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REVIEW PAPER

An overview of antimicrobial efficacy of curcumin-silver nanoparticles

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ABSTRACT

With emerging novel microorganisms, there is an ongoing effort to find antimicrobial agents. The silver nanoparticle is a synthetic material with potent antimicrobial activity that applies to a diverse library of microorganisms. However, toxicity and safety concerns of chemically prepared silver nanoparticles toward human and environment limited the extensive industrial biomedical application of silver nanoparticles. On the other hand, curcumin is a natural phenolic compound of Indian spice turmeric that contains mild antimicrobial activity against various microorganisms. However, instability, poor absorption and low solubility of curcumin prevent its wide application in biomedical researches. Simultaneous application of these two materials is the subject of the provided manuscript. Curcumin formulation and silver nanoparticles can be applied separately or together, but the state of the art is applying curcumin for the synthesis of silver nanoparticles that represent a better biocidal activity and lower cytotoxicity in comparison to chemically synthesized silver nanoparticles.

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INTRODUCTION

In recent years, curcumin (cur), which is a natural phenolic compound and the main component of dietary spice turmeric (Curcuma longa rhizome), has been well-considered by medical researchers. Many medical properties, such as wound healing activities, antitumor activity, neuroprotective activity, chemoprotective activity, antimicrobial, anti-inflammatory, antioxidant, antitumor properties and many others, were attributed to cur or its derivatives [1]. Cur shows keto-enol tautomerism (Fig. 1) which both of them are very unstable, however, it is mostly found in enol form [2]. Cur hydrophobicity and poor absorption hampered its bioavailability. Even adsorbed cur is rapidly metabolized in the liver and eliminated from systemic circulation [3]. Antimicrobial activities of cur against different microorganisms, including bacteria, parasites, fungi, and viruses, have been reported through a variety of investigations[4]. Different nanoformulations have been applied for improving cur bioavailability and antimicrobial activity [5].

With the rapid emergence of different drug-resistant bacteria strains, nanoparticles were introduced as new antimicrobial agents which are indiscriminately inhibited bacteria. In this regard, various nanomaterials and techniques have been used for antibacterial coatings for implantable devices or wound dressing [6, 7]. Among the various types of nanomaterials silver nanoparticles (AgNPs) are potent antimicrobial agents, which have also been considered by many research groups for combination therapy with cur in a separate or

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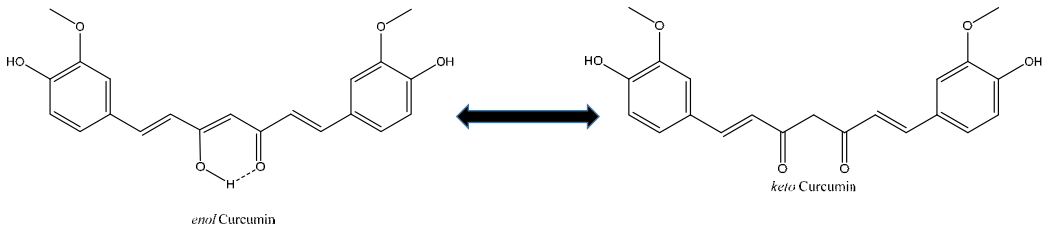

Fig. 1. Cur keto-enol tautomerism.

combined formulation [8-11]. AgNPs and cur have significant antimicrobial effect by various mechanisms. Cur is used for silver nanoparticles synthesis. Also, cur is coated on the surface of AgNPs for potential wider application. In this article, a review of the publications regarding the simultaneous treatment of AgNPs and cur alongside other mentioned subjects will be been presented.

ANTIMICROBIAL ACTIVITY OF AgNPs.

AgNPs are a powerful biocide nanoparticle for a variety of microorganisms. However, toxicity concerns of AgNPs toward humans and the environment hampered its widespread medical application [12, 13]. The antimicrobial property of metal nanoparticles such as AgNPs is related to many factors such as size, shape, surface chemistry and the release rate of the Ag ion. Smaller nanoparticles have been considered more toxic for bacteria in comparison to bigger nanoparticles [14]. Triangular AgNPs exhibited the highest bactericidal activity in comparison to rod or sphere-shaped AgNPs [15]. It has been reported that AgNPs interact with the structural components of the bacterial membrane [16]. Because of the negative charge of the cell membrane, positively charged particles are more toxic in comparison to negatively charged particles [17]. Yamanaka et al reported ATP depletion in the microorganism that has been treated by Ag ion [18]. Based on their study, expression of some proteins and enzymes including ribosomal subunit proteins was interfered by Ag ion. These proteins and enzymes are responsible for ATP production.

