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Nanoformulations of curcumin and quercetin with silver nanoparticles for inactivation of bacteria

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ABSTRACT

Antibiotic resistance in pathogenic bacteria to various types of antibiotics has resulted in the necessity of new effective strategies to get around this problem. In recent investigations, metal or metal oxide nanoparticles specifically silver nanoparticles (AgNPs) have been employed successfully to hinder antibiotic-resistant Gram-negative and Gram-positive bacteria. However, AgNPs at high concentrations have cytotoxicity for eukaryotic cells which, application of other biocompatible materials particularly plant secondary metabolites of curcumin and quercetin to reduce cytotoxicity is a critical affair. These compounds may be used directly or indirectly to produce AgNPs. In this regard, modified NPs by curcumin and quercetin have shown an increased therapeutic effect and biocompatibility and biodegredibility properties. Therefore, here, recent advances and challenges about antibacterial and biocompatibility properties of nanoformulation of AgNPs with curcumin and quercetin are presented.

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Introduction

Turmeric with the scientific name of *Curcuma longa* is a plant of the ginger family that has dried rhizomes. It is used for food and medicine and is native to the warm regions of Asia like India, Pakistan and Indonesia. Turmeric throughout history, also as a medicine and has been used as food by people and in Traditional medicine is also used as an herbal remedy for various infections. Curcumin is the active ingredient in turmeric, which has its chemical name of diferuloylmethane with the chemical formula ($C_{21}H_{20}O_6$) (1). As shown in Figures 1a-b, there are two main forms of enol and keto for curcumin. It should be mentioned that the enol form is more energetically stable compared to the keto one (2, 3). Moreover, this plant species has numerous chemical compounds including essential oils, alpha and beta turmeric, ginger, glucose, fructose, arabinose, and starch. The color of turmeric is also related to dyes such as curcumin, des-methoxy curcumin, and bisdemethoxycurcumin. In addition, antioxidant activity, curcumin, has anti-inflammatory, wound-healing (by increasing the growth of blood vessel

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density, fibroblasts, and regeneration of skin), anti-cancer, and antimicrobial properties (Figure 2) (4).

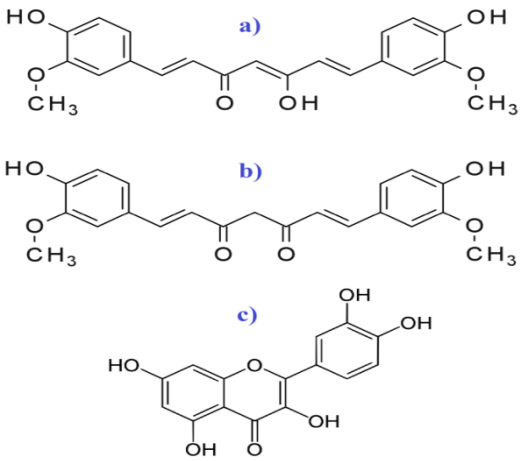

Figure 1. Chemical structures of a) enol and b) keto forms of curcumin as well as c) quercetin secondary metabolites

Quercetin ($C_{15}H_{10}O_7$) is an herbal flavonol related to the flavonoid group of polyphenols (Figure 1c), which can be found at different contents in various plant species such as green tea leaves, dill, broccoli and raw onions (Table 1). Anticancer and antimicrobial properties are reported for this metabolite or its derivatives (5). For instance, the antibacterial activity of starch aldehyde-quercetin conjugate was found against *Listeria monocytogenes*, *Staphylococcus aureus*, and *Escherichia coli* species (6).

