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Original Research Article

Exploring *Terminalia Arjuna* for in-vitro antibacterial, antifungal and in-silico antibacterial, antiviral properties

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Abstract

Human Cytomegalovirus (HCMV) poses a significant threat to immunocompromised individuals, with current antiviral agents such as ganciclovir, valganciclovir, foscarnet, and cidofovir facing increasing resistance due to mutations in viral genes like UL97 and UL54. This study explores the potential of ellagic acid, a major bioactive compound in Terminalia arjuna bark extract, as an alternative antiviral agent targeting HCMV protease, a critical enzyme in viral replication. Molecular docking simulations revealed a strong binding affinity of ellagic acid to HCMV protease, suggesting its ability to inhibit viral replication. Additionally, in vitro antimicrobial assays demonstrated significant activity against Methicillin-resistant Staphylococcus aureus (MRSA) and Enterococcus faecalis, while antifungal activity against Candida albicans was weaker. Docking studies further showed ellagic acid interacting with key bacterial resistance mechanisms, including the fosfomycin-resistant gene in Klebsiella pneumoniae. These findings highlight T. arjuna extract, particularly ellagic acid, as a promising candidate for combating HCMV and antibiotic-resistant infections, with potential applications in immunocompromised patients.

Keywords: Human Cytomegalovirus (HCMV), Terminalia arjuna, Ellagic acid, Microwave-assisted extraction, Molecular docking, Antimicrobial activity

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1. Introduction

Human Cytomegalovirus (HCMV) is a β-herpesvirus that establishes lifelong latency in hosts, posing significant health risks, particularly to immunocompromised individuals, such as organ transplant recipients and patients with AIDS.[1] In these patients, HCMV infections can lead to retinitis, pneumonia, and gastrointestinal diseases. The current antiviral drugs used for HCMV, ganciclovir, valganciclovir, foscarnet, and cidofovir have helped in controlling the infection. However, long-term use of these drugs has resulted in drug-resistant HCMV strains due to mutations in viral genes UL97 and UL54.[2] Mutations in UL97 prevent ganciclovir from being activated inside the cell, while changes in UL54 affect the viral DNA polymerase, making the virus resistant to multiple drugs. The increasing incidence of drug-resistant HCMV strains underscores the urgent need for novel antiviral agents with distinct mechanisms of action. Natural products have long been a valuable source of therapeutic compounds, offering diverse bioactive molecules with potential antiviral properties. Among these, Terminalia arjuna, a medicinal plant traditionally used in Ayurvedic medicine, has gained attention for its wide-ranging pharmacological activities, including cardioprotective, antioxidant, and anti-inflammatory effects. Ellagic acid, a prominent bioactive constituent of T. arjuna bark, has demonstrated various health benefits, such as antioxidant and anti-inflammatory properties.[3-4] However, its potential antiviral activity, particularly against HCMV, remains underexplored. Given the structural characteristics of ellagic acid and its reported bioactivities, it is hypothesized that this

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compound may interact with viral proteins essential for HCMV replication, such as the viral protease.

This study aims to evaluate the antiviral potential of ellagic acid against HCMV by investigating its binding affinity to HCMV protease through molecular docking simulations. Additionally, the study assesses the antimicrobial efficacy of T. arjuna bark extract against selected bacterial and fungal pathogens, providing a comprehensive analysis of its therapeutic potential.

2. Aim and Objective

To evaluate the antimicrobial and antiviral potential of Terminalia arjuna bark extract and its bioactive compound ellagic acid, both in vitro and in silico.

3. Materials and Methods

1. Preparation of Plant Extracts The extraction of T. arjuna bark powder was performed using Microwave-Assisted Extraction (MAE).[5] A 5 g sample was weighed on a Wensar weighing balance and mixed with 50 mL of distilled water in a 500 mL Borosil beaker. The mixture was microwaved in an LG Microwave Oven (320 W, 2 min) and cooled to room temperature. It was then centrifuged at 3000 rpm for 3 min in an Eppendorf 5702R Refrigerated Centrifuge (A-4-38 Rotor) to separate the supernatant. The supernatant was evaporated in a Meta Lab Hot Air Oven (90°C, 10 min). The dried extract was weighed and stored in an Eppendorf tube. The extraction yield was calculated using: Extract yield (%) = where W_1 is the net weight of the extract obtained after drying, and W_2 is the total weight of the bark powder used for extraction.

