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NANOCURCUMIN-A PROMISING ANTI-MICROBIAL AGENT AGAINST ORAL INFECTIONS: A REVIEW

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ABSTRACT

Nanocurcumin, a nanoscale form of the spice turmeric, has been the subject of much research for its potential anti-microbial properties. The minute size of nanocurcumin particles allows them to penetrate cell membranes more easily than its larger counterparts, making them more effective at targeting and disabling microbial cells. In addition, nanocurcumin has been found to be more stable and have a longer shelf life than regular curcumin. Research has shown that nanocurcumin is effective against a variety of bacteria, including *E. coli*, S*taphylococcus aureus*, and *Pseudomonas aeruginosa*. It is also effective against some fungi, including *Candida albicans*. In addition, nanocurcumin has been shown to be effective against certain viruses, such as the herpes simplex virus. Recent studies have also suggested that nanocurcumin may be useful in the treatment of cancer and other diseases due to its ability to modulate the activity of several enzymes. Overall, nanocurcumin appears to have promising potential for use as an antimicrobial agent, offering a safe and effective alternative to traditional antibiotics.

KEYWORDS: Nanocurcumin; natural alkaloid; Anti-microbial agent.

1. INTRODUCTION

"The Antimicrobial resistance (AMR) capital of the globe" has been referred to as India.[1] All around the world, antibiotic resistance is increasing to dangerously high levels, endangering our capacity to treat typical infectious infections.[2] On one hand, the introduction of emerging multidrug resistance (MDR) organisms presents newer diagnostic and therapeutic obstacles, but on the other, India is still working to tackle long-standing adversaries like tuberculosis, malaria, and cholera pathogens, which are getting more and more drug resistant.[3]

Antimicrobial resistance (AMR) alone is killing more people than cancer and traffic accidents combined, with 700,000 individuals losing the fight against it each year and an additional 10 million expected to do so by 2050.[4] The arsenal of potent antimicrobial medications is dwindling quickly, which has turned into a threat to global public health.[5] The urge to search for possible alkaloids has been enormous and one such component that has been exploited for research is curcumin.

Nanocurcumin is a nanoscale form of curcumin, which is the active ingredient in turmeric. It is a natural antioxidant, anti-inflammatory, and antimicrobial agent.[6,7] Its anti-microbial has been shown to be effective against resistant strains of bacteria and fungi, making it a potential alternative to traditional antibiotics and antifungal agents. In this article, new developments in curcumin's nano-based formulations and their effectiveness against microbial infections are reviewed.

2. *Curcumin*

The ginger family (*Zingiberaceae*) member *Curcuma longa*, better known as turmeric, has curcuminoid as its main ingredient. Diferuloylmethane, another name for curcumin, has the chemical formula 1,7-bis (4-hydroxy-3-methoxyphenyl) -1,6-heptadiene-3,5-dione) adiene-3,5-dione).[8] A well-known historical colouring spice, turmeric has long been a key constituent in many traditional treatments and remedies in many Asian nations.[9] Although *curcumin* has been widely used as a medicinal herb for thousands of years, research into the exact mechanisms of action and the bioactive components has just recently been conducted.[10] The numerous health benefits of curcumin have recently sparked interest on a global basis. It performs best and considerably enhances these benefits when used with substances like piperine.[11] Furthermore, research on both humans and animals have shown that curcuminoids are exceedingly safe, acceptable, and nontoxic even at very high dosages.[12,13] *Curcumin*, a very pleiotropic molecule, was first identified in 1949 for its antibacterial effects.[14] But since then, evidence has emerged that this

polyphenol has wound-healing, anti-inflammatory, hypoglycemic, and antioxidant effects.[15]

However, a number of factors can have an impact on its ability to be used in pharmaceutical formulations. The main disadvantage of *curcumin* is a limited bioavailability because of the small intestine's comparatively low rate of absorption, substantial and conjugative liver metabolism and gall bladder excretion. The restricted bioavailability of curcumin is further exacerbated by its affinity for enterocyte proteins, which may change the structure of protein.[16] Due to its hydrophobic nature, *curcumin* is essentially insoluble in water at both acidic and neutral pH levels.[8] Several initiatives are currently being attempted to reduce its disadvantages. Its aqueous solubility has been claimed to be improved by adding a number of surfactant micellar systems, including sodium dodecyl sulphate, gelatin, polysaccharides, cetylpyridinium bromide, poly ethylene glycol, and cyclodextrins.[17] These physiological barriers can be more effectively overcome by encapsulating *curcumin* in a nano-formulation. This procedure decreases curcumin's hydrophobicity, which helps to increase water solubility, bioavailability, and the half-life of blood circulation in the body. It also helps to increase permeability across the membrane barrier.[18]

