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Review Article

Antibacterial and Cytotoxic Properties of Terminalia chebula Fruits

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A B S T R A C T

Terminalia chebula fruits are recognized for their potent antibacterial and cytotoxic properties, offering significant potential as sources of bioactive compounds for therapeutic use. These fruits exhibit robust antibacterial activity against a wide array of pathogenic bacteria, encompassing both Gram-positive and Gram-negative species. The efficacy is attributed to their rich composition of tannins, flavonoids, and phenolic acids, which disrupt bacterial cell walls, inhibit essential enzymes, and chelate vital metal ions crucial for bacterial growth. This multifaceted approach not only curtails bacterial proliferation but also mitigates the risk of antibiotic resistance development. Moreover, Terminalia chebula enhances the effectiveness of conventional antibiotics through synergistic interactions, promising more efficacious treatments for bacterial infections. On the cytotoxic front, Terminalia chebula demonstrates potent activity against diverse cancer cell lines, including those associated with breast, colon, and liver cancers. Mechanistically, the fruits induce apoptosis via caspase activation and mitochondrial pathways, facilitated by key compounds such as chebulagic acid, chebulinic acid, and ellagic acid.

Keywords: Terminalia chebula, Antibacterial Properties, Anticancer Potential

Introduction

Terminalia chebula fruits exhibit significant antibacterial and cytotoxic properties, making them a promising source of bioactive compounds for therapeutic applications. The antibacterial properties of these fruits have been demonstrated against a variety of pathogenic bacteria, including both Gram-positive and Gram-negative species. The primary bioactive constituents responsible for this activity are tannins, flavonoids, and phenolic acids, which exert their effects by disrupting bacterial cell walls, inhibiting essential bacterial enzymes, and chelating metal ions necessary for bacterial growth. These compounds not only prevent the proliferation of bacteria but also reduce the risk of developing antibiotic resistance. Additionally, Terminalia chebula has been found to enhance the efficacy of conventional antibiotics, showcasing synergistic effects that could lead to more effective treatments for bacterial infections. On the cytotoxic front, Terminalia chebula fruits have shown potent activity against various cancer cell lines, including breast, colon, and liver cancers.[1] The cytotoxic effects are primarily mediated through the induction of apoptosis, characterized by the activation of caspases and mitochondrial pathways, leading to cell death. Key compounds such as chebulagic acid, chebulinic acid, and ellagic acid play a crucial role in these processes by inhibiting cell proliferation and disrupting cancer cell survival pathways, such as NF-κB and PI3K/Akt signaling. Importantly, the cytotoxic activity of Terminalia chebula is selective, targeting cancer cells while sparing normal, healthy cells, thereby reducing potential side effects. This selectivity, combined with its broad-spectrum antibacterial

efficacy, positions Terminalia chebula fruits as a valuable natural resource for developing new antibacterial and anticancer therapies.[2]

Antibacterial Properties

Antibacterial Activity Against Common Pathogens: The antibacterial activity of Terminalia chebula fruits has been widely investigated, demonstrating significant efficacy against a spectrum of common bacterial pathogens. Studies have shown that extracts from the fruits exhibit strong inhibitory effects on Gram-positive bacteria such as Staphylococcus aureus and Streptococcus pyogenes, both of which are responsible for a range of infections from skin conditions to more severe systemic infections.[3] Additionally, Terminalia chebula has been effective against Gram-negative bacteria like Escherichia coli and Pseudomonas aeruginosa, which are notorious for causing urinary tract infections, gastrointestinal diseases, and hospital-acquired infections. The antibacterial properties of Terminalia chebula are primarily attributed to its rich composition of bioactive compounds, including tannins, flavonoids, and phenolic acids. These compounds disrupt the integrity of bacterial cell walls and membranes, inhibit essential bacterial enzymes, and interfere with metabolic pathways, leading to bacterial cell death. Furthermore, the fruits contain high levels of hydrolysable tannins such as chebulagic acid and chebulinic acid, which have been shown to bind to bacterial proteins and nucleic acids, thus preventing bacterial replication and survival.[4] The multifaceted mechanisms of action reduce the likelihood of bacteria developing resistance, making Terminalia chebula a potent antibacterial agent. Additionally, research has highlighted the potential synergistic effects of Terminalia chebula when used in combination with conventional antibiotics, enhancing their efficacy and potentially reducing the dosage required for treatment. This synergy is particularly valuable in the fight against multi-drug resistant bacteria, presenting Terminalia chebula as a promising adjunctive therapy in modern medicine.

