

Antibacterial and synergistic effects of honey, plant extracts and Fig milk with antibiotics against bacteria isolated from skin infections

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Abstract

This study investigated bacterial isolates from skin infections, their antibiotic resistance, and the antibacterial activity of honey, plant extracts, and fig milk, including their synergistic effects with antibiotics. Results showed that *Staphylococcus* was the predominant Gram-positive isolate, while *Dermaococcus nishinomiyaensis* and *Kytococcus sedentarius* were identified as opportunistic pathogens. Gram-negative isolates included *Enterobacter cloacae*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*. All isolates exhibited multidrug resistance, with complete resistance to fusidic acid and ampicillin, but remained susceptible to levofloxacin. Honey effectively inhibited Gram-positive bacteria, and alcoholic plant extracts particularly pomegranate peel showed strong antibacterial activity, while fig milk displayed moderate effects. Synergistic assays demonstrated that natural products enhanced antibiotic efficacy, with pomegranate peel extract exhibiting the strongest synergy.

The study demonstrates that skin infections are often caused by multidrug-resistant bacteria, while natural products such as honey, pomegranate peel extracts, and fig milk exhibited antibacterial activity and enhanced the efficacy of antibiotics when combined. This suggests that such combinations represent a promising strategy to combat resistant bacteria and improve the treatment of skin infections.

Keywords: Skin infections, Antibiotic resistance, honey, plant extracts, Fig milk

Introduction

The skin is the largest organ of the body and serves as the primary immune barrier against various environmental factors, including microbial invasion. It hosts a diverse natural flora that plays a crucial role in protecting the skin by preventing colonization by pathogenic organisms. Any disruption in the integrity of this barrier can lead to a range of skin infections, known as skin and soft tissue infections, caused by a wide spectrum of microbes (Skowron *et al.*, 2021) [39]. These infections can range from superficial mild conditions to severe life-threatening cases, such as necrotizing fasciitis caused by *S. aureus* and Clostridium species, and cellulitis and erysipelas caused by Streptococcus species. *Staphylococcus aureus* is among the most common bacteria involved in skin infections, causing a wide range of conditions including impetigo, folliculitis, furuncles, and abscesses (Sartelli *et al.*, 2022; Essa and Younus, 2022) [15, 37].

Antimicrobial resistance (AMR) is considered one of the most critical global health challenges. It arises due to strong selective pressures from the intensive and often irrational use of antibiotics in medical, veterinary, and agricultural sectors. This resistance is primarily transmitted through human interactions in healthcare settings and communities, contributing to its widespread dissemination. Key mechanisms of resistance include the presence of beta-lactamase enzymes that inactivate certain antibiotics, efflux pumps that expel antimicrobial agents from the cell, and the acquisition of resistance genes through mobile genetic elements such as plasmids and transposons (Salam *et al.*, 2023; Tavares-Carreón *et al.*, 2023; Khalaf *et al.*, 2024) [24, 35, 42].

Honey is recognized as an effective natural therapeutic alternative for treating skin injuries and infections, particularly those caused by antibiotic-resistant bacteria. It exhibits antimicrobial properties through the production of hydrogen peroxide and the reduction of pH at the infection site, inhibiting bacterial growth and proliferation. Additionally, honey helps in skin hydration, tissue regeneration, and accelerated wound healing (Ajobiewe *et al.*, 2022; Ogwu and Izah, 2025) [3, 33]. Pomegranate peels possess a wide range of health-promoting properties, including antioxidant, anti-inflammatory, and antimicrobial activities, primarily attributed to their unique phytochemical constituents such as polyphenols, flavonoids, and tannins (Sweidan *et al.*, 2023) [41]. Grape seed extract contains rich phenolic compounds, including gallic acid, catechin, and epicatechin, which provide potent antioxidant, anti-inflammatory, and antimicrobial properties, making it a promising material for natural therapies and health supplements (Duda-Madej *et al.*, 2025) [14]. Fig milk contains proteases, chitinases, and coumarins that contribute to antimicrobial and antiparasitic activities, giving it high therapeutic value in medical applications (Mohammad and Alzweiri, 2022) [30].

