Comparative Evaluation of the Inhibitory Potential of Synthetic N-Heterocycles, Cu/Fe$_3$O$_4$@SiO$_2$ Nanocomposites and some Natural Products against Non-Resistant and Antibiotic-Resistant Acinetobacter baumannii

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Abstract

**Background:** *Acinetobacter baumannii* is a common infectious agent in hospitals. New antimicrobial agents are identified and prepared to combat these bacterial pathogens. In this context, the blocking potentials of a series of synthesized N-heterocyclic compounds, Cu/Fe$_3$O$_4$@SiO$_2$ nanocomposites, glycine, poly-L-lysine, nisin and hydroalcoholic extracts of *Trachyspermum ammi, Curcuma longa* and green tea catechins were evaluated against non-resistant and multidrug-resistant strains of *A. baumannii*.

**Methods:** Solutions of heterocyclic derivatives and hydroalcoholic extracts of *Trachyspermum ammi, Curcuma longa* and green tea catechins were prepared at initial concentration of 10240 μg ml$^{-1}$ in 10% DMSO. Other compounds were dissolved in water at the same concentrations. Their *in vitro* inhibitory activity was assessed by determination of IZD, MIC and MBC values.

**Results:** Glycine, poly-L-lysine, nisin, *Curcuma longa* and green tea catechins extracts, and thiazoles 3a, 3d and 3f were ineffective at their initial concentrations. Heterocyclic derivatives 7a-f, 3c, 3e and 3h, Cu/Fe$_3$O$_4$@SiO$_2$ nanocomposites and *Trachyspermum ammi* extract could block the growth of bacterial strains with IZDs (7.40-15.51 mm), MICs (32-1024 μg ml$^{-1}$) and MBCs (128-2048 μg ml$^{-1}$).

**Conclusion:** Among synthetic chemicals and natural products, the best antimicrobial effects were recorded with (E)-2-(5-acetyl-4-methylthiazol-2-yl)-2-(thiazolidin-2-yldene)acetonitrile (7b) and the extract of *Trachyspermum ammi*. It is imperative that their toxic and histopathologic effects were assessed in future researches. It is predicted that the essential oil of *Trachyspermum ammi* will improve its antibacterial activities.

**Key words:** Antibacterial effect, *Acinetobacter baumannii*, Cu/Fe$_3$O$_4$@SiO$_2$ nanocomposites, *Curcuma longa*, Green tea catechins, *Trachyspermum ammi*

**Introduction**

*Acinetobacter baumannii* is an aerobic Gram-negative bacillus that causes hospital-acquired infections such as pneumonia, meningitis, endocarditis and urinary tract infections.\textsuperscript{1} Strains of *A. baumannii* were resistant to the most commonly prescribed antibiotics due to their overuse. Resistant bacteria are difficult to inhibit, and expensive to treat.\textsuperscript{2} As a result, new antibiotic agents must be designed and identified to confront these important pathogens.
The medicinal properties of many herbs have been known. Although chemical drugs have been widely used in recent years, but their unpleasant side effects have pushed the researchers to natural alternatives.\(^3\)

\textit{Trachyspermum ammi} is belonging to \textit{umbelliferae} family grows in India, Iran, Iraq and Afghanistan. Its fruit consumed as spice, and prescribed to treat common cold, asthma, diarrhoea, appetite loss, stomach spasms and bloating.\(^4\) In addition, antioxidant, antiparasitic, antifungal, antinematodal, antiviral and antimosquito activities of different parts of this plant were proved in previous researches.\(^4\) \textit{Trachyspermum ammi} could inhibit the growth of \textit{Escherichia coli} and \textit{Staphylococcus aureus}.\(^5\)

Green tea catechins are produced from the fermented leaves of the \textit{Camellia sinensis} plan. It is a herbal antioxidant and anticancer that increases metabolism, alertness, focus and productivity.\(^6\) The inhibitory effects of its extract were also observed against \textit{Candida albicans}, \textit{Candida glabrata}, \textit{Eimeria maxima}, \textit{Streptococcus mutans} and \textit{Staphylococcus aureus}.\(^7\)-\(^9\)