Combination effects of AgNPs and other treatments, such as radiation [19], antibiotics [20], antibiotic peptide [21] and even other metallic nanostructure [11, 22], have been reported. Plant secondary metabolites are also a biocidal agent, which has been considered by many researchers for combination treatment with silver nanoparticles [12]. In the next section, different aspects of the antimicrobial activity of cur, which is an aimed phytochemical of this review, was shortly revised.

ANTIMICROBIAL ACTIVITY OF CURCUMIN

Cur was considered a mild antimicrobial agent that inhibits microorganisms with different mechanisms. Song et al. report indicated that cur could hamper *Streptococcus mutans* adherence to the glass surfaces coated with collagen and fibronectin [23]. The same results were obtained for treated human teeth with S. mutans that assumed that cur could inhibit biofilm formation. Genome microarray analysis of Pseudomonas aeruginosa revealed that cur could reduce the expression of 31 quorum sensing genes and inhibit various virulence factors, such as elastase/protease activity, pyocyanin biosynthesis, acyl homoserine lactone production, and biofilm formation [24]. Studies have also shown that cur inhibits cell proliferation by inhibiting the FtsZ accumulation of *Bacillus subtilis* and *Escherichia coli* [25].

Various antiviral mechanisms of cur against many viruses such as HIV, HSV, HBV, Influenza, and many others was demonstrated [4]. Cur also is an inhibitor for Inosine Monophosphate (IMP) dehydrogenase enzyme activity, which is an essential component of purine biosynthesis pathway [26]. Virulence inhibition activity of cur against multiple viruses is probably due to IMP dehydrogenase inhibition activity of curcumin that is essential for guanine nucleotides biosynthesis.

ANTIMICROBIAL ACTIVITY OF CURCUMIN-SILVER NANOPARTICLES

Both silver nanoparticles and curcumin were considered to be agents for the inhibition of biofilm formation. Mirjalili and Abbasipour claimed that both fabrics that have been dyed with turmeric or treated with silver nanoparticles demonstrate a great antibacterial activity against Gram negative bacteria *E. Coli* [8]. On the other hand, it has been noted that Ag-curcumin molecular complex

Table 1. A summary of various AgNPs and curcumin formulation for antimicrobial application

Type of nanoparticles	Format	Size of AgNPs (nm)	Microbial strain	AgNPs or Ag^+ dosage (g/ml)	Cur dosage (g/ml)	Proposed application	ref
Chitosan-PVA composite	Cur and AgNPs co loaded	16.5	***E. coli.*** *Pseudomonas, Staphylococcus, Micrococcus, C. albicans, and P. aeruginosa,*	~50	~200	Wound dressing	[10]
Acrylamide hydrogel	Cur and AgNPs co loaded	1-5	*E. coli*	~500	~250	Wound dressing	[28]
Acrylamide and 2-acrylamido-2-methyl propanesulfonic acid hydrogel	Cur and AgNPs co loaded	~10	*E. coli*	~500	~250	Wound dressing	[29]
Polymeric Micelle	Co-encapsulations of Cur and AgNPs	7-15	*P. aeruginosa , S. aureus*	0-25	0-200	Direct treatment of bacterial infections or as a coating on medical instruments to achieve continued antibacterial effect.	[31]
Polymeric micelles decorated by AgNPes (Ag@CurNPs)	Cur encapsulated in AgNPs decorated micelles	>100	*P. aeruginosa , S. aureus*	31-500	31-500	Treatment of multiple bacteria-induced infections.	[32]
AgNPs	Cur@AgNPs	10–50	*E. coli, Salmonella spp, S. aureus, Fusarium spp*	….	…	Bacterial inhibitory effect, Nucleic acid determination	[35]
AgNPs	Cur@AgNPs	25–35	*P. aeruginosa, E. coli B. subtilis, S. aureus*	1-32	unknown	Wound dressing	[36]
AgNPs	Cur@AgNPs	11.95 ± 0.23	RSV	0.24 nM	unknown	Virucide agent for RSV	[37]
AgNPs	Cur@AgNPs	45	Human immunodeficiency viruses (HIV1)	unknown	unknown	Adjuvant antiretroviral and anti-inflammatory agent	[38]

antimicrobial activity is lower than curcumin itself [9]. Possible synergistic/additive effects of combination therapy of silver nanoparticles and curcumin were investigated recently in different forms. A summary of the nanostructures consist of Cur and AgNPs in this section was presented in table 1.

