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Coumarin and Quercetin Reduce Ciprofloxacin MIC/MBC and Downregulate the *Cytolethal Distending Toxin (cdt)* Gene in Ciprofloxacin-Resistant Uropathogenic *Escherichia coli*

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Abstract

Background & Objectives: Uropathogenic *Escherichia coli* is the major causative agent responsible for urinary tract infections that contribute to a high percentage of community-acquired and nosocomial infections. The present study aimed to assess the effect of coumarin and quercetin on the expression level of gene encoding cytolethal distending toxin (*cdt*) from ciprofloxacin-resistant clinical isolates of uropathogenic *E. coli*.

Materials & Methods: From a total number of 250 patient urine samples collected due to suspected UTI, 177 positive cultures for uropathogenic *E. coli* were isolated and 20 of which were positive for *cdt* gene. All the chemicals used for antibacterial activity assay were purchased from sigma Aldrich, and serial dilutions (0.125 to 1024 µg/mL) were prepared from stock solutions of coumarin and quercetin. The antibacterial activity of coumarin, quercetin, and ciprofloxacin was determined using broth microdilution. In addition, quantitative real-time polymerase chain reaction (qRT-PCR) was used to estimate the level of *cdt* gene expression.

Results: Sub-inhibitory concentrations of coumarin (64 µg/mL) in combination with ciprofloxacin decreased the MIC and MBC values from 64 to 1 to 2 µg/mL and from 128 to 2 to 4 µg/mL, respectively. Similarly, sub-MIC concentrations of quercetin (32 µg/mL) combined with ciprofloxacin decreased the MIC and MBC values to 1 to 2 and 2 to 4 µg/mL, respectively. Additionally, the mean fold change of cdt gene expression level in treated uropathogenic *E coli* was lower than the untreated bacteria by 2.5-fold (1.9 to 3.0-fold; $p < 0.001$) in treatment with 64 µg/mL coumarin. The mean fold change of gene expression in the untreated isolates was 1.8 (0.9 to 2.0) fold higher than those treated with 32 µg/mL quercetin ($p < 0.01$). The reduction in gene expression was statistically significant in both tested treatments compared with the untreated control group.

Conclusion: The obtained results demonstrated that coumarin and quercetin could be considered as antibacterial agents against uropathogenic *E. coli* and increase the antibacterial effect of ciprofloxacin while downregulating the expression level of *cdt* virulence determinant. It is recommended to perform more extensive experiments in vitro and *in vivo* to confirm the obtained results.

Keywords: Herbal compounds, Cytolethal distending toxin, Uropathogenic *Escherichia coli*, Fluoroquinolone resistance

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Introduction

Because of uropathogenic *Escherichia coli* (UPEC) resistance, infection by this microorganism may not be treated by standard

antibiotic therapy (1). The growing prevalence of resistance to a wide range of antimicrobial agents among *E. coli* and especially UPEC is a serious clinical challenge. Therefore, the search for new antimicrobial agents and alternative treatment methods is of particular importance for treating infections caused by multidrug-resistant strains (1,2).

UPEC possesses a set of adhesins that play a critical role in the adherence to the urinary tract epithelium. Among them are type 1 fimbriae that help the bacteria adhere to the surface of the bladder epithelium cells and resist the flow of urine, which allows them to colonize the urinary tract and cause infection (2). These hair-like appendages also help bacteria resist the shear forces of the urine flow. Besides, it was found that UPEC can possess P fimbriae, which are strongly associated with pyelonephritis because of their ability to specifically bind to uroepithelial cell receptors (3). Another important virulence characteristic of UPEC is its ability to form biofilms, which are structured bacterial communities embedded within a self-produced extracellular matrix. Biofilm formation provides a protected microenvironment that enhances bacterial persistence, promotes survival within the urinary tract, and increases resistance to both host immune responses and antimicrobial agents (4, 5). This feature is particularly important in chronic and recurrent UTIs, in which biofilms contribute to persistent inflammation and treatment failure. Furthermore, certain UPEC strains can invade uroepithelial cells, allowing intracellular replication and facilitating escape from host immune surveillance (6). This intracellular lifestyle depends on multiple virulence factors that promote bacterial invasion and manipulation of host cellular machinery (6).