2. In-Vitro Antimicrobial Activity A 200 mg/mL stock solution was prepared by dissolving the extract in 1 mL of distilled water. Three test concentrations were prepared: 20% (0.1 mL stock + 0.9 mL distilled water) 40% (0.2 mL stock + 0.8 mL distilled water) 60% (0.3 mL stock + 0.7 mL distilled water) The antimicrobial activity was tested against: Enterococcus faecalis ATCC 29212 (subcultured on UTI agar) Methicillin-resistant Staphylococcus aureus (MRSA) BAA 1026 (subcultured on Mueller-Hinton Agar (MHA)) Candida albicans ATCC 14053 (subcultured on MHA) Mueller-Hinton Agar plates were swabbed with microbial suspensions using a sterile cotton swab. Wells (8 mm diameter) were made using a sterile cork borer and filled with 100 µL of each extract concentration. Distilled water served as the negative control. After incubation, the zones of inhibition were measured.

3. In Silico Molecular Docking Molecular docking studies were conducted to evaluate the binding interactions of Ellagic acid with key antibiotic resistance proteins in Klebsiella pneumoniae, Pseudomonas aeruginosa, and Escherichia coli, as well as with human cytomegalovirus (HCMV) protease (UL80). The structure of Ellagic acid was retrieved from the PubChem database (CID: 5281855) in SMILES format. For Klebsiella pneumoniae, FosA (PDB ID: 5WEW) was selected as the target due to its role in fosfomycin resistance via glutathione transferase activity.[6] Since Ellagic acid is known to inhibit glutathione transferases,[7] it was evaluated for its potential to block FosA function and enhance antibiotic efficacy. In Pseudomonas aeruginosa, docking was performed against the MVFR efflux pump protein (PDB ID: 4JVC), which plays a crucial role in antibiotic resistance by expelling drugs from the bacterial cell.[8] For Escherichia coli, Class C beta-lactamase (PDB ID: 4BJP) was selected as the target due to its role in beta-lactam antibiotic resistance. All PDB structures were obtained from the Protein Data Bank (PDB format). Docking simulations were carried out on SwissDock using AutoDock Vina.

4. Results

1. Extract yield: The extract yield of Terminalia arjuna bark obtained through microwave-assisted extraction was 262.9 grams, with a calculated yield of 5.26%.

2. Agar well Diffusion assay: The antimicrobial efficacy of T. arjuna bark extract was comparatively higher against bacterial species, as demonstrated by larger zones of inhibition, than against the tested fungal strain (**Table 2**) and (**Figure 1**).

Table 1: Diameter of Zone of Inhibition (mm) Against Test Organisms

Concentration (%)	Enterococcus faecalis (mm)	MRSA (mm)	Candida albicans (mm)
20%	2mm	2mm	2mm
40%	4mm	5mm	4mm
60%	6mm	5mm	4mm

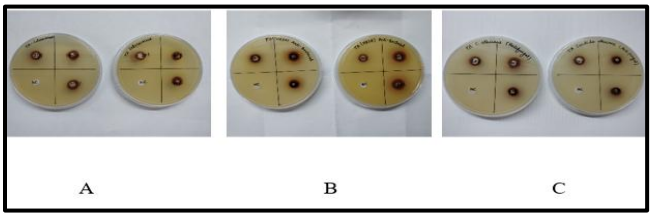

Figure 1: The inhibition zone (mm) of Aqueous extract of T. arjuna against **(A)** Enterococcus faecalis **(B)** MRSA **(C)** Candida albicans In vitro assays showed significant antibacterial activity against Enterococcus faecalis, MRSA, and moderate antifungal activity against Candida albicans, with the highest efficacy at 60% concentration.

4.1. Molecular docking

Ellagic acid demonstrated stronger binding affinities towards bacterial and viral proteins compared to fungal target (**Table 2**).

Table 2: Binding affinity of ellagic acid with different targets.