Co encapsulation of a drug and a metal nanoparticle has been demonstrated before [27]. Both formulations could be applied separately or loaded in one bigger nanostructure. In a series of studies designed to introduce curcumin and silver nanoparticles for wound dressing application, Raju et al. developed an active antimicrobial composite of chitosan and polyvinyl alcohol (PVA) which was loaded with curcumin and silver nanoparticles [10]. The role of the silver nanoparticles on antimicrobial activity is well-demonstrated in this research. Also, interestingly, in their composite, loading efficiency of curcumin was higher and it was released more gradually when it was co-loaded with silver nanoparticles in comparison to when it was loaded alone. Authors claimed that curcumin was adsorbed on the surface of silver nanoparticles, which led to higher curcumin loading efficacy and possible slower release profile. This team conducted a couple of similar investigations for acrylamide and 2-acrylamido-2-methyl propanesulfonic acid hy-drogels that have been co-loaded by silver nanoparticles and curcumin [28, 29]. In all of these composites, silver nanoparticles were synthesized in the presence of polymers. However, in the first one, sunlight was applied for Ag^+ reduction, while in the rest sodium borohydride played the role, which is probably is the main reason for the synthesis of smaller silver particles.

Because of curcumin instability and low aqueous solubility, nanoformulation of curcumin was considered by many researchers. Also, Krausz et al. demonstrated that the nanoformulation of cur was a better antimicrobial agent in comparison to bulk cur or silver sulfadiazine [30]. Instead of applying bulk curcumin, antibiofilm activity of combination treatment of AgNPs and curcumin nanoparticles (CurNPs) was investigated by Loo et al [31]. The antibiofilm activity of CurNPs which were prepared in polymeric micelle formulation was not as effective as AgNPs. Toxicity of combine

nanoformulation was low and effective eradication of mature biofilm was obtained only for combination therapy, not for Cur-NPs and AgNPs. Curcumin-loaded polymeric micelle could be coated by silver nanoparticles. For this purpose, Huang et al. applied diblock copolymer of poly aspartic acid (PAsp) and poly caprolactone (PCL) [32]. Curcumin was encapsulated in inner hydrophobic PCL core while Ag ion was reduced by $NaBH_4$ on the hydrophilic PAsp shell. Silver-decorated polymeric micelle was an active antibacterial agent against *P.aeruginosa* and *S.aureus* with or without curcumin.

Curcumin is also able to participate in silver nanoparticles synthesis as bio-reducing and stabilizer agent and form a curcumin coated silver nanoparticles (Cur@AgNPs) [33]. Cur@AgNPs with various shapes and sized was synthetized and characterized by Kundu and Nithiyanantham [34]. Authors suggested that the synthetized Cur@AgNPs may represent the pharmacological activity of curcumin.

Bacterial inhibitory activity of Cur@AgNPs was reported by El Khoury et al [35]. The synthesized Cur@AgNPs nanoparticles were stabilized by adding glycerol and polyvinylpyrrolidone in the synthesis procedure. Unfortunately, the authors do not provide any further information about nanoparticles. Jaiswal and Mishra synthesized Cur@AgNPs of size 25–35 nm, whereas curcumin alone was able to reduce Ag ion and stabilized silver nanoparticles [36]. Based on the provided results, synthesized Cur@AgNPs was an active antimicrobial agent with long period activity against both Gram class bacteria and very biocompatible for human keratinocytes cells. Minimum inhibitory concentration (MIC) value for Cur@AgNPs was 5 μg/ml, which is considerably lower than AgNPs (20 μg/ml). The concentration of cur is unknown because prepared Cur@AgNPs was washed twice for removing unreacted reagents. Curcumin coating on the surface of Cur@AgNPs was demonstrated not only by FTIR spectra, but also clearly observed on provided TEM micrographs.