CDT is a crucial virulence factor produced by various pathogenic types, such as *E. coli*, *Campylobacter jejuni*, and *Helicobacter pylori*. Nevertheless, only some strains of these pathogens carry genes for CDT. Further, UPEC strains resort to multiple means of evading the host immune response. However, only specific strains within these bacterial species harbor the CDT-encoding genes (7, 8). Furthermore, UPEC strains employ various strategies to evade the host immune responses. This includes the secretion of factors that inhibit neutrophil recruitment and function, as well as the ability to modulate cytokine responses to reduce inflammation. CDT is a virulence factor produced by several pathogenic bacteria, including *E. coli*, Campylobacter jejuni, and *H. pylori*. Some but not all strains of bacterial species carry CDT. CDT is a multi-subunit protein that acts as a cytotoxin, inducing cell cycle arrest and apoptosis in host cells (8, 9). CDT is a tripartite protein toxin consists of CdtA, CdtB, and CdtC. CdtB is responsible for the catalytic activity of the toxin, which leads to DNA damage, cell cycle arrest, and finally, cell death/apoptosis. As a result, CDT is involved in colonization and immune evasion of the host cell by disrupting several cellular processes and promoting adherence and invasion of epithelial cells by bacteria (10, 11). In addition, the toxin is also associated with cellular injury and inflammation that contribute to the pathology of diarrheal diseases, including dysentery. Moreover, CDT disturbs the host's immune response against bacteria (10, 11). To our knowledge, the correlation between fluoroquinolone resistance and the presence of *cdt* gene has not been studied yet. Coumarin is present in numerous medicinal plants since it is a phytochemical derived from nature. Coumarin biological importance lies in its ability to kill bacteria (12). Previous studies have confirmed the antimicrobial efficacy of coumarin against different pathogenic strains such as *S. aureus* and *E. coli* (13). Coumarin is also an antimicrobial combination agent, which is confirmed by the studies showing that

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it can increase the efficacy of antibiotics (14). In addition, since coumarin is a substance with a very low toxicity and regularly found in nature, it can be used in various branches of industries including food and pharmaceutical. Quercetin, being a naturally occurring flavonoid that can be found in some foods such as fruits and vegetables, is recognized for its antimicrobial properties. The antibacterial action of quercetin is caused by its capacity to complicate the integrity of bacterial membranes, prevent biofilm development, and affect the expression of genes (15, 16). Prior research shows that quercetin affects S. aureus, *E. coli*, *Salmonella* and *Listeria* spp (17). Additionally, a hypothesis appeared that quercetin's antioxidant ability is also responsible for its antibacterial effect because of diminishing bacterial oxidative stress (18). Looking at the useful properties of quercetin, the compound may be regarded as a good anti-microbial agent for application in food, medicine, and anti-microbial therapy (18). The current study aimed at analyzing the antibacterial effect of coumarin and quercetin on ciprofloxacin-resistant UPEC by evaluating the presence of the *cdt* gene (17, 18).

Materials and Methods

Bacterial Strains and Culture Conditions

Out of 250 urine samples collected from UTI patients, 177 UPEC isolates were obtained, from which twenty UPEC strains were picked up for the study on the basis of cdt-positive results. The standard biochemical tests (IMViC) and API 20E identification were used for bacterial species identification. The colonies were streaked on the Luria-Bertani (LB) agar plates and were incubated at 37°C for 24 hours. The colonies were inoculated in a sterile LB broth, incubated at 37°C and 200 rpm for 18 hours to obtain a bacterial suspension in the logarithmic growth phase. The patients of all ages could be included in the study; those who had received antibiotics in the last two weeks were excluded.

Preparation of herbal compounds

Coumarin and quercetin were purchased from Sigma Aldrich and dissolved in Mueller-Hinton broth (MHB) to prepare serial twofold dilutions ranging from 0.125 to 1024 µg/mL. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of each compound were then determined according to the Clinical and Laboratory Standards Institute (CLSI).

Determination of MIC and MBC

The MIC and MBC levels were obtained by broth microdilution following the CLSI 2024 recommendations. Briefly, MHB was distributed in a 96-well plate, followed by serial dilutions of the compounds in each well and incubation of the inoculated microtiter plate. The MIC and MBC were then determined following the CLSI guidelines.

Detection of *cdt* gene by PCR

The *cdt* gene was amplified using a multiplex polymerase chain reaction (PCR). The primers used were 5' GAAAGTAAATGGAATATAAATGTCCG 3' and 5' GAAAATAAATGGAACACA CATGTCCG 3' for *cdtA*, whereas 5' AAAT CTCCTGCAATCATCCAGTTA 3' and 5' AAATCACCAAGAATCATCCAGTTA 3' for *cdtB* . A 466-bp size PCR product was expected. Genomic DNA was isolated using the alkaline lysis method. Briefly, a 200 µL volume of an over-night bacterial culture was centrifuged, and the pellet was resuspended in 50 µL sterile distilled water and boiled for 15 minutes. After centrifugation, 10 µL of the supernatant was used as DNA for PCR amplification (19). This method is efficient, quick, and reliable and has been used previously for extracting bacterial genomic DNA (20).

