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In Vitro Antimicrobial and Anticancer Activities of Quercetin Thiourea Derivative

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ABSTRACT

Background and Aims: Quercetin is a plant-derived flavonoid with diverse biological and pharmacological properties, including antioxidant, anti-inflammatory, anticancer, antibacterial, antifungal, and antiviral activities. Flavonoid compounds such as quercetin have demonstrated therapeutic potential against several cancer types, including liver, colorectal, and breast cancers. This study aimed to evaluate the anticancer, antibacterial, and antifungal activities of thiourea derivative of quercetin.

Materials and Methods: The biological activities of the quercetin thiourea derivative were assessed against selected bacterial and fungal strains, as well as liver cancer cells. The minimum inhibitory concentration (MIC) was determined using the agar well diffusion method. Anticancer activity against liver cancer cells was evaluated using the MTT assay.

Results: The quercetin thiourea derivative exhibited antibacterial activity against *Bacillus cereus* (MW972221.1), *Burkholderia* spp., *Staphylococcus aureus*, and *Enterococcus faecalis*, with MIC values of 1, 15, 10, and 0.8 mg/mL, respectively. It also demonstrated antifungal activity against *Candida* species, with MICs of 5 mg/mL for *C. krusei* and *C. tropicalis*, 1 mg/mL for *C. albicans*, and 30 mg/mL for *C. glabrata*. The compound showed cytotoxic effects on liver cancer cells, with IC_{50} values of 300, 224, and 31.5 µg/mL at 24, 48, and 72 hours, respectively.

Conclusion: The quercetin thiourea derivative represents a biologically active compound with promising antibacterial, antifungal, and anticancer properties. Its inhibitory effect on liver carcinoma cell growth is likely mediated through apoptosis induction. These findings suggest that the quercetin thiourea derivative could serve as a potential lead compound for antimicrobial and anticancer drug development, warranting further investigation.

Keywords: Antibacterial, Anticancer, Antifungal, Liver Cancer, MIC, Quercetin, Quercetin Derivatives

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1. Introduction

Flavonoids that consist of widespread classes of phytochemicals possess significant medicinal properties, like anti-aging **(1)**, antioxidative **(2)** and anti-inflammatory properties **(3, 4)**. The 3,3′,4′,5,7-pentahydroxyflavone, called quercetin, is a polyphenolic flavonoid, which is extensively available in citrus fruits, green leafy vegetables, apples, red grapes, and onions. It is yellow in color, and its name is originated from the Latin word "quercetum". Although quercetin is easily soluble in

lipids and alcohols, it is sparingly soluble in hot water (5). Additionally, it has antiviral (6, 7), anti-inflammatory (8, 9), antitumor (10-12) and antiplatelet aggregation (3, 13) properties. Quercetin has shown efficiency against a variety of bacterial diseases due to its capacity to damage bacterial membranes, inhibit efflux pumps, and disrupt vital cellular functions (14). Mehrbod et al (15) focused on viral pathogenesis and utilization of quercetin and its derivatives as adjunctive therapy for managing influenza and its associated symptoms based on specific targets.

Aires et al (16) and da Silva et al (17) reported that flavonols represent the most biologically active class of flavonoids. These compounds exhibit a broad spectrum of biological activities, including cardiovascular protective effects, making them one of the most valuable classes of natural chemicals. To enable their effective application in drug development, the mechanisms underlying their antibacterial actions have been extensively investigated in recent years. Studies on pharmacological properties of quercetin have demonstrated it as potent natural antibacterial agent capable of inhibiting a wide range of pathogenic microorganisms (18).

Candida species have been one of the most causes of morbidity and mortality worldwide and pose a major risk to the health, particularly for individuals with weakened immune systems (19). Although additional species (non-albicans) such *Candida (C.) tropicalis*, *C. krusei*, *C. parapsilosis* and *C. glabrata* emerge as opportunistic pathogens, which cause increase in death rates in bloodstream infections, *C. albicans* is thought to be the primary source of infections (20).

Cancer is considered as one of the major causes of death all over the world. The number of deaths from various cancers and the number of new patients with various cancers rise annually. Therefore, to monitor the growth of cancer, improve the clinical manifestations, and effectively treat this condition, new and effective therapeutics must be developed (21). Malignant cancer cells in the breast, lung, stomach, ovaries, colon, and liver were remarkably inhibited by quercetin (22). Its anticancer properties is applied through several methods, including angiogenesis inhibition, cell death, P-gp channel blocking, signaling pathway regulation, and oncogene expression reduction (23). Its use as an efficient antibacterial agent is hampered by its limited oral bioavailability and absorption in the human body. To fully utilize its medicinal potential, more effort is needed to increase its bioavailability (24).

2. Materials and Methods

2.1 Quercetin Thiourea Derivative

This quercetin thiourea derivative compound was a gift from Assistant Professor Asmaa Sami Madhi, College of Veterinary Medicine, University of Basrah – Iraq. It was previously synthesized by Shaker et al (25). The synthesis and structure of the compound was illustrated in Figure 1.

2.2 Antibacterial Activity of Quercetin Thiourea

Different concentrations of quercetin thiourea (100, 70, 50 and 30 mg/mL) were used to test its biological activity (26). Agar well diffusion method was conducted to determine the antibacterial susceptibility (27-31). The well that contained DMSO was used as control.

