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A REVIEW OF THE EXTENSIVE PHARMACOLOGICAL ACTIVITIES OF *Terminalia chebula RETZ* MEDIATED NANOPARTICLES

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ABSTRACT

Terminalia chebula Retz (*T. chebula*), known as the King of Medicines, is a tree species belonging to the family Combretaceae that is widely used by Indian local communities to treat a variety of ailments. *Terminalia chebula* possesses various pleiotropic effects such as anti-oxidant, anti-diabetic, reno-protective, hepato-protective, anti-arthritic, cytoprotective, anti-microbial, anaphylactic effect, pro-kinetic effect, etc. Hence, *T. chebula* can be employed as a resourceful tool for green-synthesized nanoparticles that offer cost-effective, eco-friendly, high-yield, and sustained target delivery in contrast to conventional nanoparticle synthesis. In addition, the assessment of their pharmacological actions has shown the potential anti-microbial activity of silver, gold, and silver-palladium bimetallic nanoparticles synthesized from *T. chebula*. While silver, gold, and titanium dioxide nanoparticles have stronger anti-oxidant activities and are comparable to the standard treatments. Gold nanoparticles from *T. chebula* have more anti-inflammatory activity than the standard drug diclofenac. Furthermore, silver nanoparticles have demonstrated strong anti-urolithiatic, anti-cancer, and anti-phytopathogenic properties. Copper oxide nanoparticles have exhibited concentration-dependent anti-bacterial activity against wound pathogens. Silver, nickel oxide, and silver palladium bimetallic nanoparticles have displayed greater anti-cancer activity, and silver nanoparticles from *T. chebula* have shown a significant reduction in the IC_{50} value in comparison with *T. chebula* alone. The significance of *T. chebula* in green nanotechnology is highlighted by these findings, as well as the wide range and therapeutic potential of the nanoparticles made from it.

KEYWORDS: *Terminalia chebula* Retz, Pharmacological activities, Nanotechnology, Green synthesis.

1. INTRODUCTION

Nanotechnology, as the name suggests, is the technology of nano or dwarf materials whose sizes range between one and one hundred nanometers. Primarily it is the art of modifying properties at the nanoscale to generate novel, unique materials with extraordinary qualities. Due to its extensive applications across a wide range of fields, nanotechnology has recently drawn a lot of attention.[1] Nanotechnology, a relatively new field, creates a wide range of nano products, which include nanoparticles, nanopowders, nanotubes, nanowires, and nano colloids. The smallest particles (10^{-9} m), known as nanoparticles (NPs), have a wide range of uses and unique characteristics, which may include pharmaceutical, chemical, agricultural, environmental, and remediation industries, as well as electronic agents and catalytic factors. Because of their increased surface area, compound affinity, binding efficiency, anionic and cationic properties, and alternative use of bulk (whole) materials, metallic nanoparticles have drawn a lot of attention from researchers.[2] The synthesis of nanoparticles through physical, chemical, and green synthesis routes has been an area of extensive research lately.[1] Plant-mediated green synthesis of nanoparticles has become more popular recently because it is simple to use and eco-friendly.[3] During synthesis, phytocompounds interact with metal ions, resulting in stable compound configurations through condensation and downstream processes. Furthermore, phytocompounds have a lower toxicity level than non-targeted species. Ultimately, it has been proposed that green synthesized compounds are easily accessible, cost-effective, and eco-friendly.[2]

Since ancient times, people have utilized plants and their derivatives, and as a result of empirical knowledge, they

are now considered to be highly valued by humanity. When a plant plays a significant role in the prevention and treatment of disease, it is referred to as medicinal. These plants represent the sole means of treating particular diseases in some parts of the world.[4] One of the most ancient forms of medicine in the world, Ayurveda, provides a great deal of beneficial compounds for biomedical applications.[5] The need for novel, pharmacologically active compounds in medicinal plants is growing rapidly because of the availability of these compounds locally, in their natural origin, with higher safety margins and minimal or least adverse reaction. Based on ancient references, approximately 500 plants may have therapeutic applications and about 800 plants are currently used in domestic medicinal practices. The Indian subcontinent is home to a vast repository of healthy plants that are used in traditional medicine.[6]

Of the Combretaceae family, the genus *Terminalia* comprises between 200 and 250 species. This genus of plants grows mostly in tropical regions of the world, with Southeast Asia having the highest genetic diversity. Since the leaves originate at the very top of the shoots, the genus name *Terminalia* is derived from the Latin word terminus. Since ancient times, Ayurveda has used various plant parts of the *Terminalia* species, including *Terminalia arjuna, Terminalia bellerica, and Terminalia chebula.*[7] After screening several *Terminalia s*pecies, scientists discovered *Terminalia chebula* (*T. chebula*) Retz. as one of the most revered medicinal plants, which shows a variety of medicinal activities because of its wide variety of phytoconstituents.[8] *T. chebula* Retz, commonly referred to as 'Haritaki or Myrobalan' is widely used to treat human ailments in a variety of indigenous medicine systems, including Unani, Tibb, Ayurveda, and Siddha. In Tibet, *T. chebula* is known as the "king of medicine," as haritaki carries away all diseases, or it is considered sacred by the god Siva (Hara).[6] Its extensive therapeutic properties and exceptional healing potential have earned it the titles "wonder herb," "mother of medicines," and "king of medicines".[9] This species of tree is an evergreen that is commonly known as Chebulic Myrobalan in English. It is called "Haritaki" in Sanskrit and is an essential component of the traditional ayurvedic combination known as "Triphala." *T. chebula* is distributed throughout northern India, extending from Kumaon to Bengal and further south to the Deccan, Sri Lanka, Myanmar, and Nepal. Within the field of medicine, three varieties of haritaki are used: Bala haritaki, Chambhari haritaki, and Survari haritaki. At the immature stage, the haritaki fruit is called Chambhari; occasionally, the fruit falls off the tree and the hardened seed is called Bala haritaki; finally, the fully matured fruit is called Survari haritaki.[10]

T.chebula possesses a variety of pleiotropic effects such as anti-oxidant, anti-diabetic, reno-protective, hepato-protective, immune-modulation, anti-arthritic, cyto-protective, anti-bacterial, anti-microbial, anaphylactic effect and pro-kinetic effects, etc.[11] *T. chebula* has a lot of potential to be included in modern drug discovery because of its bioactivity. However, for its prospective pharmaceutical applications, more pre-clinical and clinical research is essential.[12] Hence, this review mainly focuses on the *T. chebula* mediated green synthesised nanoparticle and its potential pharmacological activities.