Higher virucidal activity of Cur@AgNPs in comparison with Cit@AgNPs against the respiratory syncytial virus (RSV) was demonstrated by Yang et al [37]. Cur@AgNPs is able to inactivate the virus and prevent RSV from infecting the Hep-2 cells. DLS analysis shows that Cur@AgNPs was attached to RSV surfaces and no significant difference of the Hep-2 cells cytokines expression was observed. Based on these results, authors claimed that Cur@AgNPs is possessed antiviral activity. Alongside antiviral activity, Sharma et al. claimed that Cur@AgNPs represents anti-inflammatory properties through inhibition of the transcription of various pro-inflammatory cytokines [38].

SYNTHESIS AND CHARACTERIZATIONS OF Cur@AgNPs

Various chemicals including stabilizer and reducing agents are necessary for the synthesis of stable and fine metal nanoparticles [39]. Plant phenolic compounds could be applied for metal nanoparticles synthesis as a reducing agent, stabilizer or both [12, 40, 41]. Cur could be adsorbed on the previously synthesized AgNPs through various approaches. Interaction of natural phenols such as cur with metallic ion and surfaces was studied by many researchers. Bich et al demonstrated that thee yellow compound could complex with metal ions such as Zn, Sn and Cu through C-O-Me bond. They validated their claim with Raman and FTIR data. In fact, peaks associated with solid cur were observed in a same wavenumber or with a small shift in cur bound to metal surfaces or ion such as silver. For example, the ν(C=O) and ν(C=C) for both spectrums were observed around 1600 cm^{-1} and ν(C-O) was observed at 962 cm^{-1} for solid Cur and at 963 cm^{-1} for attached cur on the metal surfaces [42]. The similar Raman peak (~940 cm^{-1}) has been mentioned for curcumin conjugation on the gold surface after curcumin has been applied for AuNPs synthesis [33].

To provide the electrons needed to chemical reduction of the silver ions, cur was applied for the synthesis of AgNPs under basic pH or high temperature. Increasing temperature lead to electronic transition which expose polar hydroxyl (−OH) and keto (>C=O) group of the molecule and increase Cur solubility. However, with increasing temperature a partial oxidation of cur was mention which characterized by change in UV-Vis spectra [43]. Similar to the high-temperature environment, in alkaline solution, cur is highly unstable and it appears to be red (λ_{max}= 466 nm in pH 11) instead of yellow (λ_{max}= 422 nm in pH 3) which indicate oxidation and degradation of cur into red colour compound such as ferulic acid, feruloyl methane and, vanillin [44-46]. Electrons from Cur oxidation or even degradation under these conditions were applied for AgNPs synthesis. Even the synthetized AgNPs could increase Cur degradation through a catalytic process. Cur is

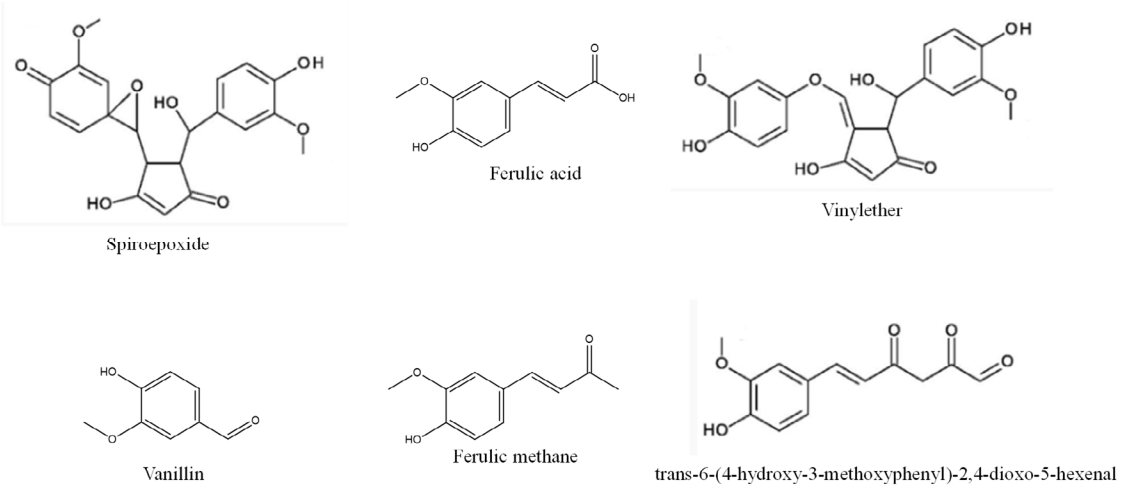

Fig. 2. Chemical structures of degradation products of curcumin in alkaline environment or under thermal degradation.