Therapeutic synergy is defined as the combination of two substances to enhance their individual effectiveness. Synergy plays a significant role in overcoming multidrug resistance by increasing the inhibitory effect of antibiotics, enabling shorter treatment durations and lower doses, while minimizing the emergence of resistant strains. Thus, synergistic strategies are valuable tools in developing more effective and safer therapeutic approaches (Hancı *et al.*, 2021; Silva *et al.*, 2019) [18, 38].

Materials and Methods

Specimens Collection

Specimens were obtained from clinically diagnosed bacterial skin infections in patients attending dermatology clinics at hospitals in Nineveh Governorate (Al-Salam Teaching Hospital, Mosul General Hospital, Sinjar General Hospital, and Ibn Sina Teaching Hospital). Patients were aged 6–50 years. Specimens were collected using sterile cotton swabs, placed in transport medium tubes, and immediately transferred to the laboratory for further analysis.

Isolation and Identification

Upon arrival, specimens were inoculated onto basic blood agar plates and incubated at 37 °C for 18–24 hours. The cultural characteristics of the resulting colonies were recorded, and representative isolates were purified and subjected to Gram staining, oxidase, and catalase tests. Isolates displaying distinct cultural, morphological, and biochemical characteristics were further identified using the VITEK system according to the manufacturer's instructions.

Antibiotic Susceptibility Test

Antibiotic susceptibility was determined using the modified Kirby–Bauer disk diffusion method, following WHO and CLSI guidelines (Wayne,2017) [44]. Commercial antibiotic disks (Bioanalyse, Turkey) included AMP (10 µg), AMX (30 µg), AMC (30 µg), AZM (15 µg), CIP (10 µg), DA (10 µg), DO (10 µg), FA (30 µg), LEV (5 µg), TE (10 µg), and TMP (10 µg). Results were interpreted according to CLSI criteria to assess resistance patterns.

Antibacterial activity of honey, plant Extracts and Fig Milk

A local natural honey stock solution was prepared at a concentration of 500 mg/mL by dissolving 1 mL (equivalent to 1.3 g) of honey in 1 mL of distilled water (Almasaudi *et al.*,2017) [6]. Regarding plant extracts pomegranate peels and grape seeds are prepared from local pomegranate and grape fruits then aqueous and alcoholic extracts of these materials were prepared. For aqueous extracts, 40 g of plant material were blended with 160 mL distilled water (1:4 w/v), homogenized in an ice bath, and kept at 4 °C for 24 h with intermittent shaking, followed by sequential filtration (gauze and Whatman No.1) to obtain the crude extract. For alcoholic extracts, 20 g of plant material were mixed with 200 mL of absolute ethanol (99%), homogenized in an ice bath, incubated at 4 °C for 24 h, filtered, and dried at <40 °C until complete evaporation of ethanol. The dried extracts were stored in tightly sealed glass bottles until use (Rios *et al.*,1987) [34]. The alcoholic extracts of the studied plants were prepared at a stock concentration of 200 mg/mL by dissolving 1 g of dried plant extract in 5 mL of dimethyl sulfoxide (DMSO). The aqueous extracts of the studied plants were prepared at a stock concentration of 400 mg/mL by dissolving 2 g of dried plant extract in 5 mL of distilled water (Al-saidy *et al.*,2013). Fresh fig milk was collected by making incisions in the trunk of fig trees, allowing viscous white sap to flow. The sap was transferred to sterile tubes and centrifuged at 14,000 rpm for 15 min to remove debris. The supernatant was sterilized at 52 °C for 10 min and stored at 4 °C as a crude extract until used in inhibition assays (Di Pierro *et al.*,2014).

The antimicrobial activity of the tested materials was assessed using the agar well diffusion method, where bacterial suspensions standardized to McFarland No.1 were spread on Mueller–Hinton agar, wells (6 mm) were filled with 100 µL of each material, incubated at 37 °C for 24 h, and inhibition zones were measured in millimeters (ISO, 2019).