Mechanism of Action: The antibacterial mechanism of action of Terminalia chebula fruits is multifaceted and involves several biochemical and physiological processes that collectively inhibit bacterial growth and viability. One of the primary mechanisms is the disruption of the bacterial cell wall and cell membrane integrity. The high tannin content, particularly hydrolysable tannins like chebulagic acid and chebulinic acid, can bind to the bacterial cell wall proteins and peptidoglycan layers, leading to cell wall damage and increased permeability. This disruption compromises the structural integrity of bacterial cells, causing leakage of cellular contents and ultimately resulting in cell ysis.[5]

Additionally, Terminalia chebula exerts its antibacterial effects by inhibiting essential bacterial enzymes. Flavonoids and phenolic acids present in the fruit extract interfere with bacterial enzymes involved in critical metabolic pathways, such as DNA gyrase and topoisomerase, which are essential for DNA replication and transcription. By inhibiting these enzymes, Terminalia chebula prevents bacterial cells from proliferating and repairing, thereby halting their growth and multiplication.

Another important aspect of Terminalia chebula's antibacterial action is its ability to chelate metal ions. Metal ions like iron and magnesium are crucial for various bacterial enzymatic functions and metabolic processes. The polyphenolic compounds in Terminalia chebula can bind to these metal ions, rendering them unavailable to the bacteria. This chelation disrupts bacterial metabolic functions and inhibits the synthesis of vital biomolecules, leading to bacterial death.

Terminalia chebula also affects bacterial quorum sensing, a process that bacteria use to communicate and regulate gene expression in response to population density. By interfering with quorum sensing signals, Terminalia chebula can inhibit the formation of biofilms, which are protective layers that bacteria form to shield themselves from antibiotics and the host immune system. This anti-biofilm activity enhances the susceptibility of bacteria to both the immune response and antibiotic treatment.[6]

Moreover, the antioxidant properties of Terminalia chebula play a role in its antibacterial activity. The reactive oxygen species (ROS) generated by its polyphenolic compounds can cause oxidative stress in bacterial cells, damaging their DNA, proteins, and lipids. This oxidative damage further contributes to the bactericidal effects of Terminalia chebula.

Synergistic Effects with Antibiotics: One of the most promising aspects of Terminalia chebula fruits' antibacterial properties is their potential to act synergistically with conventional antibiotics. Synergy occurs when the combined effect of two or more agents is greater than the sum of their individual effects. In the case of Terminalia chebula, this synergistic interaction can significantly enhance the efficacy of antibiotics, potentially reducing the dosage required and minimizing side effects associated with high doses of antibiotics.

Research has demonstrated that extracts of Terminalia chebula can potentiate the activity of various antibiotics against resistant bacterial strains. For example, studies have shown that when combined with antibiotics like amoxicillin, ciprofloxacin, and tetracycline, Terminalia chebula extracts can lower the minimum inhibitory concentrations (MICs) needed to inhibit bacterial growth. This means that smaller amounts of the antibiotics are required to achieve the

same antibacterial effect, which is particularly valuable in treating infections caused by multi-drug resistant bacteria.[7]

The mechanisms behind these synergistic effects are multifaceted. Firstly, Terminalia chebula can enhance antibiotic penetration into bacterial cells. The tannins and other polyphenolic compounds in Terminalia chebula can disrupt bacterial cell membranes, increasing their permeability. This disruption facilitates greater uptake of antibiotics into the bacterial cells, ensuring higher intracellular concentrations and more effective bacterial eradication.

Secondly, Terminalia chebula's ability to inhibit bacterial efflux pumps plays a crucial role. Efflux pumps are mechanisms used by bacteria to expel antibiotics and other harmful substances from their cells, contributing to antibiotic resistance. Compounds in Terminalia chebula can inhibit these pumps, preventing the bacteria from removing the antibiotics and thus increasing the intracellular retention and efficacy of the antibiotics.

Furthermore, Terminalia chebula's interference with bacterial biofilm formation also contributes to its synergistic effects. Biofilms are protective matrices that bacteria produce to shield themselves from antibiotics and the host immune system. By disrupting quorum sensing and inhibiting biofilm formation, Terminalia chebula makes bacterial cells more susceptible to antibiotic treatment.

Another important aspect is the antioxidant property of Terminalia chebula, which can reduce oxidative stress in the host cells and thereby enhance the host's immune response to infection. This, in turn, can work in concert with antibiotics to clear bacterial infections more efficiently.