\textit{Curcuma longa} is an ancient condiment that cultivated in India and China. It helps to the improvement of wounds, purification of blood, and reduction of inflammatory and blood cholesterol.\(^10\) It could block the growth of \textit{S. aureus} and \textit{E. coli}.\(^11\)

Copper plays a variety of critical roles in function of the body's tissues and organs such as metabolism, enzyme activity, production of brain cells and scavenging of free radicals.\(^12\) The antimicrobial properties of copper have made it as efficient agent to treat bacterial and fungal infections.\(^13\)

Poly-L-lysine homo polymer is produced from anaerobic bacteria fermentation. It doesn't show any toxicity on the nervous, immune and reproductive systems of rats.\(^14\) It is used as food preservative due to its inhibitory effects on various Gram-positive and Gram-negative bacterial pathogens.\(^15\)

Glycine as the simplest amino acid has low toxicity for humans in small doses. It protects the body against oxidative stress resulting from alcohol consumption. Its inhibitory effects were studied on \textit{Helicobacter pylori}.\(^16\)

Nisin peptide contains 34 amino acids, which produced naturally and industrially from the \textit{Lactococcus lactis}.\(^17\) It as antimicrobial agent inhibits the growth of pathogens such as \textit{Staphylococcus aureus}, \textit{Salmonella typhimurium} and \textit{Candida albicans}. These factors, together with the fact that nisin does not alter gut flora profile, have led to its recommendation as a food preservative by the World Food and Drug Administration.\(^18\)
Thiazoles, imidazolidines and tetrahydropyrimidines are three classes of heterocyclic compounds that found in many natural products and biological compounds. Some thiazole derivatives were used to treat cancer, AIDS, blood lipids and hypertension diseases. Some synthesized thiazoles showed anti-inflammatory and antioxidant activities as well as blocking properties on anopheles mosquitoes or trypanosomes and fungi *Candida albicans*. Antimicrobial effects of thiazole derivatives were evaluated against a broad spectrum of bacterial pathogens such as *Pseudomonas aeruginosa*, *Staphylococcus epidermidis* and *Bacillus subtilis*. Imidazolidine ring is present in midazolam, phenytoin and ketoconazole that applied as anesthetic, anti-seizure and antifungal medicines. In addition, antibacterial effect of synthetic imidazolidines were assessed on *S. aureus*, *Pseudomonas aeruginosa* and *E. coli*. Antifungal, antimalarial, anticancer and anti-inflammatory activities were observed with compounds containing tetrahydropyrimidine core. Tetrahydropyrimidine derivatives could efficiently confront *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. To expand and discover new antimicrobial agents, inhibitory potentials of synthetic thiazole, imidazole and tetrahydropyrimidine derivatives, Cu/Fe₃O₄@SiO₂ nanocomposites, glycine, poly-L-lysine, nisin and hydroalcoholic extract of *Trachyspermum ammi*, *Curcuma longa* and green tea catechins were studied against non-resistant and antibiotic-resistant strains of *A. baumannii*.

**Material and Methods**

**Preparation of nisin, glycine and poly-L-lysine**

Nisin was dissolved in sterile 2% HCl, heated in water bath at 80 °C for 7 min, and sterilized by 0.22 µm syringe filter. Glycine and poly-L-lysine were dissolved in water, and sterilized under the same conditions.

**Preparation of hydroalcoholic extracts**

*Trachyspermum ammi* seeds and *Curcuma longa* rhizomes were collected at harvest stages from Chah-Nimeh of Sistan region; green tea leaves were also obtained from Lahijan. Voucher specimens were deposited at the University of Zabol Herbarium. 10 g of milled plant was soaked in 100 ml of aqueous ethanol 50% for 72 h in total darkness. The mixture was filtered off, and the solvent was evaporated under vacuum to give concentrated extract. The powder extract was obtained by spray drying technique. Extract was dissolved in 10% DMSO at initial concentrations of 10240 µg ml⁻¹, and sterilized by 0.22 µm syringe filter.
**Preparation of Cu/Fe$_3$O$_4$@SiO$_2$ nanocomposites**