Evaluation of the Synergistic Effect of Antibiotics with the Studied Substances

Mueller-Hinton agar (MHA) plates were inoculated with bacterial suspension, adjusted according to the standard McFarland tube, and allowed to dry for 2–3 minutes. Antibiotic discs were then placed on the agar surface, and 10 µL of the tested substance was added to each disc to evaluate the synergistic effect. Plates were incubated at 37°C for 24 hours, and the inhibition zone diameters around each disc were measured in millimeters using a ruler (Wayne,2017) [44].

Results and Discussion

Table (1) illustrates the predominant bacterial isolates identified in the present study. *Staphylococcus* was the most frequent Gram-positive species, consistent with its role as a skin colonizer and major cause of abscesses, cellulitis, and impetigo (Long and Gottlieb,2019; Gurung *et al.*2020) [16]. Less common Gram-positive isolates such as *Dermacoccus nishinomiyaensis* and *Kytococcus sedentarius* may act as opportunistic pathogens, as previously reported in chronic skin conditions including hidradenitis suppurativa and pitted keratolysis (Katoulis *et al.*,2015; Lewicka-Potocka *et al.*,2016) [23, 26]. Among Gram-negative bacteria, *Enterobacter cloacae* complex, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* were also recovered, in line with earlier reports describing their involvement in skin and soft tissue infections, particularly as opportunistic or nosocomial pathogens (Kvopka *et al.*,2023; Cárdenas-Camarena *et al.*,2025; Belzer *et al.*,2022) [9, 12, 25].

Table 1: Predominant bacterial isolates identified in the present study

Gram negative bacteria	Gram positive bacteria
<i>Enterobacter cloacae</i> complex	<i>Staphylococcus aureus</i>
<i>Acinetobacter baumannii</i>	<i>Dermacoccus nishinomiyaensis</i>
<i>Acinetobacter haemolyticus</i>	<i>Kytococcus sedentarius</i>
<i>Stenotrophomonas maltophilia</i>	<i>Staphylococcus hominis</i>
	<i>Staphylococcus lugdunensis</i>

Antibiotic Susceptibility

Antibiotic susceptibility testing of six bacterial isolates against ten antibiotics (Table 2) revealed marked variability in resistance profiles, with all isolates exhibiting multidrug resistance (MDR), defined as resistance to three or more antibiotic classes (Santos *et al.*,2020) [36]. This can result either from spontaneous mutations induced by antibiotic pressure or from horizontal gene transfer via plasmids, transposons, or bacteriophages, while intrinsic factors such as the outer membrane of Gram-negative bacteria may also confer reduced permeability (Hasan and Al-Harmoosh,2020; O'Rourke *et al.*,2020) [19, 32]. Among the isolates, *Stenotrophomonas maltophilia* showed the highest resistance (70%), followed by *Staphylococcus aureus* (60%), *Dermacoccus nishinomiyaensis* (50%), *Kytococcus sedentarius* and *Enterobacter cloacae* (40%), whereas

Acinetobacter baumannii demonstrated the lowest resistance (30%).

Table 2: Susceptibility of the studied bacteria to different types of antibiotics

Bacterial Types	Antibiotics									
	FA	CIP	AZM	LEV	DO	DA	AMP	AMC	TMP	TE
<i>Dermacoccus nishinomiyaensis</i>	R	S	S	S	S	S	R	R	R	R
<i>Kytococcus sedentarius</i>	R	S	R	S	S	S	R	S	S	R
<i>Staphylococcus aureus</i>	R	S	R	S	S	R	R	R	S	R
<i>Enterobacter cloacae</i>	R	S	S	S	S	R	R	R	S	I
<i>Stenotrophomonas maltophilia</i>	R	R	I	S	R	R	R	R	R	I
<i>Acinetobacter baumannii</i>	R	S	S	S	S	S	R	R	S	S

Resistant (R), Sensitive (S), Intermediate (I)