3. Nanocurcumin

Although *curcumin* claims to have antimicrobial, antioxidant, anti-inflammatory, antidiabetic anticancer and antiangiogenic properties, its optimal performance is restricted by its poor solubility in neutral or acidic environments and instability under alkaline condition which results in its poor oral bioavailability and causes poor absorption, fast metabolism, and quick systemic elimination.[19,20,21,22] *Curcumin* exhibits keto-enol tautomerism in aqueous solutions. The predominant form being the keto form under natural and acidic conditions and the predominant form being the enolate form under alkaline settings. The lower chemical stability of curcumin in basic solutions can be attributed to the enol form's greater chemical lability than the keto form.[23,24,25] Weak base solvents like acetone and ethanol have previously been used to solubilize curcumin.[26] Nevertheless, considerable toxicity of these organic solvents may limit its biological uses. Reduced life span in rats was documented because of the toxicity of acetone-dissolved curcumin used for the candida management.[27]

Several strategies are currently being used to get past these limitations. One of them uses nanotechnology to produce *curcumin* nanoparticles. The advantages of these nanoparticles include their small size, which makes it simpler for them to enter cells, their improved bioavailability and increased solubility, their ability to be delivered to specific target sites and their efficiency in delivering small molecules, such as proteins and nucleic acids among others.[28] Nanotechnology is a science and technique for creating new materials at the nanoscale scale.[29] Drug delivery and tissue targeting have both been demonstrated to be extremely effective with the use of chemical modifications made by nanotechnology.[30]

The size of the particle has a significant impact on both the absorption and bioavailability as mentioned. In addition to this, the body excretes it at a rapid pace because they collect under physiological conditions rather than being filtered by capillaries.[31] An increased rate of absorption and penetration was achieved by reducing a particle size which eventually increased bio-distribution and prolonged circulation. Additionally, surface modification and entrapment with different nanocarriers also increase the bioavailability and bioactivity of *curcumin*.[31]

The main techniques for manufacturing nanocrystal drugs, such as *curcumin* nanocrystals, are high-pressure homogenization (HPH) and pearl milling.[32] After oral consumption, these systems showed improved bioavailability due to their higher dissolution rate.[33]

Curcumin is more soluble and bioavailable when it is combined with hyaluronic acid in a molecule known as *curcumin* conjugation with hyaluronic acid.[34] *Curcumin* can be made more soluble and dissolve more quickly by encapsulating it in nanocarriers such liposomes, polymeric micelles, polymeric nanoparticles, cyclodextrins, nanogels, and nanocrystals, among other materials.[35,36] For these reasons, *curcumin* can be effectively improved in terms of solubility and bioavailability by being encapsulated in nano formulations.[37,38]

4. Antibacterial effect of nanocurcumin

Antibiotic resistance is a serious challenge due to difficulty in providing long-term solutions in treating bacterial infections. Multidrug-resistant (MDR) bacterial infections result in high mortality worldwide.[39] Antibiotic resistance is primarily caused by chemical modification of antibiotics, degradation of drugs by beta-lactamase, inhibition of antibiotic cellular penetration, efflux pump-mediated expulsion, and biofilm development.[40] Nanoparticles (NPs) are ultra-small nanomaterials with dimensions varying from 1-100 nm that exhibit significant broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria.[41,42] Although the mechanism of antibacterial action of NPs is still under researched, the general and most acceptable mechanism includes oxidative stress, membrane damage, cytoplasmic leakage, and biofilm disruption that can successfully bypass the previously mentioned bacterial antibiotics-resistance mechanism, making them efficient, sustainable, and reliable tools for treating mild to severe MDR bacterial infections.[40,43] *Curcumin* is a molecule with high antibacterial potential; however, its antibacterial action is limited due to low bioavailability, large particle size, low water solubility, delayed cellular uptake, and instability. When compared to crude curcumin, nanocurcumin/nanoconjugates of