2. INTRODUCTION TO PLANT PROFILE

Figure 1: Leaf,flower and fruit of *T.chebula*.[10]

2.1. Botanical information

Kingdom**:** Plantae
Subkingdom**:** Tracheobionta
Super division: Spermatophyta
Division: Magnoliophyte
Class: Magnoliopsida
Subclass: Rosidae
Order: Myrtales
Genus: Terminalia
Species: *Terminalia chebula.*[13]

2.2. Morphological characters

The *Terminalia chebula* is a tree of medium to large size that can reach a height of 30 m and a girth of thickness of 1.15 m. It has a broad, rounded crown and is heavily branching. The bark has some lengthwise shallow fissures and is dark brownish in colour. With an acute tip and a cordate base, the leaves are elliptic. Alternate or

sub opposite leaf arrangements can be found on the petiole.[10] The flowers have short stems, are monoecious, range in colour from dark white to yellow, and are arranged in short panicles or simple terminal spikes with an unpleasant odour. Ellipsoid drupe fruit with a dried pericarp; 2-4 cm long and 2-2.5 cm wide; green when unripe, brown when ripe. Seeds are rough, bony, and obscurely angled.[6]

2.3. Ethno-medicinal uses

Since ancient times, traditional medicine has used medicinal plants and their parts to serve preventive and healing purposes all over the world. Currently, over 80% of people in low- and middle-income countries still rely on medicinal plants as their primary source of medication. In traditional medical practices, *T.chebula* is one such plant of utmost importance.[12] As per 'Bhagavad', this is the drug of choice in the therapy of vata-kapha diseases. Haritaki is advised to be taken in conjunction with rock salt for 'kapha' diseases, sugar for 'pitta' diseases, and ghee for 'vata' diseases.[10] Haritaki is an important ingredient in many Ayurvedic formulations, including Brahma Rasayana, Abhaya lavana, Agastya Haritaki Rasayana, Citraka Haritaki, Danti Haritaki, Dasamula Haritaki, Triphala Churna, Triphaladi Taila, Abhayarista, and Pathyadi Lepa.[7] *T. chebula* is used as a colon detoxifier, a laxative for chronic constipation, and a remedy for digestive problems.[10] Fruits of *T. chebula* are used to treat a variety of conditions in Ayurveda and Siddha traditional medicine, such as cough, asthma, candidiasis, hepatomegaly, dyspnea, dyspepsia, urinary discharge, haemorrhoids, constipation, ulcers and other gastrointestinal tract disorders.[7] Fruits effectively minimise swelling, speed up healing, and clean wounds and ulcers. They also prevent pus build-up in skin diseases and promote the healing of wounds, particularly burns. Because the fruit has anti-inflammatory properties, it is also used to relieve conjunctivitis. Additionally, it is also used as an anti-astringent and a mouth rinse.[13] Finely ground fruit powder from *T. chebula* is beneficial to treat tooth caries, bleeding gums, and chronic ulcers. The bark is used as a heart tonic and diuretic.[6] However, in certain situations, its astringent and hot nature make it contraindicated despite its enormous health benefits.[9]

2.4. Phyto-chemistry

Terminalia chebula Retz is abundant in bioactive substances and fruits are widely known for having high concentrations of phenolic compounds, which include tannins, flavonoids, and phenolic acids. Likewise, the fruits are also rich in vitamin C (ascorbic acid).[7] The fruits of *T. chebula* are abundant, with tannin ranges depending on the geographical distribution and typically between 32% and 34%.[14] Gallic acid, ellagic acid, chebulic acid, chebulinic acid, punicalagin, terflavin A, corilagin, galloyl glucose, and tannic acid are the tannins that are most prevalent in the fruit. Flavonoids that are readily available, such as quercetin, catechin and kaempferol are found at the same time. Fruit also contains saccharides such as quinic acid, shikimic acid, D-glucose, and D-fructose.[6] The leaves of *T.Chebula* contain polyphenols such as punicalin, punicalagin, and terflavins B, C, and D.[5] From the fruits of *T. chebula*, sterols like daucosterol and β-sitosterol have been isolated. The fruits of *T. chebula* contain 14 essential oils, the main peaks of which are furfural, phenylacetaldehyde, 5-methyl furfural, and palmitic acid. Several triterpenoid glycosides have been identified, including chebulosides I and II, arjunin, arjunglucoside, and 2α-hydroxyursolic acid. It has been found that the plant contains phenolic acids like ferulic, p-coumaric, caffeic, and vanillic acids, as well as phloroglucimol and pyrogallol.[14]

3. NANOTECHNOLOGY

The field of nanotechnology offers an endless array of possibilities for developing novel nanomaterials with applications in the natural sciences and clinical pharmaceuticals. These nanomaterials can now be synthesized in various structures, which gives them adaptable biomedical and physical properties.[15] In a sustainable approach to the environment, the synergy between nanotechnology and biotechnology appears as an effective alternative for a variety of applications.[4] Combining traditional and modern knowledge may result in a more reliable source of active disease treatment ingredients with fewer adverse effects. Since medicinal plants have an important role in the synthesis of nanoparticles (NPs), nanoparticles can be produced using a variety of physico-chemical methods to control the problem of toxicity in synthesis. Phytochemical compounds found in plant biomolecules, such as quinines, phytosterols, phenolic compounds, and saponins, exhibit both preservative and reductive properties.[5] In contrast to chemical synthesis, the green synthesis of metal nanoparticles was carried out under ambient conditions and took a shorter duration. Still, the maximum yield and productivity are achieved by the stability and longevity of green synthesized nanoparticles. Compounds derived from phytal extract act as reducing, stabilizing, and capping agents during the green synthesis of nanoparticles. The bio merits of medicinal substances bound to nanoparticles are many, which may include good availability, an extended half-life *in vivo* system, and the ability to achieve a sustained release at an effective concentration.[16]