At the individual drug level, complete resistance (100%) was observed to fusidic acid and ampicillin, while high resistance was detected to amoxicillin-clavulanic acid (83.3%). Moderate resistance rates were reported to clindamycin and tetracycline (50% each), trimethoprim and azithromycin (33.3% each), and the lowest to ciprofloxacin and doxycycline (16.6% each). All isolates, however, remained susceptible to levofloxacin, indicating its potential as an effective therapeutic agent. These resistance patterns likely reflect multiple mechanisms, including β -lactamase production, efflux pump activity, and biofilm formation, which collectively enhance bacterial survival under antibiotic stress (Bhandari *et al.*, 2022; Wajeah *et al.*, 2018) [10, 43].

Susceptibility of studied bacteria to tested substances

Susceptibility to Honey: The antibacterial activity of four different types of honey (Sinjar, Thyme, Aqra, and Mountain) was evaluated against the studied bacterial isolates, as presented in Table (4). Overall, natural honey exhibited inhibitory effects against a variety of bacterial species, with varying degrees of susceptibility. *Dermacoccus nishinomiyaensis* showed the highest sensitivity, with inhibition zones ranging from 30 to 37 mm for all honey types. *Staphylococcus aureus* and *Kytococcus sedentarius* also demonstrated considerable susceptibility, with average inhibition zones of 20–22 mm and 23–26 mm, respectively,

suggesting that Gram-positive bacteria are generally more sensitive to honey compared to Gram-negative bacteria, likely due to the presence of an outer membrane in Gram-negative species that limits honey penetration (Hulea *et al.*, 2022) [20].

Among Gram-negative isolates, *Stenotrophomonas maltophilia* exhibited moderate sensitivity, with inhibition zones of 20 mm for Mountain honey and 18 mm for Sinjar and Aqra honeys. *Enterobacter cloacae* displayed partial resistance, showing sensitivity only to Aqra honey (inhibition zone 18 mm), while *Acinetobacter baumannii* was highly resistant, with a maximum inhibition zone of 8 mm across all honey types. The antimicrobial activity of honey is attributed to multiple factors, including low pH, osmotic effect, low water activity, high viscosity preventing bacterial colonization, hydrogen peroxide production, and the presence of bioactive plant-derived compounds such as phenols and flavonoids (McLoone *et al.*, 2020) [29].

The findings of the present study are consistent with (Bouacha *et al.*, 2023) [11], who reported inhibition zones of 20–38 mm for Gram-positive bacteria (including *S. aureus*) and 8–12 mm for Gram-negative species. However, they differ from (Kačániová *et al.*, 2022) [22], where Gram-positive bacteria showed maximum inhibition zones of 13 mm and Gram-negative bacteria 17 mm. Regarding the efficacy of individual honey types, Sinjar, Thyme, and Aqra honeys showed similar antibacterial activity against five out of six isolates (83.33%), whereas Mountain honey was less effective, inhibiting four out of six isolates (66.66%).

Table 4: Susceptibility of the studied bacteria to different types of honey (inhibition zone diameter in mm)

Bacterial Types	Aqra Honey	Thyme honey	Sinjar honey	Mountain honey
<i>Stenotrophomonas maltophilia</i>	18	19	18	20
<i>Enterobacter cloacae</i>	18	15	12	9
<i>Dermacoccus nishinomiyaensis</i>	35	37	33	30
<i>Acinetobacter baumannii</i>	6	6	8	7
<i>Staphylococcus aureus</i>	22	21	22	20
<i>Kytococcus sedentarius</i>	25	26	25	23

Susceptibility to Plant Extracts and Fig Milk: The antibacterial activity of plant extracts (both alcoholic and aqueous) and fig milk against the bacterial isolates was evaluated using the well diffusion method, as shown in Table (3). The results revealed notable variability in the susceptibility patterns among the studied isolates. Several studies have demonstrated the antimicrobial potential of plant and herbal extracts against multidrug-resistant pathogens, highlighting their role as promising alternatives to conventional antibiotics (Ahmed *et al.*, 2021) [2].