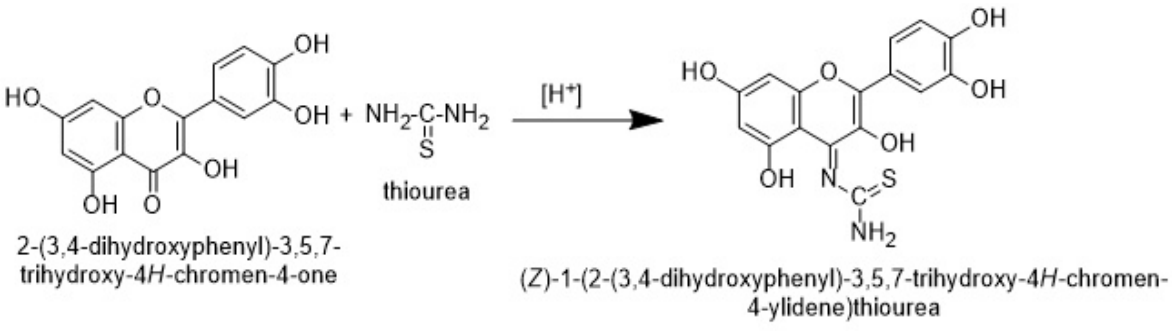


Figure 1. Synthesis and structure of quercetin thiourea derivative **(Prepared by Authors, 2025)**.

2.3 Minimum Inhibitory Concentration of Quercetin Thiourea

The susceptibility of four bacterial strains to the synthesized compound was examined using various concentrations of the compound (20, 15, 10, 5, 2, 1, 0.8 and 0.5 mg/ml). Well diffusion method was applied to calculate minimum inhibitory concentration (MIC) of the compound for each bacterium (27-29). The compound was dissolved in DMSO at several concentrations. The agar plate was 4

mm depth and 6 mm well diameter. The concentration of 0.5 McFarland (corresponding to approximately 5 × 10^5 CFU/mL for broth microdilution tests (CLSI M07-A10) was applied to the bacteria-containing suspension **(30-32)**.

2.4 Antibacterial Activity of Quercetin Thiourea

The compound primary susceptibility test toward clinical fungal isolates, *C. albicans*, was conducted under various conditions. *C. albicans* was incubated for 24-48 hr. The Sabouraud dextrose agar (SDA) plates for fungi were filled with 100 µL of the yeast solution, which were distributed using an L-shaped glass spreader. After allowing the plates to dry for 15 min at room temperature, sterile wells (6 mm diameter) were punched. Each concentration (100, 70, 50, 30, 20, 15, 10, 5, 2, 1, 0.8, 0.5 mg/mL) was added in 100 µL to each hole and incubated for 24-48 hr. DMSO was used as control. In order to measure the inhibitory effect, inhibition zone diameters were measured in millimeter **(33-35)**.

2.5 Anticancer Activity of Quercetin Thiourea Against Liver Cancer Cell

Hepatocellular carcinoma (HCC) cells were grown in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS). Anticancer activity of the compound was tested using MTT assay. The cells were seeded in 96-well plates ($1*10^4$ cells/well). The compound different concentrations (7.5, 15, 31, 62.5, 125, 250, 500, 1000 mg/mL) dissolved in DMSO were added to the cells (100 µL/well) in triplicate and incubated for 24, 48 and 72 hr at 37°C 5% CO_2 incubator. Viability of the cells was measured using ELISA reader (EPOCH/ BioTek Instruments-USA) at 570 nm for the absorbance measurement. The cells not exposed to the compound were used as control **(36-38)**. This test was performed at the Central Laboratory, Mashhad University of Medical Sciences.

2.6 Statistical Analysis

The data presented as mean±SD were analyzed by SPSS software (version 26). Chi-square test was performed to assess the correlation between data, with the level of significance set at 5%.

3. Results

3.1 Antibacterial Activity Results

The antibacterial activity of the compound was examined against Gram-positive bacteria; *Staphylococcus aureus*, *Burkholderia*, *Enterococcus faecalis,* and *Bacillus cereus* and Gram-negative bacteria; *Klebseilla* and *Escherichia coli* (mentioned in Table 1) at different concentrations. Inhibition zones are shown in Figure 2. No inhibition zone was observed in the control.

3.2 The MIC Results Against Bacterial Isolates

According to Table 1 and Figure 3, the compound MIC for *Escherichia coli* and *Klebsiella* was No inhibition, while MICs for *Bacillus cereus*, *Burkholderia*, *Staphylococcus aureus*, and *Enterococcus faecalis* were 1, 15, 10, and 0.8 mg/mL, respectively. There were highly significant differences (P<0.001). There was no inhibition zone in the control.

3.3 Antifungal Activity Results

The quercetin thiourea showed clear effect on several types of Candida, such as *C. krusei, C. glabrata*, *C. tropicalis* and *C. albicans*. The antifungal activity of the compound was revealed at concentration of 10 mg/mL, while the MICs against Candida *spp.* were 2 and 4 mg/mL, respectively (Table 2). Inhibition zones are shown in Figure 4. There were significant differences between Candida *spp* (*C. krusei, C. glabrata*, *C. tropicalis* and *C. albicans*) and control. P-value<0.001 was obtained for all Candida *spp*. except *C. glabrata* (P=0.044).

