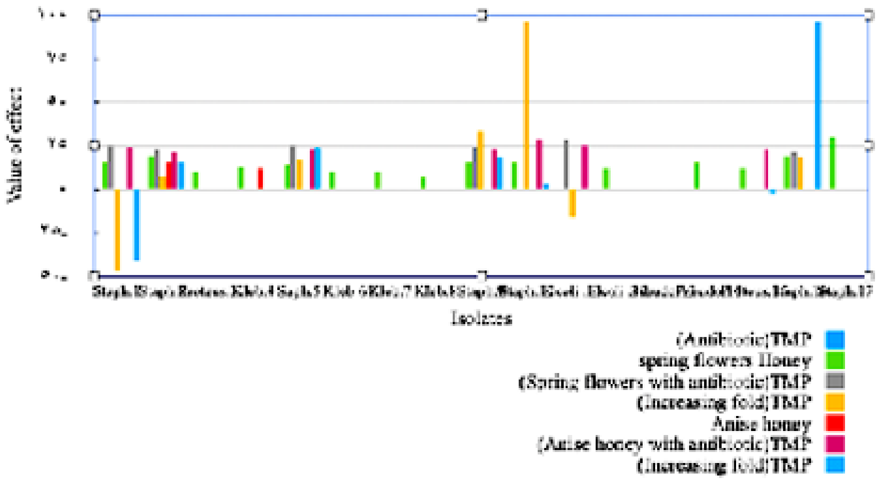

Figure 10. *Antibiotic susceptibility for (TMP), Spring flowers honey, Anise honey, increasing fold of TMP and honey*

In the result, it can be noticed that 10 isolates 58.82% were resistant to the antibiotic Tetracycline while the sensitive isolates were (5) 29.42%. The nitrofurantoin antibiotic has shown resistance in 8 isolates 47.05%, intermediate for 5 isolates 29.41%, and sensitivity for 4 isolates only 23.52%. The antibiotic norfloxacin had shown resistance for 4 isolates at 23.52% when the sensitivity to this antibiotic was high with a ratio of 76.47% in 13 isolates. Both trimethoprim and trimethoprim-sulphamethoxazole had shown the same activity on the tested isolates with a ratio of 58.82 58.82%for 10 isolates and a sensitivity ratio of for 7 isolates 41.17%. From the result, we can notice that the most resistant antibiotic was for norfloxacin13 isolates, followed by tetracycline, trimethoprim, and trimethoprim-sulphamethoxazole 10 isolates, nitrofurantoin 8 isolates, and this may be a reference improve for spreading of antibiotic resistance strains worldwide which lead to degrading of the antibiotic by the resistant bacteria by the different method according to the group of the antibiotic and the generation that belong to [12].

In the synergism effect using spring flowers honey with antibiotics, the synergistic effect was observed as follows:

1. 6 isolates (35%) showed an increase when used with Nitrofurantoin 5 isolates with no effect29.4%and 4 isolates 23.5% had antagonism,

2. 3 isolates (17.6%) showed an increase with trimethoprim,9 isolates had no effect 52,9%, and 3 isolates had antagonisms 17.6%.

a. 4 isolates (23.5%) showed an increase with trimethoprim-sulfamethoxazole,10 isolates with no effect 58.8%, and 2 isolates with antagonism 11.7%.

b. 6 isolates (35.2%) showed an increase with tetracycline,11 isolates with no effect 64.7%, and no antagonism effect.

c. 6 isolates (35.2%) showed an increase in norfloxacin,7 isolates with no effect 43.7%, and 4 isolates antagonism 23.5%.