It is possible to create nanoparticles with a variety of structures using physical, biological, and chemical technologies. However, the use of physical and chemical methods frequently leads to low yields, costly production, high energy consumption, and adverse environmental effects. Biological synthesis is a synthesizing method that uses microbes and plants as reducing agents. Owing to their exceptional thermal, strong optoelectronic, catalytic, and surface volume ratio characteristics, metal nanoparticles are vital in the medical field, which may be because of their excellent

physicochemical properties.[17] After the capping process of nanoparticles, the pharmacological characteristics of a plant must be preserved, which means the biological properties of the bioactive compounds cannot be reduced during the synthesis process, and they should exhibit low toxicity. Hence, developing novel formulations using nanotechnology holds great promise for enhancing the pharmacological activity of *T. chebula* and improving the potential activity of the plant.[18]

4. DIFFERENT TYPES OF METALIC NANOPARTICLES

4.1. Silver nanoparticles

When silver nanoparticles (AgNPs) are made chemically, they often result in toxic, non-ecofriendly products.[17] AgNPs produced from plants or plant extracts using biological techniques are now preferred for therapeutic use in humans because they are safer and more eco-friendly alternatives to physical and chemical methods. Compared to most other metals, silver has a comparatively low toxicity and a high biocompatibility, which significantly increases its potential for use in healthcare and pharmaceutical industries. Ag NP synthesized from *Terminalia chebula* fruit extract has a spherical morphology with an average diameter of 22 nm, which was investigated by High-Resolution Transmission Electron Microscopy (HR-TEM) analysis.[18] Field emission scanning electron microscopy (FESEM) has shown that silver nanoparticles from leaf extract of *T.chebula* are sphere-shaped and uniformly dispersed, with an average size of 60 nm. Fourier Transform Infrared Spectroscopy (FTIR) showed that oxidized polyphenols present in Ag NPs from *T. chebula* leaf extract act as capping agents.[5] Acids such as ellagic acid, chebulic acid, and tannin present in the plant extract might be involved in the reduction and formation of Ag nanoparticles, which were analyzed by FTIR.[16]

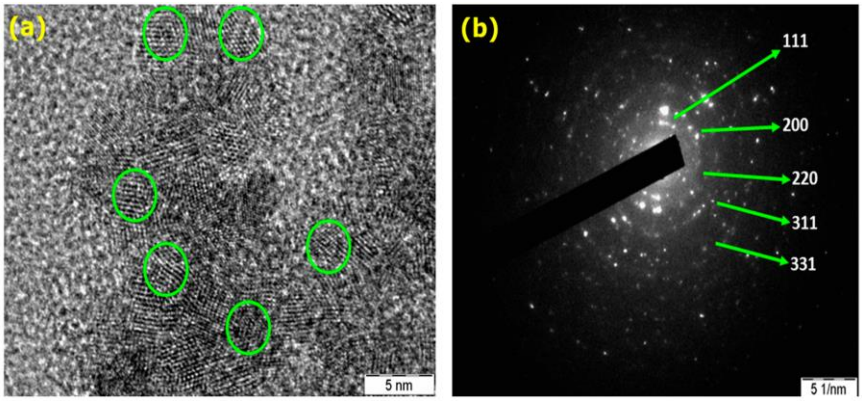

Figure 2: (a) HR-TEM and (b) Selected Area Electron Diffraction (SAED) images AgNPs prepared using *T.chebula* Fruit extract.[18]

4.2. Gold nanoparticles

Gold nanoparticles (Au NPs) were synthesized by several chemical methods, most of which involved the use of toxic reductants and capping agents. Since Au NPs were used in numerous applications involving human contact, it is necessary to stay away from toxic chemical methods. Several methods have been successfully employed to synthesise Au NPs besides chemical reduction, which may include aerosol technologies, ultrasonic fields, and laser ablation, but these methods are highly expensive. Gold nanoparticles (AuNP) have the advantages of nontoxicity, biocompatibility, drug-making potential, and antibacterial action in synthesizing nanoparticles.[19] The aqueous extracts of *Terminalia chebula* were used as a reducing and stabilizing agent in an in situ green biogenic synthesis of gold nanoparticles, where the hydrolyzable tannins present in the extract of *T. chebula* are responsible for the reductions and stabilization of gold nanoparticles. A Transmission Electron Microscopy (TEM) analysis showed that the morphology of the resulting particles included 6–60 nm-sized anisotropic gold nanoparticles.[3]

4.3. Palladium nanoparticles

Palladium nanoparticles, or PdNPs, have drawn interest in the last ten years from the fields of biomedicine, engineering, and electronics because of their easy accessibility, low cost, and unique catalytic and optical properties. PdNPs are currently gaining attention as photo-thermal and pro-drug activator agents for anti-microbial and anti-cancer therapies. Due to an enormous rise in demand for nanoparticles across a range of industries, researchers are focusing on green synthesis since it is sustainable and friendly to the environment.[20] The aqueous extracts of *T. chebula* act both as reducing and capping/stabilizing agent in the synthesis of Pd NPs due to the presence of polyphenols. Therefore, it can serve as an alternative to chemical methods that inevitably require the use of toxic, pricey organic solvents as well as hazardous reducing, capping, or stabilizing agents. Transmission Electron Microscopy (TEM) image of Pd NPs showed that the particle size was below 100 nm. TEM image reveals the formation of anisotropic NPs such as triangular and pentagonal shapes.[21]