The Fe$_3$O$_4$ nanoparticles were prepared using electrochemical system as previously reported.$^{41}$ A solution containing 0.90 g of copper chloride in 50 ml of aqueous ethanol 50% was added to a stirred mixture in an electrochemical cell including 0.27 g of Fe$_3$O$_4$@SiO$_2$ in 50 ml of aqueous ethanol 50%. Then, 1.6 ml acetic acid and 8 ml ethylene glycol were added dropwise to them over 4 h under reduced pressure. Finally, the particles were separated using a magnet, washed with distillated water and calcined at 180 °C for 13 h to give Cu/Fe$_3$O$_4$@SiO$_2$ nanocomposites.$^{41}$

**Synthesis of thiazoles 3a-f**

A mixture including 1 mmol of thioamide 1 (0.23 g), 1-bromocarbonyl compounds 2a-f and sodium bicarbonate (0.08 g) in 1 ml DMF was stirred at ambient temperature (Figure 1). When the reaction was completed, the reaction mixture was added to crashed ice; the solid was gathered and recrystallized from methanol.$^{42}$

![Diagram of thiazole synthesis](image)

**Figure 1.** The synthesis of thiazoles 3a-f

3-Methyl-4-(4-methylthiazol-2-yl)-1-phenyl-1H-pyrazol-5-amine (3a)
1-(2-(5-Amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-4-methylthiazol-5-yl)ethan-1-one (3b)
Ethyl 2-(5-amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-4-methylthiazole-5-carboxylate (3c)
Ethyl 2-(5-amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)thiazole-4-carboxylate (3d)
2-(5-Amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-4(5H)-one (3e)
2-(5-Amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5-methylthiazol-4(5H)-one (3f)

**Synthesis of imidazolidines 6a-c and tetrahydropyrimidines 6d-f**
A mixture including 10 mmol of both carbon disulfide 5 (0.76 g), diaminoalkanes 4a-h as well as 2.5 mmol of MgO nanoparticles (0.1 g) was stirred in 20 ml ethanol at ambient temperature (Figure 2). After the reaction was completed, 10 ml DMSO was added to it, and the mixture was filtered off to remove MgO nanoparticles. The obtained solution was added to crashed ice. The solid was gathered and washed with water and ethanol several times.\(^{43}\)

Figure 2. The synthesis of imidazolidines 6a-c and tetrahydropyrimidines 6d-f

Imidazolidine-2-thione (6a)
4,4-Dimethylimidazolidine-2-thione (6b)
Octahydro-2\(H\)-benzo[\(d\)]imidazole-2-thione (6c)
Tetrahydropyrimidine-2(1\(H\))-thione (6d)
5,5-Dimethyltetrahydropyrimidine-2(1\(H\))-thione (6e)
4-Ethyltetrahydropyrimidine-2(1\(H\))-thione (6f)

Preparing bacterial suspension

Non-resistant strain (PTCC 1855) and strain resistant to cefotaxime, amikacin, levofloxacin, imipenem, gentamicin, trimethoprim-sulfamethoxazole, ciprofloxacin, meropenem and ceftazidime (PTCC 1797) of \(A.\) \textit{baumannii} were prepared from the Persian Type Culture Collection (PTCC). The multi-drug resistant strain has been isolated by Dr. Seyed Javadein from urine culture of a 60-year-old woman suffered from recurrent UTI. Finally, the 0.5 McFarland turbidity standard of each bacterial strain was prepared in Mueller-Hinton broth (MHB) medium.\(^{44}\)