Similarly, when the synergistic effect of Anise honey with the antibiotics was observed, the fold increase was as follows:

a. 7 isolates showed a 41% increase with Nitrofurantoin, while 4 isolates had no effect 23.5% and5 isolates showed antagonism 35.2%.

b. 5 isolates showed a 29.4% increase with trimethoprim,11 isolates had no effect 64.7% no effect, and 1 isolate 5.8% antagonism.

c. 5 isolates showed a 29.4% increase with trimethoprim-sulfamethoxazole,10 isolates with no effect 58.8%, and 2 isolates 11.7% antagonism.

d. 7 isolates showed a 41% increase with tetracycline,10 isolates with no effect 58.8% and all the isolates had increased in the inhibition zone after the use of honey with antibiotic,

e. 8 isolates showed a 47% increase with norfloxacin,4 isolates showed no effect 23.5% , and 5 isolates showed antagonism 29.4% .

Discussion

With the rapid and global emergence of MDR bacteria, new antibiotic techniques are required, the bacterial species become more resistant to the known antibiotics so the need to develop new antibacterial activity ways to avoid the resist mechanisms become one of the new century needs, one of the most known embower antibacterial along centuries that used against the bacteria is honey with medicinal used for healing and especially with skin infections[10,18], in our study the result had shown this difference between increasing and diminished in the inhibition zone.

Mainly many theories are put to discuss the effect that happens between the drugs used in combination, the first: is hypothesized as work of the both drugs separately but in double shout which makes it difficult for bacteria to resist both and this can lead to kill simply. Another theory hypothesized that make new drug can not resist the ordinary methods of bacteria and this can be approved by the resistance or diminished of the inhibition zone by creating a new bridge connecting the two drugs and this held on the active location. In addition, the drugs work as a carrier for the other anti-bacterial and this leads to taking it inside the bacterial cell in adequate amounts to give an appropriate effect [10,14].

Anise honey shows a synergistic effect with antibiotics due to its unique antimicrobial properties. The combination of honey with antibiotics enhances the effectiveness of the antibiotics against bacteria, including multi-drug resistant strains. This synergistic action can be attributed to several factors:

Antibacterial Compounds: Honey contains hydrogen peroxide, phenolic acids, and flavonoids, which possess antibacterial properties. These compounds can damage bacterial cell walls, leading to increased permeability and

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allowing antibiotics to enter more easily and act more effectively.

pH and Osmotic Effect: Honey's low pH and high sugar content create an inhospitable environment for bacteria, further enhancing the antibacterial action of antibiotics.

Studies have shown that combining honey with antibiotics can lower the minimum inhibitory concentration (MIC) of the antibiotics, making them more potent against bacteria. For example, the combination of Manuka honey with antibiotics like rifampicin and vancomycin has demonstrated partial synergy and additive effects against various staphylococcal strains, reducing the MIC values significantly (Frontiers) (ResearchBib) (Chat GPT).

Springflower honey exhibits a synergistic effect with antibiotics due to several factors related to its unique composition and properties:

Antibacterial Compounds: Springflower honey contains a variety of antibacterial compounds such as hydrogen peroxide, methylglyoxal, and various phenolic acids and flavonoids. These compounds can disrupt bacterial cell walls and enhance the permeability of antibiotics, making the bacteria more susceptible to antibiotic action (Frontiers) (Frontiers).

Physicochemical Properties: The antimicrobial activity of honey is influenced by its physicochemical properties, such as pH, water content, and the presence of hydrogen peroxide. The acidic pH and osmotic effect of honey create an environment that is inhospitable for bacterial growth, which complements the action of antibiotics. Additionally, hydrogen peroxide in honey acts as an antiseptic, further enhancing its antibacterial properties (Frontiers) (MDPI).

These combined factors make spring flower honey a potent adjunct to antibiotic therapy, helping to overcome bacterial resistance and improve treatment outcomes.

Further study needs to make for a proper formula that can used as an antibacterial. The revolution of incorrect use of antibiotics led to the creation of superbugs that can not be killed in any type with antibacterial drugs so the need for new-generation drugs became one of the most important cases of this century.

Many alternative antibacterials have been raised like honey which is approved as a strong antibacterial and gives a good result in use with no side effects.

Conclusion

The overuse of antibiotics leads to the end of the antibiotic era which leads to looking for alternative methods or another substance.

Honey is one of the oldest antibacterial that is used in medicine. the development of the use of honey and use it in healing becomes one of the most important cases that need to be.

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