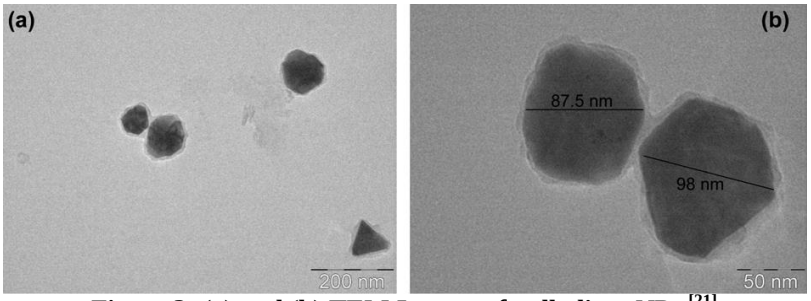

Figure 3: (a) and (b) TEM Images of palladium NPs.[21]

4.4. Nickel Oxide nanoparticles

Green synthesized Nickel Oxide nanoparticles (NiO NPs) from *T. chebula* have FCC cubical structure and particle size within the range of 20–25 nm, which were characterized by X-Ray Diffraction (XRD) and TEM analysis. FT-IR analysis confirmed that biomolecule chains (flavonoids & reducing sugars) present in the fruit extract of *T.chebula* are the reason for the capping of nanoparticles, which may lead to prolonged stability.[15]

4.5. Copper Oxide nanoparticles

T. chebula serves as both a reducing and capping agent in the green synthesis of copper oxide nanoparticles because of the presence of bioactive compounds like tannins, flavonoids, and phenolic compounds. UV-visible spectrophotometry suggested that Copper Oxide nanoparticles (CuO NPs) are small, as the absorption maximum was observed at 440 nm since larger particles usually have absorption peaks at longer wavelengths. The scanning electron microscopy (SEM) analysis of *T. chebula*-mediated CuO NPs discovered that nanoparticles have a uniform spherical shape, and the average size was found to be approximately 120 nm. The transmission electron microscopy (TEM) analysis revealed the size distribution of CuO nanoparticles, and the majority of the nanoparticles were observed within the range of 10–12 nm.[22]

5. PHARMACOLOGICAL ACTIVITIES

5.1. Anti-microbial activity

The fruit extract of *T. chebula* has anti-microbial activity due to its high efficacy against both gram-negative and gram-positive bacteria. Ankegowda VM *et al* (2020) investigated the potential anti-microbial activity of silver nanoparticles (AgNPs) prepared from the fruit extract of *T. chebula*. It was confirmed that phyto-synthesized AgNPs from *T.chebula* fruit extract have a significant effect on growth inhibition of gram negative bacteria than gram positive bacteria which may be due to the difference in the composition and structure of bacterial cell walls. *Bacillus subtilis* was more susceptible to the anti-bacterial activity of silver nanoparticles prepared from *T. chebula* fruit extract, followed by *Pseudomonas aeroginosa,* which was assessed by measuring the zone of inhibition. On the other hand, *Escherichia coli* and *Streptococcus mutans* were less sensitive to the silver nanoparticles where the bactericidal tests were carried out by microdilution and well diffusion methods. The phyto-constituents present in the *T. chebula* will adhere to the silver nanoparticle surfaces, which leads to damage to the bacterial outer membrane by destroying cell wall proteins, ultimately causing leakage of cellular matter. Then AgNPs enter the cell membrane, causing rupturing and leakage of intracellular substances, which in turn inhibit the bacterial respiration process and bacterial growth.[18] While Espenti C *et al* (2016) reported the anti-microbial activity of silver nanoparticles prepared from *T. chebula* leaf extract, where they effectively inhibit human pathogens such as *Escherichia coli* and *Bacillus subtilis*, which was examined using the agar well-diffusion method at different compositions and Gentamycin was used as a positive control. From this study, it was concluded that the antibacterial activity of *T. chebula* was enhanced when *T. chebula* leaf extract was associated with silver nanoparticles.[5]

Similarly, Giridharan B *et al* (2016) studied the anti-bacterial efficacy of *T. chebula*-coated AgNPs at various concentrations against *Escherichia coli, Pseudomonas aeruginosa, and Candida albicans. T. chebula*-coated AgNP demonstrated significant anti-microbial activity against *Escherichia coli, Pseudomonas aeruginosa, and Candida albicans* at a concentration of 25 µg. *T. chebula* containing AgNPs showed a higher zone of inhibition at 100 µg in contrast to dose dependence. Significant activity was observed by *T. chebula* coated on AgNPs alone at higher concentrations as compared to lower concentrations.[16]

Sathvika K *et al* (2021) examined the anti-microbial activity of different dilutions of Ag-NPs prepared from the fruit extract of *T. chebula* against three dental pathogens: *Streptococcus mutans, Staphylococcus aureus, and Enterococcus faecalis*, by using the well diffusion method. At all tested concentrations of Ag-NPs, the zone of inhibition for *Staphylococcus aureus* was significantly higher than that of the standard antibiotic Amoxicillin, while for *Enterococcus faecalis*, it was significantly lower than that of Amoxicillin. At lower concentration, the zone of inhibition for *Streptococcus mutans* was significantly lower than that of amoxicillin, while there was no significant difference with amoxicillin at higher concentrations.[23]