Lastly, the broad-spectrum antibacterial activity of Terminalia chebula ensures that it can target a wide range of bacterial species, including those that may not be fully susceptible to the antibiotics used in treatment. This broadens the scope of antibacterial action and ensures a more comprehensive eradication of bacterial pathogens.[5,6]

Cytotoxic Properties

1. **Anticancer Potential:** The fruits of Terminalia chebula have garnered significant interest for their potent anticancer properties, which have been demonstrated across various cancer cell lines. The anticancer potential of Terminalia chebula is attributed to its rich content of bioactive compounds, such as chebulagic acid, chebulinic acid, and ellagic acid, which exhibit strong cytotoxic effects against cancer cells. These compounds exert their anticancer activity through multiple mechanisms, including the induction of apoptosis, inhibition of cell proliferation, and disruption of cancer cell signaling pathways.
2. **Induction of Apoptosis:** One of the primary mechanisms by which Terminalia chebula exerts its anticancer effects is through the induction of apoptosis, a programmed cell death process that is often dysregulated in cancer cells. Studies have shown that extracts of Terminalia chebula can trigger apoptosis in various cancer cell lines, including breast cancer (MCF-7), colon cancer (HCT-116), and liver cancer (HepG2) cells. The induction of apoptosis by Terminalia chebula involves the activation of caspases, a family of proteases that play a crucial role in the execution of apoptosis. Specifically, Terminalia chebula extracts have been found to activate caspase-3 and caspase-9, leading to the cleavage of key cellular proteins and eventual cell death.[8]
3. **Inhibition of Cell Proliferation:** Terminalia chebula also inhibits the proliferation of cancer cells, thereby preventing tumor growth and progression. This antiproliferative effect is mediated through the disruption of the cell cycle, particularly at the G0/G1 phase, leading to cell cycle arrest. The bioactive compounds in Terminalia chebula interfere with the expression and activity of cyclins and cyclin-dependent kinases (CDKs), which are essential for cell cycle progression. By halting the cell cycle, Terminalia chebula effectively reduces the number of actively dividing cancer cells.
4. **Disruption of Cancer Cell Signaling Pathways:** Another important aspect of Terminalia chebula's anticancer potential is its ability to disrupt key signaling pathways that are critical for cancer cell survival and proliferation. The bioactive compounds in Terminalia chebula have been shown to inhibit the NF-κB and PI3K/Akt signaling pathways, which are often activated in cancer cells and contribute to their growth, survival, and resistance to apoptosis. By inhibiting these pathways, Terminalia chebula reduces the survival signals in cancer cells, making them more susceptible to apoptosis and less capable of sustaining uncontrolled growth.
5. **Anti-angiogenic and Anti-metastatic Effects:** Terminalia chebula also exhibits anti-angiogenic and anti-metastatic properties, further contributing to its anticancer potential. Angiogenesis, the formation of new blood vessels, is a critical process for tumor growth and metastasis. Terminalia chebula extracts have been found to inhibit angiogenesis by downregulating the expression of vascular endothelial growth factor (VEGF) and other angiogenic factors. Additionally, the extracts can impair the invasive and migratory capabilities of cancer cells, thereby reducing their metastatic potential.[9]

Table 1.Effect of Terminalia chebula on different Cancer cell lines[3,4]

Cancer Cell Line	Key Compounds	Mechanisms of Action	Observed Effects
Breast Cancer (MCF-7)	Chebulagic acid, Chebulinic acid, Ellagic acid	Induction of apoptosis via caspase activation, inhibition of NF-κB signaling	Reduced cell viability, cell cycle arrest at G0/G1 phase
Colon Cancer (HCT-116)	Chebulagic acid, Chebulinic acid, Ellagic acid	Mitochondrial pathway activation, inhibition of PI3K/Akt signaling	Increased apoptotic cell death, decreased proliferation
Liver Cancer (HepG2)	Chebulagic acid, Chebulinic acid, Ellagic acid	Caspase-3 and -9 activation, oxidative stress induction	Induced apoptosis, suppressed tumor growth
Cervical Cancer (HeLa)	Chebulagic acid, Chebulinic acid, Ellagic acid	Disruption of mitochondrial membrane potential, ROS generation	Enhanced apoptosis, inhibition of cell migration
Prostate Cancer (PC-3)	Chebulagic acid, Chebulinic acid, Ellagic acid	Inhibition of cell proliferation, caspase-dependent apoptosis	Reduced cell survival, induction of apoptotic markers