RNA Extraction

Total RNA was isolated from the UPEC isolates using the RNeasy Mini Kit from Qiagen according to the manufacturer's instructions. Bacterial cells were pelleted by centrifuging at

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4000 × g for 10 minutes and resuspended in 350 µl of lysis buffer. After adding 350 µl of ethanol, the mixture was transferred to an RNeasy spin column. Total RNA was isolated after washing the spin column following the instructions provided and eluting the RNA in 30 µl of RNase-free water. The RNA concentration and quality were determined using a NanoDrop 2000 Spectrophotometer from Thermo Fisher Scientific.

cDNA Synthesis

Complementary DNA was synthesized from total RNA using High-Capacity cDNA Reverse Transcription Kits from Thermo Fisher Scientific. The reaction mixture contained 1 µg of total RNA, 1 µl of reverse transcriptase, and reaction mixture components in a total volume of 20 µl. The reaction was incubated at 25°C for 10 minutes and then at 37°C for 120 minutes. The cDNA was heated at 85°C for 5 minutes to terminate the reaction.

Quantitative Real-Time PCR (qRT-PCR)

The expression of *cdt* was evaluated by quantitative real-time PCR. Specific primers for the cdtI gene were 5'-TGGTGAGAATCGGAACTG-3' F and 5'-CATTCCATCAGGTTTGTC-3' R (21). The housekeeping gene *gyrA* (131 bp) was used as an endogenous reference gene with specific primers 5' CGAGCTGGTGAAAGAGAAGAA 3' F and 5' CGTAGAGGTTGTTGAGGATCAC 3' R (22). Amplification reactions were carried out using SYBR Green PCR Master Mix (Applied Biosystems, Foster City, CA, USA). A total reaction volume of 20 µl containing 10 µl SYBR Green master mix, 1 µl of each primer (10 µM), 2 µl cDNA, and 6 µl RNase-free water was used. Thermal cycling conditions were 95°C for 10 min, followed by 40 cycles of denaturation at 95°C for 15s and annealing at 60°C for 1 min. All real-time PCR reactions were done in triplicate, and a no-template control was included in each reaction. Relative *cdt* expression levels were calculated using the $2^{-\Delta\Delta CT}$ method with threshold cycle (Ct) values determined by the comparative Ct method.

Data Analysis

The results were analyzed using GraphPad Prism version 8.1. The differences in the gene expression levels among the UPEC isolates were determined using the chi-square test. A p-value of < 0.05 was considered statistically significant.

Results

MIC and MBC levels

The MIC and MBC values of coumarin against UPEC isolates were found to be in the range of 128–256 µg/mL and 256–512 µg/mL, respectively. However, the MIC and MBC values of quercetin were found to be in the range of 64–256 µg/mL and 128–256 µg/mL, respectively. In contrast, the MIC and MBC values of ciprofloxacin were found to be in the range of 4–8 µg/mL and 8–16 µg/mL, respectively. Notably, MIC and MBC values of ciprofloxacin reduced to 1–2 µg/mL and 2–4 µg/mL in the presence of a sub-MIC concentration of coumarin (64 µg/mL). In a similar manner, combination of ciprofloxacin with a sub-MIC concentration of quercetin (32 µg/mL) resulted in a reduction of MIC and MBC values to 1–2 µg/mL and 2–4 µg/mL, respectively.

Gene expression analysis

The mean expression of the *cdt* gene was 2.5-fold higher in the untreated UPEC isolates than in the isolates treated with 64 µg/mL coumarin, being approximately 0,4-fold relative expression value compared to the control, which was statistically significant ($p < 0.05$). In addition, the mean expression of the gene was 1.8 higher in the untreated group compared to the isolates treated with 32 µg/mL quercetin, equivalent to 0,56 relative expression value compared to the control ($p < 0.05$). As shown in the Figure 1, treatment of UPEC isolates with sub-MIC concentrations of coumarin and quercetin significantly decreased *cdt* gene expression.