Siddhan N *et al* (2014) evaluated the anti-bacterial activity of the silver nanoparticle prepared from *T. chebula* seeds by the agar-well diffusion method, and it

was found that organic solvent extracts exhibit strong antibacterial activity. The greater antibacterial activity was maintained in 50 µl and 100 µl of ethanol and acetone seed extract in a dose-dependent manner. The ethanol extract displayed strong inhibition against all tested organisms at 50 µl concentration. *Pseudomonas aeroginosa, Klebsiella pneuminiae* and *Staphylococcus aureas* showed highest level of inhibition while *Salmonella typhi* and *Escherichia coli* showed a moderate inhibition. All other solvent extracts, with the exception of acetone against *Pseudomonas aeruginosa*, did not actively inhibit the growth of the bacteria at 50 µl concentration. The growth of *Pseudomonas aeruginosa* was inhibited by all of the seed extracts at 100 µl concentrations; the ethanol extract showed the maximum inhibition, with the zone of inhibition being larger than that of the standard drug chloromphenicol. Likewise, ethanol seed extract displayed maximum inhibition to the growth of *Klebsiella pneumoniae* than chloromphenicol. However, compared to chloromphenicol, other extracts showed less inhibitory activity.[24]

Likewise, Sivamaruthi B *et al* (2019) assessed the *in vitro* anti-microbial activity of silver-palladium (AgPd) bimetallic nanoparticles synthesised from the aqueous fruit extract of *T.chebula* against methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa.* The anti-microbial activity of AgPd NPs was evaluated by the Kirby-Bauer disc diffusion method against gram +ve and gram –ve bacterial strains. As positive controls, ampicillin, kanamycin, and gentamycin were used. AgPd NPs exhibited a dose-dependent reduction in bacterial growth against methicillin-resistant *Staphylococcus aureas* and *Pseudomonas aeruginosa* with bacteriostatic activity at the lowest concentrations of 160 and 320 µg/ml, respectively. Synergistic effect caused by silver and palladium nanoparticle may be the reason for the enhanced antibacterial activity of AgPd NPs. These nanoparticles interact with the bacterial cell membrane, which changes the fluidity and releases the intracellular content, leading to the death of bacterial cells. They also causes the induction of free radical formation, ultimately leading to oxidative stress-mediated cell death by silver and palladium nanoparticles.[20]

Gold nanoparticles are more susceptible to cell damage from gram negative *E. coli* with a thin cell wall as compared to gram positive *Staphylococcus aureus* with a thick cell wall. However, Mohan Kumar K *et al* (2013) reported that the gold nanoparticles synthesised from *T. chebula* seed have better anti-microbial activity against gram postive *Staphylococcus aureus* in contrast to gram negative *Escherichia coli,* which were assessed by the standard well diffusion method. Since these results might depend on strain, suggesting the need for further research to shed light on the issue. Similarly, the strain of microorganisms used also affects the damage to the bacterial cell wall.[3] Gold nanoparticles get adsorbed and agglomerated on the bacterial cell wall, which results in an alteration in the cell wall membrane and membrane permeability. After Au NP enters the bacterial cells, gold nanoparticles may induce the release of reactive oxygen species (ROS) within the cells, and ROS cause oxidative stress, damaging cellular components and disrupting bacterial metabolism. Sometimes, phytoconstituents like tannin, flavonoids, and phenols present in the plant extract also contribute to the antibacterial activity of gold nanoparticles, where AuNP can interact with the bacterial cell wall, which changes its structure and damage bacterial cells. Also, gold ions may be released into the bacterial environment, where they interact with bacterial proteins and enzymes, interfere with their function, and ultimately cause disruption of bacterial growth and viability.[25]

From these studies, it can be anticipated that *T. chebula*-mediated silver nanoparticles, gold nanoparticles, and silver-palladium nanoparticles exhibit significant anti-microbial potential against various pathogens. The zone of inhibition of *T. chebula* against different bacterial strains has been enhanced when green synthesized metallic nanoparticles are employed. Gold nanoparticles have shown a clear zone of inhibition against gram-positive bacteria, at 25 µl and 50 µl, while silver-palladium nanoparticles demonstrated a zone of inhibition at 30 µg/ml against both gram-positive and gram-negative bacteria. The silver nanoparticles from *T. chebula* have a clear zone of inhibition against several microbial pathogens, and the green synthesized silver nanoparticles are comparable to the standard anti-microbial drugs.

5.2. Anti-oxidant activity

The accumulation of reactive oxygen species (ROS) causes oxidative DNA damage, protein oxidation, lipid peroxidation, and the inactivation of anti-oxidant enzymes within the cell, which may result in a number of chronic diseases, including atherosclerosis, cancer, diabetes mellitus, inflammation, and cardiovascular disease.[6] *T.chebula* has been shown to possess anti-inflammatory, anti-bacterial, and anti-oxidant properties. Certain tannins, including gallic acid, chebulagic acid, corilagin, and chebulic acid, are in responsible for antioxidant activity of *T. chebula.*[17]

Gold nanoparticles have gained a lot of attention because of their inert nature, which makes them resistant to oxidation.[18] Polyphenols in the form of hydrolyzable tannins present in the *T. chebula* facilitate the synthesis of in situ gold nanoparticles, while oxidised polyphenols can act as capping agents for the gold nanoparticles.

Chanchal Katariya *et al* (2023) evaluated the antioxidant activity of gold nanoparticles synthesized from *T. chebula* seed by the DPPH (2,2-diphenyl-1-picrylhydrazyl) assay, and it was found that the gold nanoparticles made from *T. chebula* exhibit strong antioxidant activity and are comparable to the standard treatment Butylated Hydroxy Toluene (BHT). As the

concentration increases, the anti-oxidant activity of gold nanoparticles has been enhanced. The study concluded that gold nanoparticles synthesized from *T. chebula* have remarkable antioxidant properties and can be added to dental materials to further improve their characteristics.[19]