3.4 MIC of Quercetin Thiourea Against Fungal Isolates

The compound MIC was obtained 5 mg/mL for both *C. krusei* and *C. tropicalis*, but it was 30 and 1 mg/mL for *C. glabrata* and *C. albicans*, as shown in Table 2 and Figure 5.

3.5 Anticancer Activity of Quercetin Thiourea Derivative against Liver Cancer Cells

The compound effectiveness on inhibiting liver cancer cell growth was evaluated using different concentrations (7.5, 15, 31, 62.5, 125, 250, 500, 1000 mg/mL) at 570 nm at 24, 48 and 72 hr as shown in MTT cell viability assay. Results are shown in Figures 6, 7, and 8.

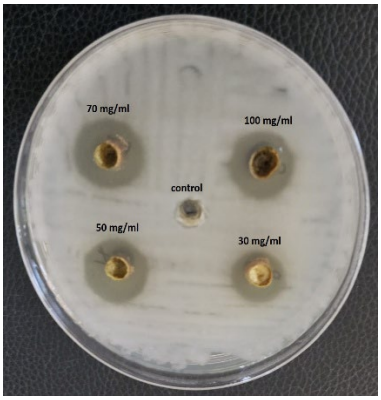
Table 1. Antibacterial activity results of quercetin thiourea derivative.

Conc. mg/ml	Bacteria/ inhibition zone (mm) (mean ±SD)					
	Bacillus cereus	*Burkholderia*	*Staphylococcus aureus*	*Enterococcus faecalis*	*Echerichia coli*	*Klebsiella*
100	16.5±0.7	24.0±0.0	14.5±0.7	24.5±0.7	No inhibition	No inhibition
70	14.4±0.7	21.0±1.4	12.0±1.4	24.0±1.4	No inhibition	No inhibition
50	16.5±0.7	21.0±1.4	12.0±1.4	21.0±1.4	No inhibition	No inhibition
30	12.0±1.4	16.0±1.4	6.5±0.7	19.5±0.7	No inhibition	No inhibition
20	8.0±0.0	11.5±0.7	4.0±1.4	15.0±0.0	No inhibition	No inhibition
15	7.5±0.7	9.5±0.7	4.0±0.0	14.0±1.4	No inhibition	No inhibition
10	7.0±0.0	No inhibition	2.5±0.7	13.5±0.7	No inhibition	No inhibition
5	7.0±0.0	No inhibition	No inhibition	12.5±0.7	No inhibition	No inhibition
2	5.5±0.7	No inhibition	No inhibition	12.0±1.4	No inhibition	No inhibition
1	4.0±1.4	No inhibition	No inhibition	11.5±0.7	No inhibition	No inhibition
0.8	No inhibition	No inhibition	No inhibition	4.0±1.4	No inhibition	No inhibition
0.5	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition

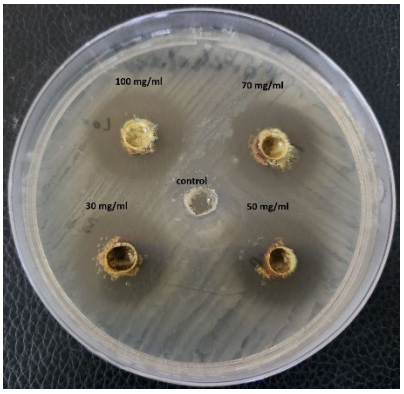
Table 2. Antifungal activity of quercetin thiourea derivative.

Conc. mg/ml	Bacteria/ inhibition zone (mm) (mean ±SD)	
	C. albicans	Control
100	23.0±1.4	No inhibition
70	22.5±0.7	No inhibition
50	22.0±0.0	No inhibition
30	21.0±1,4	No inhibition
20	21.0±1.4	No inhibition
15	15.5±0.7	No inhibition
10	11.5±0.7	No inhibition
5	10.0±0.0	No inhibition
2	4.0±0.0	No inhibition
1	3.0±0.0	No inhibition
0.8	No inhibition	No inhibition
0.5	No inhibition	No inhibition