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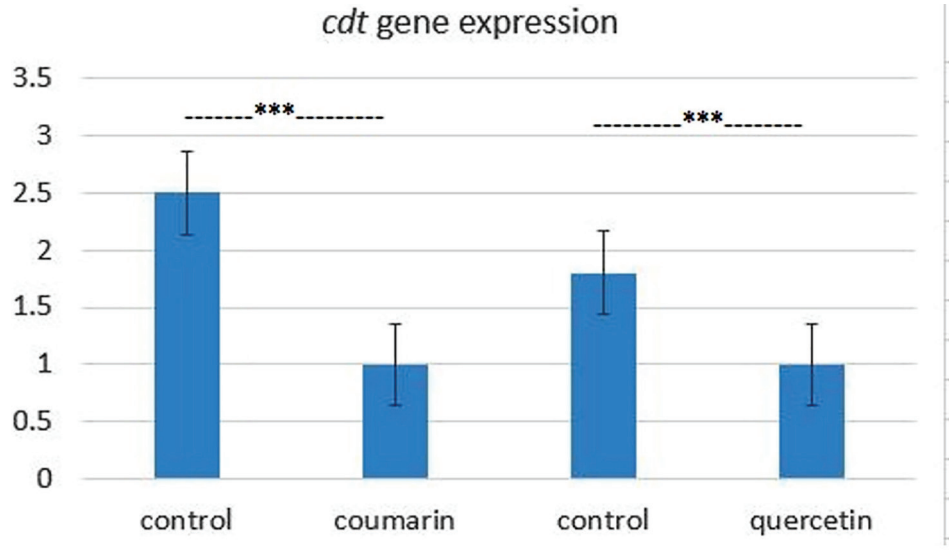

Figure 1. The expression of *cdt* gene between control and treated groups.

Discussion

A variety of virulence factors are often expressed by antimicrobial-resistant bacterial pathogens, resulting in increased severity of disease and treatment difficulties. In this context, it has been studied that phytochemicals like flavonoids, alkaloids, and essential oils exhibit antibacterial properties. Considering the current antimicrobial resistance crisis globally, the use of natural products along with classical antibiotics has been recommended as a way to treat infections. Medicinal plants such as phenolic acids, proanthocyanidins, triterpenoids, flavonols, glycosides, anthraquinones, catechins, terpenes, sterols, phenolic derivatives, silymarin, quercetin, tannins, saponins have shown their antiseptic and anti-pathogenic properties against UTIs (23-26).

In the presented research, coumarin has been shown to have MIC of between 128-256 µg/ml and MBC values were reaching to 256-512 µg/ml. In similar manner, MIC values of quercetin abated between 64-256 µg/ml and their MBC was between 128-256 µg/ml. While comparing with ciprofloxacin, MIC was ranging between 4-8 µg/ml and MBC was in the range of 8-16 µg/ml. The remarkable finding of our research is that when ciprofloxacin was added to sub-MIC level of coumarin of 64 µg/ml, its MIC and MBC were all of a sudden reduced down to 1-2 and 2-4 µg/ml respectively. The same effect was shown when quercetin was added to the sub-MIC solution of ciprofloxacin reaching the MIC and MBC values down to 1-2 and 2-4 µg/ml.

The mean *cdt* expression level was 2.5-fold (range: 1.9-to-3.0) higher in the untreated group than in the UPEC isolates treated with 64 µg/mL coumarin. Similarly, the mean *cdt* expression level in the untreated isolates was 1.8-fold (range: 0.9-to-2.0) higher than in the isolates treated with 32 µg/mL quercetin. Overall, these results demonstrate that sub-MIC coumarin and quercetin decreased *cdt* gene expression ($P<0.05$). The precise mechanism by which coumarin and quercetin downregulate *cdt* expression is unclear. However, the antibacterial potential of these phytochemicals against UPEC has been demonstrated. For instance, coumarin and quercetin have been previously reported to suppress bacterial virulence by acting through different mechanisms, for example, disrupting bacterial signaling pathways (27), reducing toxin gene transcription (28), inhibiting

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regulatory factors, impeding membrane integrity (29) and bacterial redox state (28-30).

In conclusion, the current study hypothesizes that the combination of antibiotics with natural products may lead to more effective antibacterial interventions with reduced virulence. Specifically, combinations of antibiotics with coumarin and quercetin may help combat antibiotic resistance in UPEC infections.

Limitations

This study had several limitations, including variations in the UPEC strains used and environmental factors that could affect gene expression. These limitations should be considered while interpreting this study's results.

Conclusion

Coumarin and quercetin showed antibacterial activity against UPEC and decreased the MIC values of ciprofloxacin *in vitro*. Besides, the reduction of *cdt* gene expressions following the sub-MIC exposure of these flavonoids was observed. Thus, they might be considered as promising antibacterial agents; however, additional mechanistic, phenotypic and *in vivo* studies should be undertaken to confirm this hypothesis.

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Author contributions

Y.A. conceptualized the study and wrote the draft.

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