In a study conducted by Tharani M *et al* (2023), dried fruit extract of *T. chebula* acted as a mediator in the synthesis of silver nanoparticles. The antioxidant activity of silver nanoparticles from *T. chebula* was tested using DPPH assay while Butylated Hydroxy Toluene and ascorbic acid were used as standards.[17] Studies have shown that green synthesized silver nanoparticles, which contain a variety of biomolecules on their surface, have greater anti-oxidant activity and can be employed as radical scavengers to prevent damage from free radicals.[27] DPPH test results suggested that silver nanoparticles from *T.chebula* are good free radical scavengers. In this instance, *T. chebula* fruit extract (TCF) mediated silver nanoparticles (AgNPs) significantly increased anti-oxidant activity at higher concentrations in comparison with ascorbic acid. TCF-AgNPs had a percentage inhibition which was equivalent to standard drug ascorbic acid at 500 µg/ml and 1000 µg/ml. AgNPs mediated by *T. chebula* displayed strong free radical scavenging ability against DPPH free radicals, which were produced as the result of oxidative stress. These results emphasize the capping action of secondary metabolites in the plant extract, which increases anti-oxidant activity.[17]

Titanium dioxide (TiO_2) nanoparticles exhibit greater anti-oxidant, anti-microbial, and photo-catalytic degradation features, making them the most promising metallic nanoparticles. Kannadasan N *et al* (2023) investigated the anti-oxidant activity of TiO_2 nanoparticles synthesized from *T. chebula*, where they exhibited significant inhibitory activity against free radicals. The efficiency of scavenging oxygen radicals rises with an increase in TiO_2 nanoparticle concentration synthesized from *T. chebula*. The strong anti-oxidant activities of green-synthesized TiO_2 nanoparticles have been achieved due to the presence of active phyto-metabolites in *T. chebula* that reduce reactive oxygen species.[2]

The gold nanoparticles derived from *T. chebula* have demonstrated antioxidant properties greater than the standard values, with an exception at concentrations of 40 µl and 50 µl, and the highest percentage inhibition was found to be 86.2% at 20 µl. The silver nanoparticles from *T. chebula* displayed a percentage inhibition of 93.47±8.19% at a concentration of 500 µg/mL, which was equivalent to that of the standard drug ascorbic acid (109.81±5.78%). At 1000 µg/mL, silver nanoparticles demonstrated a significant increase in antioxidant activity (124.33 ±17.8%) in comparison to the other concentrations tested; this was also equivalent to the standard drug (137.29 ±5.79%). Meanwhile, green-synthesized titanium dioxide nanoparticles from *T. chebula* have demonstrated strong antioxidant activity at the highest concentration (400 µg/ml). Using the in-vitro DPPH assay, the percentage inhibition at 400 µg/ml was 67.53%, while the FRAP assay yielded 21.57% at the same concentration (400 µg/ml).

5.3. Anti-inflammatory activity

Inflammation, which is characterized by redness, pain, swelling in the affected area, and disrupted physiological functions, is the protective response initiated by the body which is meant to inactivate or eliminate the invading organism or to eliminate any irritants that could cause tissue injury, infection, or destruction. This is because of the chemical mediators released from damaged tissue.[25] Phytochemical constituents like arjunolic acid, arjunic acid, chebulinic acid, and 2,3,6-trio-O-galloyl-β_D-glucose, which are present in *T. chebula*, are potentially responsible for anti-inflammatory activities of the plant.[7]

Gold nanoparticles (AuNPs) trigger the polarisation of macrophages towards the M2 phenotype. M2 macrophages are related to anti-inflammatory reactions, where they assist in the reduction of inflammation. AuNPs also hinder the expression of pro-inflammatory cytokines. By regulating cytokines, gold nanoparticles endorse the overall anti-inflammatory environment. Sometimes gold nanoparticles interfere with the adhesion of leucocytes by preventing the accumulation of immune cells at inflammatory cells. Gold nanoparticles also reduce the oxidative stress associated with inflammation. Hence, gold nanoparticles are a promising area for treating anti-inflammatory conditions.[29]

Chanchal Katariya *et al* (2023) investigated the anti-inflammatory properties of *Terminalia chebula* mediated gold nano particles. The anti-inflammatory activity of *Terminalia chebula* seed extract-mediated gold nanoparticles was higher than that of standard treatment, diclofenac sodium, at 40µl and 50µl concentrations, which was assessed by bovine serum albumin assay. The highest concentration of 50 µl was found to have the highest level of inhibition, with the percentage of inhibition being highest at 40 µl (62%) and 50 µl (72.5%). Gold nanoparticles synthesized from *Terminalia chebula* are expected to exhibit anti-inflammatory activity comparable to that of the standard drug diclofenac.[19]

5.4. Anti-cancer activity

Based on ethnopharmacology, *T.chebula* has potent antioxidant activity against free radicals and anti-cancer, anti-diabetic, anti-fungal, anti-viral, and anti-bacterial properties. The fruit of *T. chebula* is abundant in flavonoids, terpenoids, and gallic acid, which is considered to be the cause of the redox reactions. Fatima Ibrahim *et al* (2018) studied the *in vitro* cytotoxicity activity of green synthesized nickel oxide nanoparticles (NiO NP) from *T. chebula* extract against MCF-7 cells.

Green synthesized NiO NPs from *T. chebula* fruit extract act as a chemical coating and reducing agent. NiO NPs from *T. chebula* fruit extract show cytotoxicity activity on breast cancerous cells, MCF-7 cells, which was assessed by the MTT (3-(4,5-dimethyl thiazol-2yl)-2,5-diphenyl tetrazolium bromide) assay. When MCF-7 cells were exposed to NiO NPs using an extract of *T.chebula* at various concentrations, cell viability declined in a dose-dependent manner. NiO NPs from *T.chebula* also reduce the mitochondrial membrane potential (MMP) of MCF-7 cells in a dose-dependent manner, as shown by both quantitative data and fluorescence microscopy, while the MMP of cancerous cells decreases during apoptosis. At 100 µg/mL, NiO NPs from *T.chebula* suppressed the proliferation of human normal MCF-10A breast cells, but at 20–80 µg/mL, they had no toxic effects on non-tumourigenic breast cells.[15]