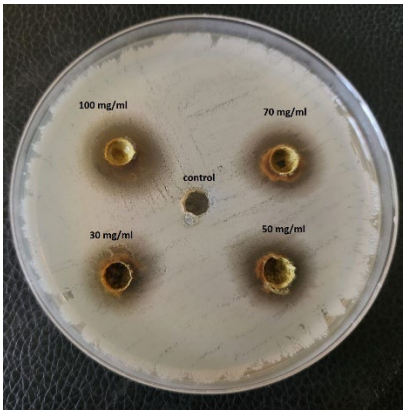
Bacillus cereus



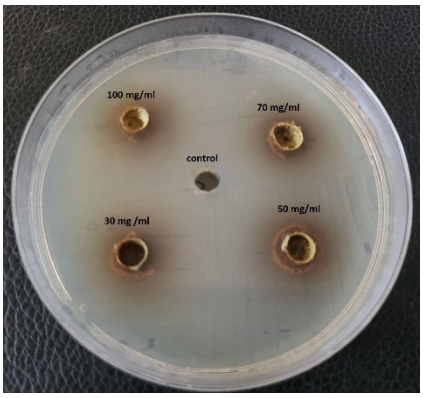
Burkholderia



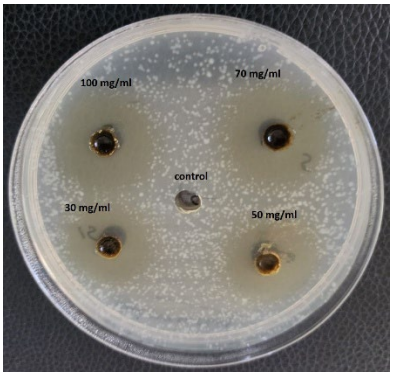
Staphylococcus aureus



Escherichia coli



Enterococcus faecalis



Klebsiella pneumonia

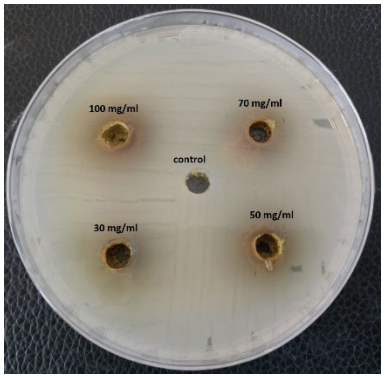
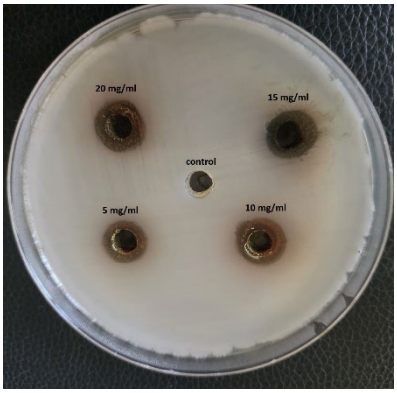
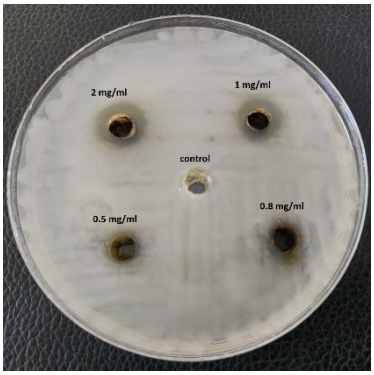


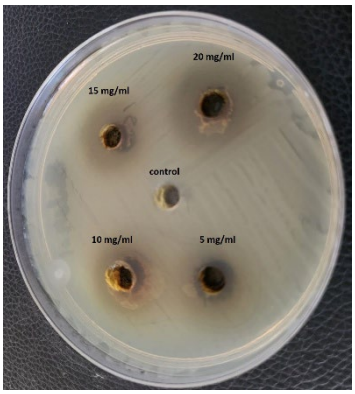
Figure 2. Inhibition zones of antibacterial activity of quercetin derivative **(Prepared by Authors, 2025)**.