breakdown into smaller and more polar aromatic in alkaline environment (Fig. 2), that could form a polymerized phenolic compound on the surface of AgNPs [45]. This phenolic coating on the surface of metal nanoparticles that have been synthetized by phenolic compound is characterized by high resolution electron microscopy [12]. The phenolic coating around the nanoparticles gives the silver nanoparticle higher stability in comparison with citrate coated nanoparticles. Yang et al have shown that in comparison with citrate capped silver nanoparticles the Cur@AgNPs represent much higher solubility and stability in RPMI cell culture environment based on UV-Vis Spectroscopy [37].

TOXICITY CONSIDERATION FOR Cur@ AgNPs

One of the main deterrent factors for nanoparticles biomedical application is their toxic concerns on human health or environment. The degree of nanomaterial toxic effect depends on many characteristics such as size, shape, concentration and surface chemistry [47]. Various nanoformulation of cur has been studied for their toxicity concerns. Krausz et al have declared that unlike cur a nanoformulation of cur could enhance collagen deposition of wounded skin without inducing necrosis or inflammation. Also, the cur nanoformulation does not cause a significant Murine PAM212 keratinocytes cell death up to 0.625 mg/ml based on fluorescein diacetate (FDA) assay. Even in the highest tested concentration (5 mg/ml), 81% of cells remained alive [30].

Based on our previous review paper, metal nanoparticles that have been coated by plant secondary metabolites are more biocompatible than nanoparticles that have been coated by synthetic chemicals [12]. Specifically, curcumin coated gold nanoparticles are more biocompatible in comparison with citrate coated gold nanoparticles in murine fibroblast L929 cell lines. They have lower cytotoxicity and generate much less reactive oxygen species [33]. Similarly, Cur@AgNPs are more biocompatible in compare to citrate coated silver nanoparticles in HepG-2 cell lines [37] and ACH-2 cells [38]. In HepG-2, no significant cell death was observed cells treated with Cur@AgNPs for 72 h. While about half of the cells treated with citrate coated silver nanoparticles were killed [37]. However, Loo et al declared that both Cur@AgNPs and citrate coated silver nanoparticles are almost nontoxic for healthy human bronchial epithelial cells (BEAS2B) [31]. Quite different results were also obtained by Abdellah et al. They showed that Cur@AgNPs are much more toxic than AgNPs [48]. These results are probably due to the presence of unreacted substances in the Cur@AgNPs solution, which has not been removed through the washing process by the researchers. Also, the protocol that has been applied for nanoparticles synthesis in this research is very different from other methods that have been described by other research groups.

Unlike citrate coated AgNPs, it has been showed that the anti-inflammatory effect of Cur@AgNPs is significant. Jaiswal and Mishra investigated the secretion of IL-6 and TNFα in THP1 cell line that has been treated by AgNPs and Cur@AgNPs. Based on their results the treatment of cells with Cur@

AgNPs lead to less secretion of IL-6 and TNFα in comparison with AgNPs [36]. However, to fully understand the different toxicity aspect of Cur@AgNPs more researches are needed.

CONCLUSION AND FUTURE ASPECTS

In conclusion, the material presented in this review suggests that both AgNPs and Cur could be applied for antimicrobial application. But simultaneous application of Cur and AgNPs lead to a better result. Synthesis of biocompatible Cur@AgNPs is achieved by applying Cur as a both bioreluctant and a stabilizer. The applied synthesis techniques for preparation of Cur@AgNPs are not preserving curcumin in the pristine form but the Cur@AgNPs is representing higher antimicrobial properties in compare to cur or AgNPs. Cur@AgNPs could be applied against various pathogenic microorganisms, including different viruses, fungi, protozoa and bacteria. Robust scientific methods need to be developed to prove the safety and biocompatibility of Cur@AgNPs so that they can be used in a variety of biomedical applications instead of chemically prepared AgNPs.

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DECLARATION OF INTEREST

None.

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