Because of the selective cytotoxicity of *T. chebula*, relatively few studies have been carried out to fully understand its potential as an anti-breast cancer agent. Ankegowda VM *et al* (2020) investigated the anti-cancer activity of phyto-mediated synthesis of silver nanoparticles from *T.chebula* fruit extract. However, AgNPs exhibit great potential as anti-cancer agents. They affect the cancerous cell cycle and proliferation by inducing apoptosis and generating oxidative stress. Greater cytotoxic effects against cancer cell lines have been demonstrated by plant-mediated silver nanoparticles at lower doses. *T. chebula* fruit extract has cytotoxic activity against the MCF-7 cell line in a dose-dependent manner. A higher concentration of *T.chebula* fruit extract (TCE) was needed for a significant anti-proliferative effect as compared to AgNPs. On the other hand, the tumoricidal potential of the constituents at very low concentrations was substantially raised by the TCE-mediated preparation of AgNPs. During the TCE + AgNPs treatment of MCF-7 cells, a significant reduction in IC_{50} was observed, which was nearly one-third of TCE and half of AgNPs treatments.[18]

Sivamaruthi *et al* (2019) evaluated the *in vitro* anti - cancer activity of silver palladium bi metallic nanoparticles (AgPd NPs) from the aqueous fruit extract of *T. chebula*. AgPd NPs from *T. chebula* have anti-cancer potential against lung cancer cells (A549) which were assessed by MTT and LDH assay. Comparing AgPd NPs to the standard drug cisplatin (IC_{50} value of 18.09 ± 0.012 µg/ml), AgPd NPs showed dose-dependent cytotoxicity against A549 cells (IC_{50} concentration of 48.45 ± 0.04 µg/ml). Aqueous extract of *T. chebuala* alone doesn't have any significant cytotoxic effect against A549 cells. In contrast to the vehicle control, Ag Pd NPs-treated cells exhibited a higher percentage of apoptotic cells. The bimetallic nanoparticles have anti-cancer potential because they activate the apoptotic cascade pathway, which in turn causes cellular death, by generating more reactive oxygen species (ROS) through respiratory chain dysfunction, which results in the loss of mitochondrial membrane potential (MMP) and ROS-mediated DNA damage of cancerous cells. AgPd-NPs treated cells exhibited apoptotic-mediated death rather than necrosis. AgPd bimetallic NPs demonstrated no cytotoxic or hemolytic effect up to it's maximum dose (200 µg/ml) based on the *in vitro* toxicity studies, confirming the biocompatibility of nanoparticles.[20]

The potent phytochemical constituents like gallic acid, ellagic acid, chebulic acid, tannin, and terflavin present in *T. chebula* may be responsible for the reduction of AgNO3 to Ag-NPs. In medical applications, there is a growing demand for silver nanoparticles as an antimicrobial agent. However, investigation into the cytotoxic effects of biologically produced AgNPs against colon cancer cell lines is still insufficient.

Bupesh Giridharan *et al* (2016) reported the enhanced anti-cancer activity from *T. chebula* medicinal plant rapid extract by phytosynthesis of silver nanoparticles core-shell structures. This study compares the cytotoxic effect of biosynthesized AgNPs against normal vero cells and the colon cancer HT-29 cell line. Silver nanoparticles synthesised from the methanolic fruit extract of *T. chebula* exhibited cytotoxic effects only on human colon cancer HT-29 cells but not in normal vero cells. A possible pathway for the anti-proliferative activity of biosynthesized silver nanoparticles is apoptosis. AgNPs exhibited significant toxicity against normal vero cells at higher concentrations. The IC_{50} value against HT-29 cells of biosynthesised AgNPs is 15 µg/mL for 24 hours and 10 µg/mL for 48 hours. Yet, biosynthesized *T. chebula* coated on AgNPs has a significant cytotoxic effect on in vitro cells at 20 µg/mL for 24 hours and 30 µg/mL for 48 hours.[16]

While, Nandagopal S *et al* (2014) studied the anti-cancer activity of silver nanoparticles synthesized using *T. chebula* seed extract. Silver nanoparticles synthesized using *T. chebula* seed extract have exhibited anti-cancer activity against HEP2 cell lines by using MTT assay. LD_{50} growth inhibition has been seen at 1000 µg/ml. Different concentrations of the *T. chebula* seed extract showed a dose-dependent increase in cytotoxicity.[30]

5.5. Anti-Urolithiatic Activity

Infectious stones associated with urinary tract infections are called struvite crystals. Higher salt levels in the urine, a urinary tract infection, and a decrease in the natural inhibitors that prevent the formation of crystals can all lead to the serious condition termed struvite crystal formation. FT-IR spectroscopy studies revealed that phyto-constituents present in *T.chebula* are mainly responsible for the capping and reduction of silver nanoparticles. *T. chebula* bark-mediated silver nanoparticles have uniformity in shape and crystalline nature, which were confirmed by Transmission Electron Microscopic (TEM) and X-ray diffraction studies (XRD) analysis. Vidya S d *et al* (2021) studied the *in vitro* anti-urolithic activity of *T. chebula* bark-mediated silver nanoparticles, which was assessed by the single gel

diffusion method, where pure magnesium acetate was used as a control. The inhibition activity of *T. chebula* mediated silver nanoparticles is caused by the silver ions capped with bio-organic molecules found in the phyto-constituents. The size and average weight of the grown struvite crystals were gradually reduced by increasing the percentage of *T. chebula* bark-mediated silver nanoparticles. Silver nanoparticles synthesized from *Terminalia chebula* exhibited a maximum inhibition efficiency of 87.9%, while the extract from *Phyllanthus emblica* demonstrated approximately 60% inhibitory effect on struvite crystal growth. Compared to *Phyllanthus emblica*, silver nanoparticles synthesized from *Terminalia chebula* are more effective at controlling struvite stone formation.[31]