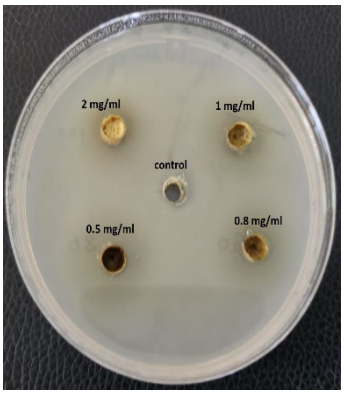
Bacillus cereus



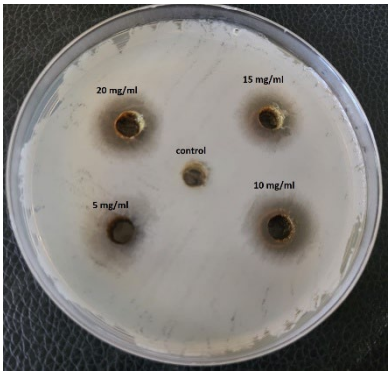


Burkholderia cepacia

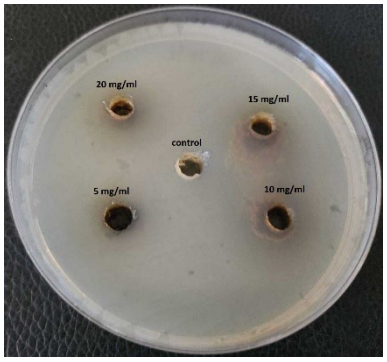




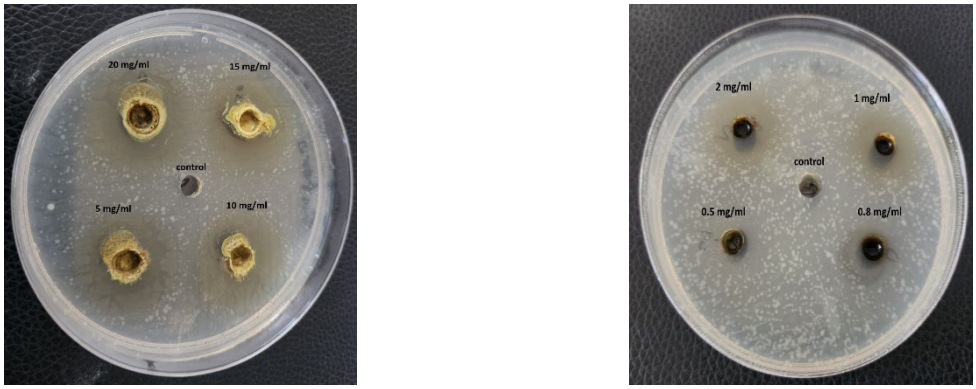
Staphylococcus aureus



Escherichia coli



Enterococcus faecalis



Burkholderia cepacia

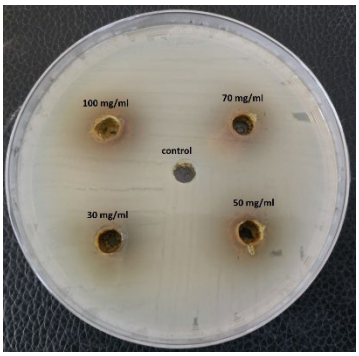
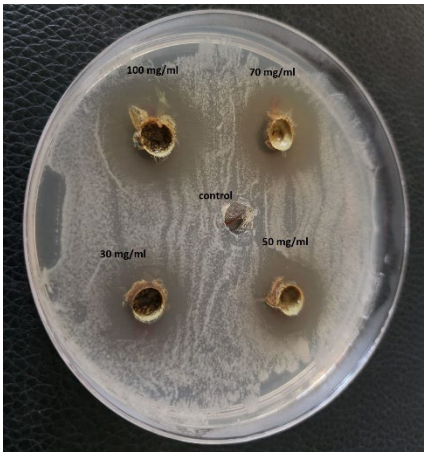
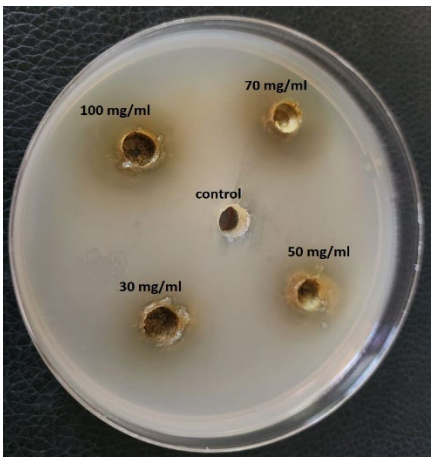


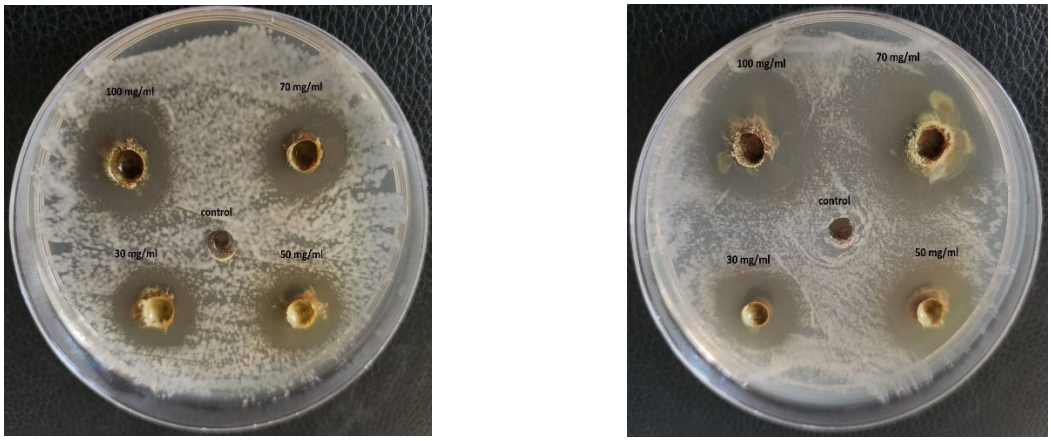
Figure 3. The antibacterial and MICs of quercetin compound in different concentrations (100, 70, 50, 30 mg/mL) on bacterial isolates **(Prepared by Authors, 2025)**.