1. **Bioactive Compounds and Mechanisms:** The anticancer activity of Terminalia chebula is attributed to several bioactive compounds, including chebulagic acid, chebulinic acid, and ellagic acid. These compounds induce apoptosis through the activation of caspases and the mitochondrial pathway, leading to the release of cytochrome c and subsequent cell death. Moreover, the inhibition of NF-κB and PI3K/Akt signaling pathways by these compounds results in reduced cell proliferation and enhanced sensitivity of cancer cells to chemotherapeutic agents.
2. **Tannins:** Tannins are polyphenolic compounds that are abundant in Terminalia chebula fruits, particularly in the form of hydrolysable tannins such as chebulagic acid and chebulinic acid. These tannins are known for their strong antioxidant properties and contribute significantly to the fruit's antibacterial activity by binding to bacterial cell walls and inhibiting bacterial enzymes.[10]
3. **Flavonoids:** Terminalia chebula contains various flavonoids, including quercetin, kaempferol, and myricetin derivatives. Flavonoids are potent antioxidants that scavenge free radicals and protect cells from oxidative damage. They also contribute to the fruit's anticancer activity by inducing apoptosis in cancer cells and inhibiting tumor growth.
4. **Phenolic Acids:** Phenolic acids such as gallic acid and ellagic acid are abundant in Terminalia chebula and contribute to its antioxidant and anticancer properties. These compounds exert anti-inflammatory effects and can inhibit cancer cell proliferation through various mechanisms, including cell cycle arrest and apoptosis induction.
5. **Selectivity and Safety:** Terminalia chebula exhibits notable selectivity towards target cells, particularly in its therapeutic applications for antibacterial and anticancer treatments. This selectivity is crucial for its safety profile and therapeutic efficacy:
6. **Anticancer Selectivity:** Terminalia chebula demonstrates a remarkable ability to selectively induce apoptosis and inhibit proliferation in cancer cells while sparing normal, healthy cells. Studies have shown that the cytotoxic effects of Terminalia chebula extracts are more pronounced in cancer cell lines compared to non-cancerous cells. This selectivity is attributed to the differential expression of cell surface receptors and intracellular signaling pathways between cancer cells and normal cells. By targeting cancer-specific molecular pathways such as NF-κB and PI3K/Akt, Terminalia chebula minimizes the risk of cytotoxicity to normal tissues, thereby reducing adverse effects associated with traditional chemotherapeutic agents.[11]
7. **Antibacterial Selectivity:** In antibacterial applications, Terminalia chebula exhibits selective activity against pathogenic bacteria while preserving the beneficial bacteria essential for maintaining microbial balance in the body. The antibacterial mechanism involves disrupting bacterial cell walls and enzymes critical for bacterial survival, which selectively targets pathogenic bacteria without adversely affecting commensal bacteria. This selective action reduces the likelihood of disrupting the body's natural microbiota, minimizing the risk of dysbiosis and secondary infections.

8. **Safety Profile:** Terminalia chebula is generally recognized as safe for consumption when used in appropriate doses. Traditional medicinal uses and modern pharmacological studies have highlighted its low toxicity profile and absence of significant adverse effects in humans. The fruit extracts have been consumed as part of dietary supplements and traditional remedies for centuries without reported cases of major toxicity. However, as with any herbal medicine, it is advisable to use Terminalia chebula under the guidance of healthcare professionals to ensure safe and effective use, especially in individuals with pre-existing medical conditions or those taking medications.
9. **Pharmacological Studies:** Pharmacological studies have supported the safety of Terminalia chebula by evaluating acute and chronic toxicity, genotoxicity, and mutagenicity. These studies have consistently shown minimal toxicity and no mutagenic effects, reinforcing its safety profile for therapeutic use.

In conclusion, Terminalia chebula demonstrates selectivity towards target cells in both anticancer and antibacterial applications, ensuring efficacy while minimizing adverse effects on normal tissues and beneficial microflora. Its established safety profile and extensive traditional use underscore its potential as a safe and effective natural remedy in integrative medicine practices.[8,9,12]

Conclusion

Terminalia chebula fruits exhibit remarkable antibacterial and cytotoxic properties, making them a valuable resource for developing new therapeutic agents. The broad-spectrum antibacterial activity, coupled with the potential to enhance conventional antibiotics, highlights their significance in combating antibiotic-resistant infections. Additionally, the selective cytotoxicity towards cancer cells underscores their potential in anticancer therapy. Future research should focus on clinical trials and the development of standardized extracts to fully harness the therapeutic potential of Terminalia chebula fruits.

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