Organisms	Target Proteins	PDB ID	Binding Affinity (kcal/mol)
Klebsiella pneumoniae	Fosfomycin-resistant gene	5WEW	-5.557
Pseudomonas aeruginosa	Minimum Viable Functional Receptor (MVFR)	4JVC	-4.856
Escherichia coli	Beta-lactamase (Class C)	2BJP	-2.840
Human Cytomegalovirus (HCMV)	HCMV protease	2WPO	-8.013

Table 2: Binding Affinity of Ellagic Acid with Different Targets

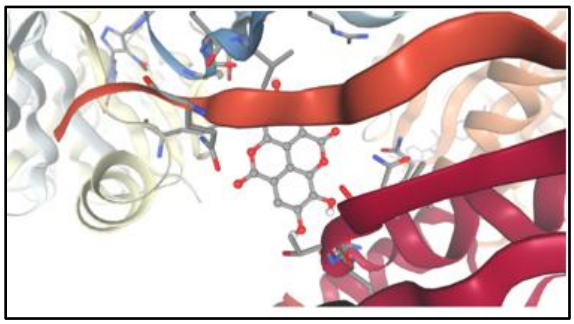

Figure 2: Ellagic acid–FosA docking

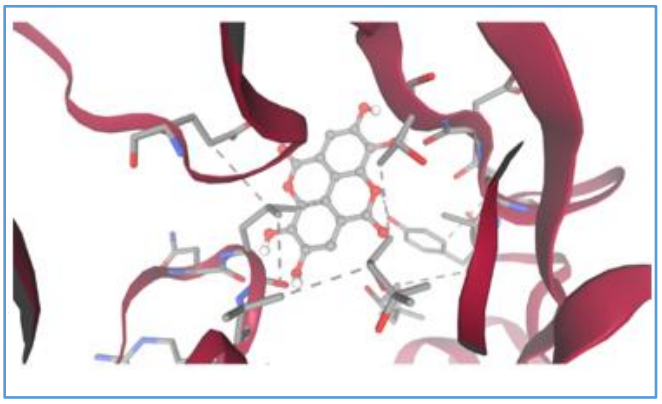

Figure 3: Ellagic acid–MvfR docking

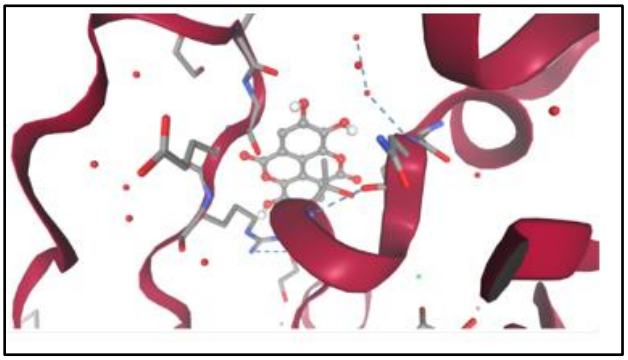

Figure 4: Ellagic acid–β-lactamase docking

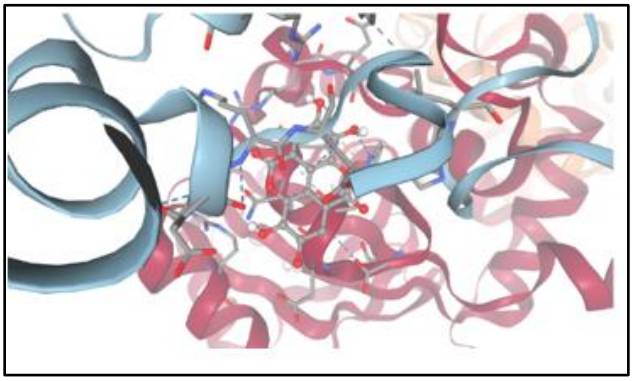

Figure 5: Ellagic acid–protease docking

The in silico molecular docking analysis using the SwissDock server revealed significant binding affinities of ellagic acid, a bioactive compound from Terminalia arjuna, with multiple microbial and viral targets. Notably, ellagic acid exhibited the strongest interaction with Human Cytomegalovirus (HCMV) protease (PDB ID: 2WPO) with a binding energy of -8.013 kcal/mol, indicating a strong potential for antiviral activity against HCMV. Among bacterial targets, it showed considerable binding to the FosA enzyme in Klebsiella pneumoniae (-5.557 kcal/mol), followed by the MvfR efflux pump of Pseudomonas aeruginosa (-4.856 kcal/mol), and the Class C β-lactamase of Escherichia coli (-2.840 kcal/mol).