C. albicans



C. glabrata

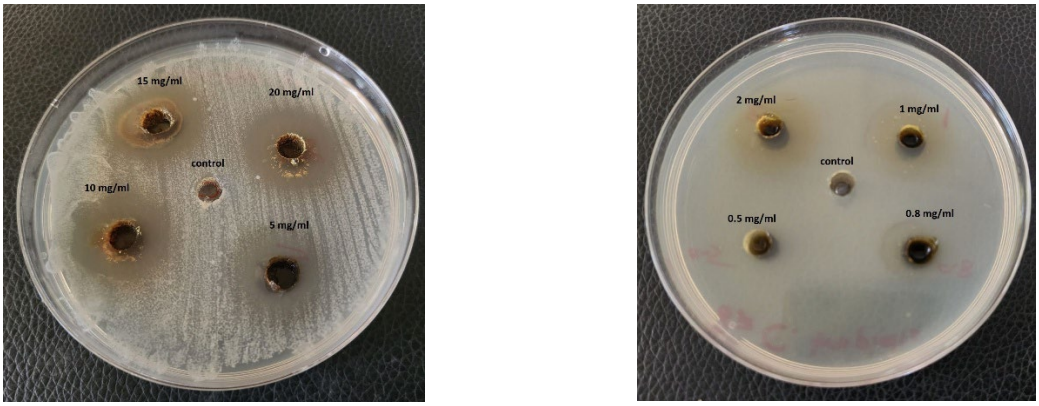




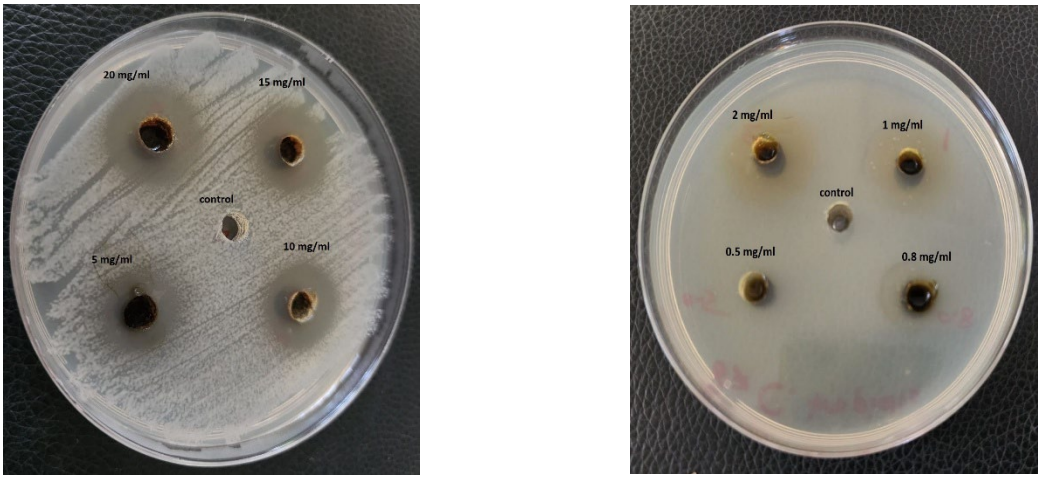
C. krusei *C. tropicalis*

Figure 4. Inhibition zones of antifungal activity of quercetin thiourea derivative **(Prepared by Authors, 2025)**.

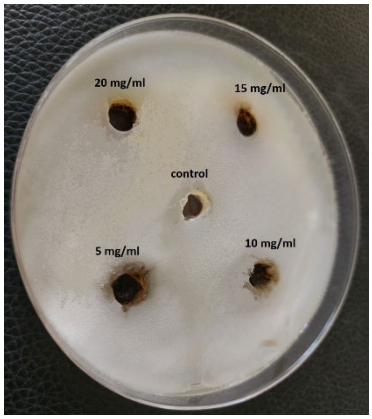
C. albicans



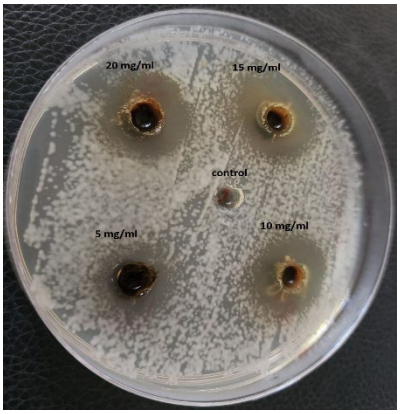
C. tropicalis



C. glabrata



C. krusei



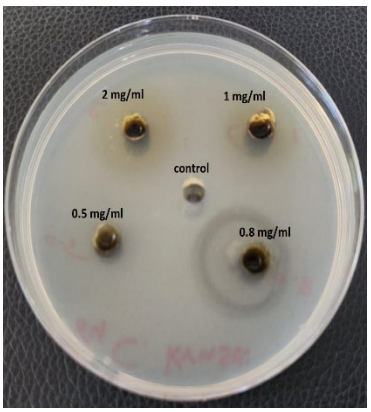


Figure 5. MIC of quercetin thiourea derivative against *Candida spp.* **(Prepared by Authors, 2025)**.