Overall, alcoholic extracts exhibited higher inhibitory activity compared to aqueous extracts, likely due to the

enhanced solubility and extraction of bioactive compounds such as phenols and flavonoids (Noveiri *et al.*, 2023) [31]. Among the tested extracts, pomegranate peel showed the strongest antibacterial effect, with inhibition zones of 33 mm (alcoholic) and 30 mm (aqueous). Grape seed extract produced inhibition zones of 25 mm (alcoholic) and 28 mm (aqueous). The superior activity of pomegranate peel is attributed to its high content of phenolic compounds, including ellagic acid and punicalagin, which can penetrate bacterial cell walls and disrupt cellular activity (Hanafy *et al.*, 2021) [17]. Fig milk also demonstrated antimicrobial

activity, producing an average inhibition zone of 15 mm, consistent with the findings of (Ali *et al.*,2018) [5]. Regarding overall susceptibility, *Staphylococcus aureus* and *Acinetobacter baumannii* were the most sensitive isolates, showing inhibitory responses to all plant extracts and fig milk. In contrast,

Stenotrophomonas maltophilia was the least sensitive, exhibiting resistance to fig milk. Notably, *Kytococcus sedentarius* displayed the highest inhibition zone (33 mm) against alcoholic pomegranate peel extract, representing the strongest activity among all tested plant materials against the studied isolates.

Table 3: Susceptibility of the studied bacteria to some plant extracts and fig milk (inhibition zone diameter in mm)

Bacterial Types	Pomegranate peel extract		Grape seed extract		Fig Milk
	Alcoholic	Aqueous	Alcoholic	Aqueous	
<i>Stenotrophomonas maltophilia</i>	20	18	22	28	0
<i>Enterobacter Cloacae</i>	24	25	21	8	14
<i>Dermacoccus nishinomiyaensis</i>	15	30	25	24	0
<i>Acinetobacter baumannii</i>	21	18	22	15	15
<i>Staphylococcus Aureus</i>	28	26	24	18	16
<i>Kytococcus Sedentarius</i>	33	26	21	18	0

Synergistic Effects of studied substances with Antibiotics

Synergistic Effects of Honey: Synergy experiments were performed to evaluate the combined effect of honey with antibiotics against five antibiotic-resistant bacterial isolates (Table 5). The results revealed variable synergistic effects depending on the bacterial species. *Staphylococcus aureus* showed the highest synergy, responding to five antibiotics (DA, AMC, AZM, AMP, FA). *Kytococcus sedentarius* exhibited synergy with four antibiotics (AZM, AMP, TE, FA), while *Enterobacter cloacae* showed synergy with three antibiotics (DA, AMC, AMP). *Stenotrophomonas maltophilia* and *Dermacoccus nishinomiyaensis*

demonstrated synergy with two antibiotics each (DO, FA) and (AMP, FA), respectively.

These findings indicate that honey can enhance the efficacy of antibiotics against resistant isolates from skin infections, potentially converting resistant strains to susceptible ones. This observation aligns with previous studies, where reported improved antibiotic activity in combination with honey against a broad spectrum of resistant bacteria (Abd-El Aal *et al.*,2007) [1]. Additionally, other studies have shown that inhibition zones are larger when antibiotics are combined with honey compared to antibiotics used alone (Masoud *et al.*,2015) [28].

Table 5: Number and type of antibiotics that showed synergy with honey against the studied bacterial strains.