Inhibition zone diameter (IZD) measurement

100 \(\mu\)l of bacterial suspension was spread on a plate 10 cm containing Mueller-Hinton agar (MHA). Some blank discs were placed on it. 10 \(\mu\)l of 10240 and 17.6 \(\mu\)g ml\(^{-1}\) compounds and antibiotics respectively, were poured onto them. The plates were incubated at 37 \(^{\circ}\)C for 24 h. Finally, the IZD values were measured by caliper.\(^{44}\)
The minimum inhibitory concentration (MIC) determination
Bacterial suspensions were diluted to 300 times with MHB. 20 μl of compounds dissolved in DMSO (20480, 10240, 5120, 2560, 1280, 640, 320, 160, 80, 40, 20, 10 μg ml\(^{-1}\)), 80 μl of MHB and 100 μl of diluted microbial suspensions were added to all wells of a twelve-row of 96-well microliter plate. The plates were incubated at 37 °C for 20 h under shaking at 100 rpm. The MIC values were determined as the lowest concentration of compounds without visible turbidity.\(^{44}\)

The minimum bactericidal concentration (MBC) determination
Samples of all wells without visible turbidity in the former test were cultured in MHA. The plates were incubated at 37 °C for another 24 h. The lowest concentration that resulted in no bacterial survived, was considered as the MBC value.\(^{44}\)

Results
In this context, spindle-shaped Cu/Fe\(_2\)O\(_4\)@SiO\(_2\) nanocomposites were prepared with mean diameter of 80 nm according to the FE-SEM micrograph (Figure 3-A).\(^{41}\) Their size distribution were characterized by DLS to obtain the mean hydrodynamic diameter (~ 50 nm), as is shown in Figure 3-B. PDI (polydispersity index) of the prepared nanocomposites was 0.368.

![Figure 3. FE-SEM micrograph (A) and size distribution by DLS (B) of synthesized Cu/Fe\(_2\)O\(_4\)@SiO\(_2\) nanocomposites](image)

The magnetic property of nanoparticles was determined using vibration sample magnetization (VSM) technique. Figure 4 shows the VSM curve of the Cu/Fe\(_2\)O\(_4\)@SiO\(_2\) nanocomposites measured at room temperature under the applied magnetic field of 8000 Oe.\(^{41}\)
Figure 4. The VSM curve of Cu/Fe$_3$O$_4$@SiO$_2$ nanocomposites

Table 1. Data of magnetic nanoparticles of samples

<table>
<thead>
<tr>
<th>Magnetic remanence (emu/g)</th>
<th>Coercivity (Oe)</th>
<th>Magnetic saturation (emu/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.50</td>
<td>70</td>
<td>23.2</td>
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</table>

No inhibitory activity was observed with imidazolidines 6a and 6c, tetrahydropyrimidine 6e, glycine, poly-L-lysine, nisin, Curcuma longa and green tea catechins extracts. Cu/Fe$_3$O$_4$@SiO$_2$ nanocomposites, thiazoles 3c-f and tetrahydropyrimidine 6d were only effective on non-resistant strain with IZD of 6.76-11.64 mm, MIC of 64-512 µg ml$^{-1}$ and MBC of 256-1024 µg ml$^{-1}$. Inhibitory effects of Trachyspermum ammi extract, thiazoles 3a,b, imidazolidine 6b and tetrahydropyrimidine 6f were proven on both non-resistant and antibiotic-resistant strains with IZD of 6.00-15.51 mm, MIC of 32-1024 µg ml$^{-1}$, and MBC of 64-2048 µg ml$^{-1}$. The best results belonged to thiazole derivative 3b (Table 2).

Table 2. Antibacterial effect of compounds on A. baumannii

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Non-resistant strain</th>
<th>resistant strain</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>IZD</td>
<td>MIC</td>
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<tr>
<td>3a</td>
<td>6.48</td>
<td>512</td>
</tr>
<tr>
<td>3b</td>
<td>14.74</td>
<td>32</td>
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<tr>
<td>3c</td>
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<td>3d</td>
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<td>3e</td>
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<td>128</td>
</tr>
<tr>
<td></td>
<td>IZD (mm)</td>
<td>MIC (µg ml⁻¹)</td>
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<td>----</td>
<td>----------</td>
<td>---------------</td>
</tr>
<tr>
<td>3f</td>
<td>11.52</td>
<td>64</td>
</tr>
<tr>
<td>6a</td>
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<td>-</td>
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<td>6b</td>
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<td>6c</td>
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<td>6d</td>
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<td>6e</td>
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</tr>
<tr>
<td>6f</td>
<td>8.62</td>
<td>512</td>
</tr>
<tr>
<td>Cu/Fe₃O₄@SiO₂ NCs</td>
<td>6.76</td>
<td>512</td>
</tr>
<tr>
<td>Trachyspermum ammi extract</td>
<td>15.51</td>
<td>64</td>
</tr>
<tr>
<td>Glycine</td>
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<td>-</td>
</tr>
<tr>
<td>Nisin</td>
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<td>-</td>
</tr>
<tr>
<td>Poly-L-lysine</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Curcuma longa extract</td>
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<td>-</td>
</tr>
<tr>
<td>Green tea catechins extract</td>
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<td>-</td>
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<tr>
<td>Imipenem</td>
<td>18.36</td>
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</tr>
</tbody>
</table>