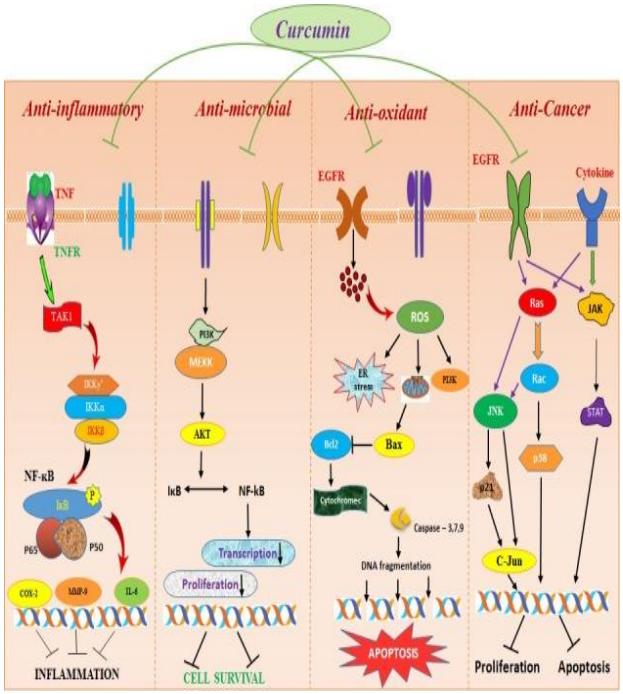

Figure 2. different medicinal applications of curcumin (Tumor necrosis factor (TNF), tumor necrosis factor receptor (TNFR), transforming growth factor beta-activated kinase 1 (TAK1), epidermal growth factor receptor (EGFR), nuclear factor kappa B (NF-κB), interleukin 6 (IL-6), protein kinase B (Akt), phosphatidylinositol-3-kinase (PI3K), Bcl-2-associated X protein (BAX), cyclooxygenase (COX), and c-Jun is a component of the transcription factor AP-1 (under permission of Creative Commons Attribution License 3.0 (CC BY 3.0))(7).

Antibiotic resistance as a major hindrance in combat bacterial pathogens is increasing owing to acquisition resistance mechanisms in new bacterial strains (8, 9). Nanotechnology by presenting numerous nanomaterials with unrivaled physicochemical properties has obtained high attention (10). Nanoparticles specifically metal or metal oxide nanoparticles have a large surface area-to-volume ratio and more reactivity relative to bulk materials appropriate to therapeutic applications such as antibacterial or anticancer agents (11). In this regard, silver (Ag), gold (Au), copper/copper oxide (Cu/CuO), zinc oxide (ZnO_2), titanium dioxide (TiO_2), and platinum (Pt) are common metallic nanoparticles (12). Among these nanoparticles, AgNPs have shown prominent antibacterial capacity with disadvantages of cytotoxicity in higher doses (13, 14). In this way, conjugation or combination of AgNPs with plant materials particularly curcumin and quercetin has been presented as an effective strategy. Therefore, this review has discussed this issue in recent years for getting a novel comprehensive scope of future studies.

Table 1. Quercetin contents of some plant species

Plant species	Quercetin contents (mg/100g)	Ref.
Leaves of green tea	255.55	(15)
Dill	79	(16)
Red onions	45.25	(17)
Oregano	42	(16)
Okra	20.03	(17)
Lettuce	15.39	(17)
Broccoli	13.7	(16)
Green pepper	10.27	(17)
Blueberry	9.92	(17)

AgNPs-curcumin

As shown in Figure 3a, curcumin compound can form AgNPs by reducing the reaction of Ag+ ions in colloidal solution resulting from several possible sites of carbon and oxygen atoms for electrophilic attack (3). As noted in the introduction section, AgNPs at high concentrations are toxic for eukaryotic cells. Therefore, using other biocompatible materials to modify NPs and reduce cytotoxicity is an indispensable affair. In a comparative study, $AgNO_3$, AgNPs, AgNPs-curcumin, curcumin, kanamycin, and chloramphenicol exhibited minimum bactericidal concentration (MBC) values of 2.5, 20, 10, 280, 4, and 12.5 mg/L toward *S. aureus* ATCC 9144, respectively. The concentration for inhibition 90% of the cells (IC_{90}) of AgNPs-curcumin against human keratinocytes was 156 mg/L less than 5 mg/L of minimum inhibition concentration (MIC) for *S. aureus* (18). In order to the formulation of AgNPs-curcumin for healing of infected wounds, other supporter materials such as polymers can offer new advantages of stability and sustained drug release in physiological conditions. Gelatin derived from collagen is an example of natural polymers suitable for obtaining stable nanocomposites based on AgNPs-curcumin-gelatin under ultraviolet (UV) irradiation owing to the conversion of amine groups of gelatin structure to nitrite via the metal ion-induced oxidation. According to different concentration (1.25%, 1%, 0.75%, and 0.5%) of gelatin solution, MBCs against *Pseudomonas aeruginosa* were 250, 125, 125, and 250 µL/mL, respectively with desirable biocompatibility at 125 µL/mL (19).

It is worth noting that curcumin-AgNPs can induce mutagenic effects as the recovered abilities to fabricate histidine amino acid in TA98 and TA100 strains of *Salmonella typhimurium* at the presence of S9, a liver extract that simulates the hepatic metabolism (20). Curcumin-AgNPs can be more functionalized using natural and synthetic polymers. In this regard, the monomer 2-(2-methoxyethoxy)ethyl methacrylate (MEO_2MA), crosslinking monomer of tetraethylene glycol dimethacrylate (TEGDMA), and reducer/stabilizer agent of trisodium citrate dehydrate were applied to functionalize curcumin-AgNPs to obtain Ag@curcumin-P(MEO_2MA) NPs with core-shell morphology and a size range of 34-64 nm dependent on curcumin weight % (1.05-3.80%) (21).