Bacterial Types	Number of antibiotics that showed synergy	Type of antibiotics that showed synergy
<i>Dermacoccus nishinomiyaensis</i>	2	(FA, AMP)
<i>Kytococcus sedentarius</i>	4	(AZM, AMP, TE, FA)
<i>Staphylococcus aureus</i>	5	(DA, AMC, AZM, AMP, FA)
<i>Enterobacter cloacae</i>	3	(DA, AMC, AMP)
<i>Stenotrophomonas maltophilia</i>	2	(FA, DO)

Synergistic Effects of Plant Extracts: The synergistic activity of antibiotics with plant extracts—including ethanolic pomegranate peel and ethanolic grape seed was assessed against various bacterial isolates (Tables 6–7). The results showed variation depending on both the type of extract and the bacterial species. Plant extracts are well-known for their antibacterial properties and for enhancing antibiotic efficacy. Their active compounds can modulate or inhibit resistance mechanisms, rendering bacteria more susceptible or enabling antibiotics to act at lower doses, thereby reducing required doses and side effects (Stefanović, 2017) [40]. Ethanolic pomegranate peel demonstrated the highest synergistic activity. It showed synergy with five antibiotics against *D. nishinomiyaensis* (FA, AMP, AMC, TMP, TE), four antibiotics against *S. aureus* (FA, AZM, DA, AMC), and four antibiotics against

K. sedentarius (AZM, AMP, TE, FA). Moderate synergy was observed with *E. cloacae* (DA, TE), while limited synergy occurred with *S. maltophilia* and *A. baumannii*, each showing synergy with only one antibiotic (CIP and TMP, respectively). These results indicate that pomegranate peel extract effectively enhances antibiotic activity, although the extent of synergy varies with bacterial species and antibiotic type.

Ethanolic grape seed extract exhibited synergistic activity with antibiotics against five out of six tested bacterial isolates (Table 7). The highest synergistic effect was observed against *D. nishinomiyaensis* with two antibiotics (FA, TE), while synergy was noted with AZM in *K. sedentarius* and *S. aureus*. Additionally, grape seed extract showed synergy with TMP against *A. baumannii* and with DA against *S. maltophilia*.

Table 6: Number and type of antibiotics that showed synergy with alcoholic pomegranate peel extract against the studied bacterial strains

Bacterial Types	Number of antibiotics that showed synergy	Type of antibiotics that showed synergy
<i>Dermacoccus nishinomiyaensis</i>	5	(FA, AMP, AMC, TMP, TE)
<i>Kytococcus sedentarius</i>	4	(AZM, AMP, TE, FA)
<i>Staphylococcus aureus</i>	4	(FA, AZM, DA, AMC)
<i>Enterobacter cloacae</i>	2	(DA, TE)
<i>Stenotrophomonas maltophilia</i>	1	(CIP)
<i>Acinetobacter baumannii</i>	1	(TMP)

Table 7: Number and type of antibiotics that showed synergy with alcoholic grape seed extract against the studied bacterial strains

Bacterial Types	Number of antibiotics that showed synergy	Type of antibiotics that showed synergy
<i>Dermacoccus nishinomiyaensis</i>	2	(FA, TE)
<i>Kytococcus sedentarius</i>	1	(AZM)
<i>Staphylococcus aureus</i>	1	(AZM)
<i>Acinetobacter baumannii</i>	1	(TMP)
<i>Stenotrophomonas maltophilia</i>	1	(DA)

Synergistic Effects of Fig Milk: Fig milk demonstrated synergistic effects with antibiotics against three tested isolates (Table 8). Synergy was observed with DA against *E. cloacae*, TMP against *A. baumannii*, and with two antibiotics against *S. aureus*.

The observed synergistic effects of plant extracts are likely due to their ability to inhibit multidrug-resistant efflux

pumps (MDR-efflux pumps), beta-lactamase activity, and remove resistance-carrying plasmids (R-plasmids). These mechanisms facilitate the antibiotics' efficacy by suppressing or circumventing bacterial resistance pathways. Overall, the combination of natural products with antibiotics represents a promising strategy to combat resistant bacterial isolates from skin infections (Ala'a and Essa,2021)^[4].

Table 8: Number and type of antibiotics that showed synergy with fig latex against the studied bacterial strains

Bacterial Types	Number of antibiotics that showed synergy	Type of antibiotics that showed synergy
<i>S. aureus</i>	2	(AZM, DA)
<i>Enterobacter cloacae</i>	1	(DA)
<i>Acinetobacter baumannii</i>	1	(TMP)

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