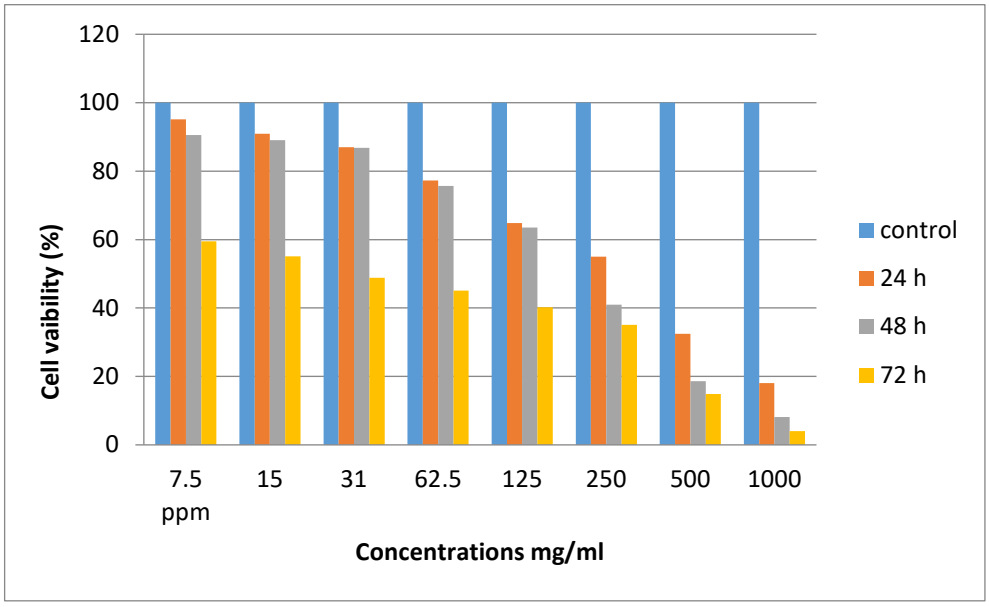


Figure 6. Cell viability of MTT assay at different time points **(Prepared by Authors, 2025)**.

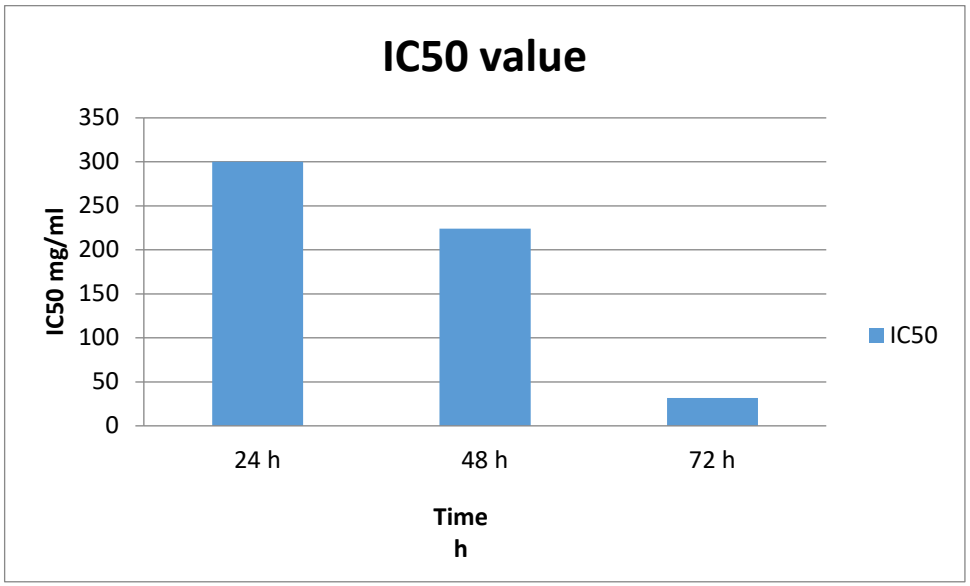


Figure 7. IC_{50} values **(Prepared by Authors, 2025)**.

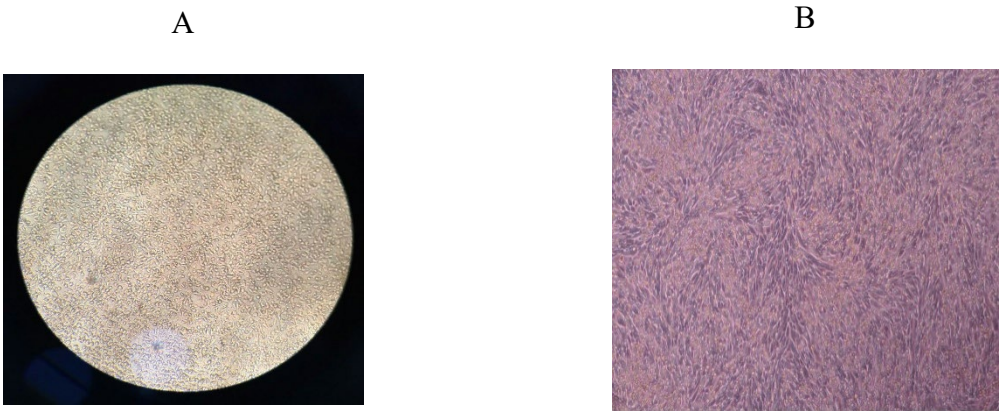


Figure 8. Effect of quercetin on HCC cells. A) Untreated, B) Treated with quercetin **(Prepared by Authors, 2025)**.

4. Discussion

Quercetin, a pentahydroxyflavone, is one of the most significant flavonoid that is present in several foods. It has widespread biological activities such as anti-cancer, anti-inflammatory, antioxidant, anti-microbial, cardiovascular disease prevention, anti-diabetic, neuroprotective, and anti-obesity properties **(39)**.

The rise in microbial cause diseases and increases in the rate of resistant germs have encouraged scientists to focus on developing novel antimicrobial medications **(40)**.