- : No inhibitory effects in the initial concentrations, IZD (mm), MIC (µg ml⁻¹), MBC (µg ml⁻¹)

**Discussion**

In this study, antibacterial effects of plants extracts, peptides, an amino acid, metallic nanoparticles and heterocyclic derivatives were evaluated against non-resistant and resistant strains of *A. baumannii*.

The synthesized nanocomposites were characterized with FE-SEM, DLS, VSM and PDI techniques. The obtained PDI implies that they can be applied in drug delivery due to their homogeneous distribution. According to the results obtained in Figure 4 and Table 1, it can be seen that the VSM curve of Cu/Fe₃O₄@SiO₂ nanometer-sized particles behaves like paramagnetic particles. The origin of magnetic property of Cu/Fe₃O₄@SiO₂ is related to the Fe₃O₄. These properties didn’t change significantly in the presence of Cu atoms. So, the VSM curve of Fe₃O₄@SiO₂ will be same to that of Cu/Fe₃O₄@SiO₂.

No inhibitory activity was observed with glycine on *A. baumannii*. This amino acid blocks the growth of bacteria via prevention of the biosynthesis of bacterial cell wall peptidoglycan. Its inhibitory effects are more evident on Gram-positive bacteria. Glycine in zwitterionic form,
is called glycine betaine, can stop the growth of *A. baumannii* by plasma membrane proton pump inhibition.\textsuperscript{47}

Poly-L-lysine did not show inhibitory activity on *A. baumannii*. This peptide can destruct bacterial proteins, and alter bacterial morphology. It changes the electrical conductivity and penetrability of bacterial membranes as well as the cellular metabolisms.\textsuperscript{48} The pH and temperature of a culture medium affect on its antimicrobial potentials.\textsuperscript{49}

Nisin was ineffective on *A. baumannii*. It pierces the cell membrane, changes ionic exchanges, and disrupts ATP production.\textsuperscript{50} It is mostly effective on Gram-positive bacteria due to the presence of an additional outer membrane in Gram-negative strains. Even though inhibitory effect of nisin has been reported against *E. coli*.\textsuperscript{18}

Extracts of *Curcuma longa* and green tea catechins can't stop the growth of *A. baumannii*. Antimicrobial effects of green tea catechins especially against Gram-positive strains are caused by the destruction of phospholipid membranes.\textsuperscript{51,52} The researchers believe that phenolic compounds of *Curcuma longa* play an essential role in dealing bacterial pathogens. Inhibitory effect was observed with *Trachyspermum ammi* extract on both non-resistant and resistant strains of *A. baumannii*. Thymol as its most important component is responsible for antibacterial properties of this plant. It blocks bacteria via membrane inflation.\textsuperscript{53,54} Electron microscopic find in showed that extract causes an increase in extracellular potassium levels and ATP as well as change in shape of *Bacillus cereus*.\textsuperscript{55} In addition, antibacterial effects of *Trachyspermum ammi* have been reported on Gram-negative strains such as *Pseudomonas aeruginosa*, *Salmonella typhimurium* and *Enterobacter aerogenes*.\textsuperscript{55}