5.6. Anti-Phytopathogenic activity

Gallic acid, isolated from *Terminalia chebula* fruit, will be used for synthesizing silver nanoparticles. The shape and structure of gallic acid-reduced silver nanoparticles were found to be spherical and face-centred cubic (FCC) structures, which were characterised by Transmission Electron Microscopic (TEM) and X-ray diffraction studies (XRD).Sulthana A *et al* (2014) investigated the anti-phytopathogenic activity of gallic acid-reduced *T. chebula* silver nanoparticles against the pathogen *Xanthomonos axonopodis* pv.*malvacearum.* The broth microdilution method was used to assess the minimum inhibitory concentration MIC, where maximum activity was found at a concentration of 70 µg/ml. The gallic acid reduced *T.chebula* silver nanoparticles have antibacterial activity against *Xanthomonos axonopodis pv. malvacearum* at a low concentration in comparison with the control streptomycin.[28]

5.7. Wound management

An essential trace element, copper, plays a significant role in physiological processes such as angiogenesis, skin regeneration, and immune response. As a result of the special physicochemical characteristics of copper oxide nanoparticles (CuO NPs), they have been able to efficiently transport copper ions to the sites of wounds, accelerating the healing process. These nanoparticles also have strong anti-bacterial properties, which increases their potential for inhibiting wound infections.

Tharani M *et al* (2023) evaluated the potential anti-microbial activity of CuO NPs synthesized from *T. chebula* against three distinct wound pathogens, including *S. aureus, P. aeruginosa,* and *E. coli* which were assessed through agar-well diffusion, time-kill curve, protein leakage analysis, and anti-biofilm assays. CuO NPs from *T. chebula* have shown concentration-dependent antibacterial activity, with more significant reductions in bacterial counts arising at higher concentrations. At the highest concentration of 1000 µg/ml, *S. aureus* and *P. aeruginosa* exhibited significant rapid susceptibility to green-synthesized CuO NPs, whereas *E. coli* displayed a slower response. The comparison with the control group demonstrates that CuO NPs significantly affect bacterial counts. This also highlights the potential of CuO NPs as anti-bacterial agents for wound management. The disruption of cell membrane integrity by CuO NPs has been proven by protein leakage analysis in all tested wound pathogens. The effects were concentration-dependent, with more significant protein leakage being induced by higher CuO NP concentrations. This disruption indicates a possible mechanism for CuO NPs antibacterial properties. CuO nanoparticles synthesised from *T. chebula* have proven concentration-dependent efficacy in disrupting biofilm, which is vital for wound management applications. CuONPs have the potential to be an effective treatment for wound-related infections due to their concentration-dependent antibacterial, antibiofilm, and protein leakage activities against wound diseases.[22]

6. CONCLUSION

To minimize the adverse effects of chemical synthetic routes of nanoparticles based on toxic or hazardous chemical reagents, plant products can still be used in the synthesis of nanomaterials, which enables the properties of nanomaterials to be associated with those found in plant extracts. Due to the emerging need for environmentally benign technology in the synthesis of nanoparticles, green synthesis has been getting a lot of attention recently. *Terminilia chebula* Retz, a resourceful plant known as the “King of Medicine”, has a lot of pleiotropic pharmacological activities, including anti-inflammatory, anti-oxidant, anti-diabetic, reno-protective, hepato-protective, immune-modulator, anti-arthritic, cytoprotective, anti-bacterial, anti-microbial, anaphylactic, and prokinetic effects, etc.

In the present study, various metallic nanoparticles synthesized from *T. chebula* were highlighted, including silver, gold, palladium, copper oxide, nickel oxide, titanium dioxide, etc. The phytochemicals such as polyphenols, tannins, and flavonoids present in *T. chebula* act both as reducing and capping/stabilizing agents for the synthesis of nanoparticles, serving as an alternative method to the chemical or physical method. The green synthesized nanoparticles have been shown to have significant pharmacological activities in addition to exceptional structural and morphological properties. The phyto-synthesized nanoparticles from *T. chebula* have shown better penetration as well as therapeutic activities than the *T. chebula* plant extract.

The *T. chebula* plant itself possesses anti-microbial activity against various microorganisms. By synthesizing metallic nanoparticles from *T. chebula*, the anti-microbial activity is always enhanced. Owing to the promising results, the green synthesized nanoparticles from *T. chebula* may create new anti-microbial agents that may be used alone or in combination with antibiotics where they have better therapeutic potential. Additionally, it has been noticed that silver nanoparticles from *T. chebula* have better antimicrobial properties than

silver palladium bimetallic nanoparticles and gold nanoparticles. Silver nanoparticles from *T. chebula* have a broad spectrum of anti-microbial activities, which include both gram-positive and gram-negative bacterial strains.

Silver nanoparticles exhibit greater anti-oxidant activity than gold and TiO_2 nanoparticles synthesized from *T. chebula*, while the anti-oxidant activity of silver nanoparticles from *T. chebula* has shown equivalent free radical scavenging activity to the standard drug ascorbic acid. Compared to nickel oxide and silver-palladium bimetallic nanoparticles, *T. chebula* silver nanoparticles have been shown to possess greater anti-cancer activity. Silver, nickel oxide, and palladium nanoparticles have been proven to be employed in various cytotoxicity cell line studies, and they play a vital role in the induction of apoptosis in cancerous cells. These nanoparticles offer great potential for future targeted therapy. The gold nanoparticles synthesized from *T. chebula* have higher anti-inflammatory activity than the standard drug diclofenac while copper oxide nanoparticles synthesized from *T.chebula* have potent anti-bacterial activity against wound pathogens.

All of these results demonstrate the versatile therapeutic potential of *Terminalia chebula* Retz-derived nanoparticles. It is anticipated that there will be synergistic activity when combining nanoparticles with *T. chebula* based on extensive exploration of the comprehensive pharmacological activities of *T. chebula*-mediated nanoparticles. Thus, this plant plays a vital role in both the treatment and prevention of diseases, as well as in safeguarding the body from injuries and damage. Hence, further studies on *T. chebula*-mediated nanoparticles will provide a prospective framework for the treatment of various ailments in the future.

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