curcumin have increased bioavailability, reduced particle size, better solubility, and improved antibacterial efficacy. Because of their increased aqueous solubility, small particle size, and better stability, nanocurcumin/nanoconjugates of curcumin can easily penetrate and disrupt the outer bacterial membrane barrier. Once inside the cell, these nanocurcumin/nanoconjugates stimulate the synthesis of different reactive oxygen species (ROS)that enable membrane and cytoplasmic leakage and hinder several enzymes essential cellular metabolic processes critical for bacterial survival, growth, and biofilm formation, slowing bacterial growth and eventually killing the bacterial cell.[44] *Curcumin* prevents the formation of bacterial biofilms.[45] The amphipathic property of curcumin enables it to enter the bacterial cell membrane and make it permeable to antibiotic uptake. *Curcumin's* antibacterial mode of action includes cell wall or cell membrane damage, interference with cellular processes via DNA and protein targeting, and inhibition of bacterial quorum sensing. Curcumin hinders the growth of bacteria, including *Staphylococcus aureus, E. coli, Salmonella paratyphi, Bacillus subtilis, Bacillus macerans, Bacillus licheniformis,* and *Azotobacter*. *Curcumin* influenced L-tryptophan metabolism in *Staphylococcus aureus* (Gram-positive) but not in *Escherichia coli* (Gram-negative), caused lipid peroxidation, and increased DNA breakage in both bacteria. These findings, along with increased levels of thiol and antioxidant capacity found after *curcumin* treatment of bacterial cells, indicated that oxidative stress may be the mechanism of *curcumin*'s antibacterial action.[46] *Curcumin* is highly effective in eliminating methicillin-resistant *S. aureus* (MRSA), a dangerous pathogen that causes nosocomial and community-associated infections.[47] Seventeen monocarbonyl curcuminoids synthesised demonstrated strong antibacterial activity against MSSA and MRSA and moderate activity against *E. coli.*[48] *Curcumin* inhibited the development of antibiotic-resistant *Pseudomonas aeruginosa, Acinetobacter baumannii* and *Klebsiella pneumoniae*.[49]

5. Antifungal effect of nanocurcumin

Curcumin has been shown to be efficacious against 20 different *Candida* species. *Curcumin* inhibited the development of *C. albicans* reference strains and clinical isolates, as well as *Candida parapsilosis, Candida glabrata, and Candida dubliniensis* reference strains.[50] Another study demonstrated the anti-*Candida Curcumin* activity against various *Candida* strains, including fluconazole resistant strains and clinical isolates of *Candida albicans, C. glabrata, C. krusei, C. tropicalis,* and *C. guilliermondii.* Intracellular acidification via inhibition of H+-extrusion has been identified as a potential mechanism for *Candida* species cell death.[51] *Curcumin* inhibits the adhesion of *Candida* species isolated from AIDS patients and was found to be more efficient than fluconazole. *Curcumin's* antifungal impact is due to the downregulation of 5,6 desaturase (ERG3), which results in a significant decrease in fungal cell ergosterol. As a consequence, biosynthetic precursors of ergosterol accumulate, leading to cell death via reactive oxygen species generation (ROS).[52,53] Other potential mechanisms for *curcumin's* fungicidal action include decreased proteinase secretion and changes in the membrane-associated properties of ATPase activity.[54] Inhibiting H+-extrusion, resulting in intracellular acidification, could be a cause for Candida species cell death.[55] *Curcumin* repressed the growth of *Cryptococcus neoformans* and *Cryptococcus dubliniensis. Curcumin* was found to be effective against *Paracoccidioides brasiliensis*, further having no effect on *Aspergillus* strains.[56]

6. CONCLUSION

Nano curcumin is a promising antimicrobial agent with a wide range of activity against both gram-positive and gram-negative bacteria. Its antifungal activities have also been investigated, with promising results. Nanocurcumin has the potential to be used as an effective alternative to traditional antibiotics, as it can be used to target drug-resistant bacterial strains. Further studies are needed to fully understand the potential of nanocurcumin's efficacy in clinical settings.

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