In this study, antibacterial potentials of Cu/Fe\textsubscript{3}O\textsubscript{4}@SiO\textsubscript{2} nanocomposites were also screened on *A. baumannii*. Cu NPs are antimicrobial agents that inhibit the growth of bacteria using degradation of DNA, oxidation of protein, peroxidation of lipid and generation of reactive oxygen species.\textsuperscript{56} Antibacterial effects of nanoparticles are related to their size and morphology as well as growth media and carrier. Antibacterial activities of the synthesized n-Cu@T-ZnO nanocomposites were studied on *Escherichia coli* and *Staphylococcus aureus*, their inhibitory effects were higher than those of pristine T-ZnO and the n-Cu nanoparticles.\textsuperscript{57} The polymers were widely used as the carrier in incorporation with copper nanoparticles, these nanocomposites are effective on a variety of harmful organisms and microorganisms.\textsuperscript{58} Inhibitory activity of copper-doped montmorillonite nanocomposites were also evaluated against *E. coli* and *S. aureus*.\textsuperscript{59} It is important to mention that the Fe\textsubscript{3}O\textsubscript{4} nanostructures as the most magnetic nanoparticles, have received a wide attention in the biomedical applications,
especially for targeted gene/drug delivery systems due to their outstanding features in magnetism, lower toxicity, biocompatibility, biodegradability, and so on. The Fe$_3$O$_4$ nanostructures are easy to oxidize and aggregate, and thus they are often made with different coating agents such as SiO$_2$ as stabilizers to realize superior properties for gene/drug delivery. Thiazoles are potent antibacterial agents against both Gram-positive and Gram-negative pathogenic bacteria.$^{60,61}$ In this study, all synthetic thiazole derivatives were effective on the non-resistant strain of $A$. baumannii. However, only two derivatives 3a, b could inhibit its resistant strain. It has been suggested that thiazoles inhibit eCKASIII or FabH enzymes, which are required for the synthesis of fatty acids in bacteria, and DNA gyrase enzyme, a catalyst for ATP-dependent DNA, and Hfq protein, which is essential for replication of bacteria.$^{62,63}$ The substituents attached or fused to thiazole ring affect its inhibitory activities. It seems that pyrazole substituent has improved antibacterial activity of thiazole derivatives.$^{64}$ Inhibitory potentials of imidazolidine derivatives were studied on $E$. coli, $P$. aeruginosa and $A$. baumannii.$^{65-67}$ Inhibitory effect of imidazolidine 6b was also proven against $A$. baumannii. It is proposed that imidazolidine derivatives can inhibit dihydrofolate reductase (which plays a key role on the synthesis of tetrahydrofolic acid) as well as lipid synthesis.$^{68}$ Nitroimidazole derivatives can also stop bacteria via free radical generation.$^{69}$ Tetrahydropyrimidine derivatives 6d and 6f inhibit strains of $A$. baumannii. It is proposed that tetrahydropyrimidines act as channel blockers or inhibitors of cell surface receptors in the face with bacteria.$^{70}$ Some synthesized tetrahydropyrimidines showed excellent antimicrobial activities on Gram-negative and Gram-positive bacteria.$^{71,72}$ Williams et al. assessed the inhibitory potency of some synthetic tetrahydropyrimidines on $A$. baumannii by measuring the MIC values.$^{73}$

**Conclusion**

In this study, good to excellent antibacterial effects were observed with $Trachyspermum$ ammi extract, thiazolyl pyrazoles 3a and 3b, imidazolidine-2-thione 6b, tetrahydropyrimidine-2-thione 6f and Cu/Fe$_3$O$_4$@SiO$_2$ nanocomposites against both non-resistant and multidrug-resistant strains of $A$. baumannii. While, the extracts of $Curcuma$ longa and green tea catechin, nisin, poly-$L$-lysine, glycine and cyclic thioureas 6a, 6c and 6e were ineffective on tested strains. Thiazole 3b exhibited the best inhibitory activities. Effective compounds especially natural plant extract and nanoparticles can be introduced as efficient antimicrobial agents if their toxicity tests were satisfactory.
Ethical Issues
Not applicable.

Conflict of Interest
The authors report no conflicts of interest.

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Reference