In this study, the quercetin thiourea derivative was used against bacterial strains. Its effects was shown on Gram-positive bacteria such as *Staphylococcus aureus, Enterococcus faecalis*, *Burkholderia*, and *Bacillus cereus*. No effect was observed on Gram negative bacteria like *Escherichia coli* and *Klebsiella*. The interactions and good solubility of quercetin with the cell membrane of bacteria that are performed by quercetin hydroxyl groups might be associated with its antibacterial properties.

Gram-negative bacteria compared to Gram-positive bacteria are generally resistant to quercetin bactericidal actions **(18, 40, 41)**. The efficiency of this compound may be altered by phosphorylation and sulfating at different hydroxyl groups, which could alter its solubility **(5, 42)**. Quercetin can inhibit β-ketoacyl carrier protein synthases, which were involved in the bacterial fatty acids production. The removal of biofilm has been suggested as an additional possible course of action **(23)**. The MIC of quercetin thiourea derivative on bacteria in this study, which inhibited bacterial growth approximately showed the lowest concentration among flavonoids.

Flavonoids have also shown antifungal activities **(18)**. The quercetin derivative in this study also exhibited notable antifungal activity against Candida spp. such as *C. albicans*, *C. glabrata*, *C. krusei* and *C. tropicalis*. Quercetin reduced the biomass and metabolic efficacy of every tested fungus strain **(23)**. We expect that antifungal mechanism refer to the suppression of fungal cell walls production, damage into the integrity of fungal cell membranes and interference with fungal and cell signaling pathways. The antifungal properties of quercetin thiourea indicate that it may be useful treatment for candidiasis **(43)**.

This study demonstrated that quercetin thiourea derivative makes excellent activities against bacteria and fungi and it is an outstanding option for the creation of strong antibacterial and antifungal drugs.

Other studies showed a direct comparison between quercetin and other derivatives of the flavonoid family (naringenin and catechin), where quercetin was found to have the highest dissolving capacity on bacterial cell membrane, and anti-hemolysis activity compared to its other derivatives **(44)**.

Cancer is the second common cause of death worldwide and is a problem of global importance. This illness has a significant impact on both public health and economies. The conventional methods of treating cancer are being closely examined by drug development researchers **(45)**. This study showed good activity of quercetin thiourea derivative against liver cancer cells as compared to other studies that showed the same results. Through the modulation of multiple intracellular processes, quercetin may play significant functions against liver cancer cells, including cell cycle arrest and apoptotic cell death **(46)**.

In this evaluation, cells cancer cells appeared irregularly shaped, covered most of the space indicating rapid proliferation and loss of contact inhibition, as well as lack of large spaces between cells. That indicates dense and aggressive cell growth (Figure 7A).

After treatment the cells became more elongated and appeared more regularly spindle-shaped compared to their irregular shape in Figure 7A. The number of cells reduced, indicating decreased mitotic activity, growth inhibition or cell death (apoptosis) (Figure 7B).

Cell viability decreased by increasing quercetin derivative compound exposure to the cells. This indicates the significance of drug exposure time as extended exposure might result in improved cytotoxic effects and higher drug absorption **(47)**.

Because quercetin and its derivatives have several modes of action, they offer a promising way to improve cancer treatment. The expanding research shows quercetin potential to work in concert with traditional treatments while reducing their toxicity is becoming more well acknowledged **(48)**.

Kullenberg et al **(49)** obtained the same results after 24 hr of exposure suggesting that prolonged exposure increases drug capacity to stop the proliferation of tumor cells. Saeed et al **(50)** also reached the same result when using thiadiazol substances against prostate cancer cells, and the effect of substance increased during the time.

5. Conclusion

The quercetin derivative compound showed outstanding antimicrobial properties against Gram-positive bacteria such as *Basillus cereus*, *Burkholderia*, *Staphylococcus aureus*, *Enterococcus faecalis*, and some fungi such as Candida *spp* like *C. krusei, C. glabrata*, *C. tropicalis* and *C. albicans*. This natural molecule showed the potential to function as a narrow spectrum antibacterial and antifungal. It also showed anticancer activity *in vitro* against liver cancer cells in elevated concentrations and extended exposure times. The addition of quercetin appears to stop or reduce the proliferation of cancer cells, and may cause cell death or stimulate them toward a less aggressive differentiation pathway. This compound requires further investigation to be used as drug.

6. Declarations

6.1 Acknowledgment

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6.2 Ethical Considerations

The study was approved by the Ethical Committee of the Institutional Review Board (IRB), University of Basrah, Al-Zahraa College of Medicine (Approval No. REC E/T/46, dated March 1, 2024). Written informed consent was obtained from all participants prior to their inclusion in the study.

6.3 Authors' Contributions

All authors contributed equally to this work.

6.4 Conflict of Interests

The authors declare that they have no competing interests.

6.5 Financial Support and Sponsorship

For this study, the researchers received no financial support.

6.6 Using Artificial Intelligence Tools (AI Tools)

All authors declare that there is no use of AI Tools in this study, including the writing of this manuscript.

Abbreviations

P-gp: P-glycoprotein

DMSO: Dimethyl sulfoxide

MIC: Minimum inhibitory concentration

SDA: Sabouraud dextrose agar

CFU: Colony forming unit

MIC: Minimum Inhibitory Concentration

DMEM: Dulbecco's Modified Eagle Medium

ELISA: Enzyme-Linked Immunosorbent Assay

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