5. Discussion

The present study demonstrates that Terminalia arjuna bark extract, particularly its bioactive compound ellagic acid, exhibits notable antimicrobial and antiviral properties. In vitro assays confirmed effective inhibition of Enterococcus faecalis and MRSA, with moderate antifungal activity against Candida albicans. These findings align with earlier reports that T. arjuna possesses diverse pharmacological activities, including antimicrobial and cardioprotective effects, largely attributed to ellagic acid and related polyphenols.[3,4]

The molecular docking results further support the antimicrobial efficacy of ellagic acid, which showed strong binding affinities to resistance-associated bacterial proteins such as FosA in Klebsiella pneumoniae and the quorum sensing regulator MvfR in Pseudomonas aeruginosa. This is consistent with previous studies reporting ellagic acid as an inhibitor of glutathione S-transferases and efflux pump regulators, thereby potentially restoring antibiotic activity.[6-8] These observations are significant in the context of rising antimicrobial resistance, where natural polyphenols are being explored as adjunct therapies to conventional antibiotics.[12]

Of particular interest, ellagic acid demonstrated the strongest binding affinity to the HCMV protease, suggesting its potential as a novel antiviral candidate. Current first-line antivirals against HCMV—ganciclovir, valganciclovir, foscarnet, and cidofovir—have been effective but face increasing resistance due to mutations in the UL97 kinase and UL54 DNA polymerase genes.[1,2] Such mutations can render HCMV refractory to multiple antivirals, especially in immunocompromised populations such as transplant recipients.[9-11] Recent evidence shows that dual resistance, particularly to ganciclovir and maribavir, is emerging in clinical settings,[11,16] emphasizing the urgent need for compounds with alternative mechanisms of action.

Novel antivirals like letermovir and maribavir have expanded the treatment arsenal, yet their lower genetic barrier raises concerns about rapid resistance development.[16,18] The promising docking interaction of ellagic acid with HCMV protease indicates a different antiviral mechanism that could potentially complement or overcome current resistance issues. This finding is in line with recent efforts to explore phytochemicals as antiviral leads against resistant CMV strains.[14,17]

Furthermore, our study highlights the dual therapeutic potential of ellagic acid against both bacterial resistance factors and viral replication proteins. This dual activity is particularly relevant in immunocompromised patients, who often face co-infections with drug-resistant bacteria and CMV.[10,13,15] Preventive and therapeutic strategies in such patients increasingly emphasize combined approaches, including novel antivirals, prophylaxis regimens, and adjunct therapies from natural sources.[13,18]

Taken together, the present findings suggest that T. arjuna extract and its constituent ellagic acid represent promising candidates for the development of future antimicrobial and antiviral therapeutics. While the docking results provide strong theoretical evidence, further validation through molecular dynamics, in vitro viral assays, and in vivo studies is warranted to substantiate these effects and assess pharmacological safety.

6. Conclusion

This study highlights the antimicrobial and antiviral potential of Terminalia arjuna bark extract. In vitro assays showed significant antibacterial activity against Enterococcus faecalis, MRSA, and moderate antifungal activity against Candida albicans, with the highest efficacy at 60% concentration. Molecular docking revealed that ellagic acid, a key compound in the extract, strongly binds to bacterial resistance-related targets, such as the fosfomycin-resistant gene (Klebsiella pneumoniae), MVFR (Pseudomonas aeruginosa), and beta-lactamase (Escherichia coli). It also showed promising affinity for HCMV protease, indicating potential antiviral activity. These findings suggest that ellagic acid may interfere with key resistance mechanisms in Gram-negative bacteria and inhibit viral replication by targeting viral proteases. Overall, the bioinformatics analysis supports ellagic acid as a promising lead molecule for the development of novel antimicrobial and antiviral therapies. Further computational and experimental validations, including molecular dynamics and in vivo studies, are warranted to substantiate its therapeutic potential.However, in vivo validation and further pharmacological studies are needed to confirm its clinical relevance.

7. Acknowledgement

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8. Conflict of Interest

The authors declare no conflict of interest.

9. Source of Funding

This research received no external funding.

10. Ethical Committee Approval

Not applicable. This study did not involve human or animal experiments requiring ethics approval.

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