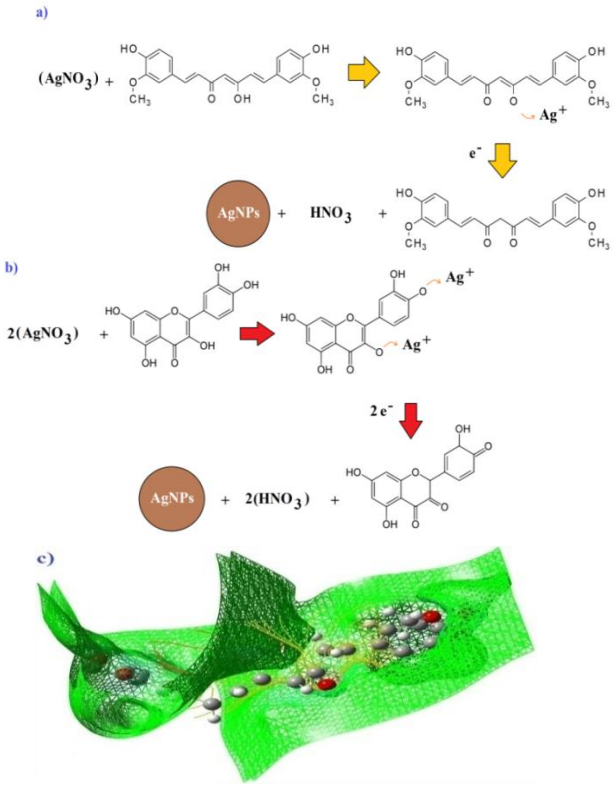

Figure 3. Possible reaction for formation of AgNPs by curcumin (a) quercetin (b) metabolites, and surface of curcumin with the different electron density (c) (under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)) (22).

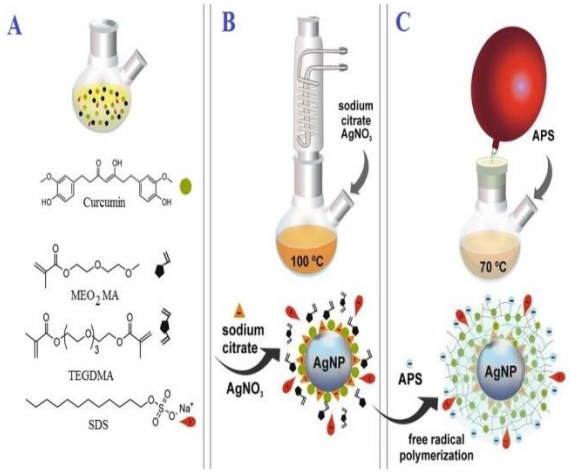

Figure 4. Three steps for fabrication of Ag@curcumin-P(MEO_2MA) NPs with core-doped shell structure; SDS and APS are sodium dodecyl sulfate and ammonium persulfate respectively (copyright permission under http://creativecommons.org/licenses/by/4.0/) (21).

AgNPs-quercetin

Metal and metal oxide NPs can cause the deformation and destruction of bacterial cells via direct and indirect interactions. Adhesion of NPs or metallic ions to the bacterial membrane or cell wall is found as direct interaction, while production of reactive oxygen species (ROS) such as superoxide radicals and damaging biological macromolecules in the bacterial medium are indirect antibacterial effects for these NPs (23). As shown in Figure 3b, quercetin as a plant flavonoid can contribute to the synthesis of AgNPs by reduction of Ag^+ ions in the redox reaction. In addition to synergistic antibacterial activity against Gram-negative and Gram-positive bacteria, the increased antioxidant property is expected for a combination of AgNPs with quercetin, as antioxidant capacity of 82.3% at a concentration of 400 ppm was led by AgNPs-quercetin with the mean size of 20 nm (24). Quercetin may be used directly to synthesize AgNPs. A combination of quercetin as an efficient free radical scavenger and $AgNO_3$ at 40 °C for 60 minutes was employed to fabricate AgNPs with spherical shape and mean size of 11 nm. *P. aeruginosa* and *S. aureus* displayed 2 and 4 µg/mL MBC values upon quercetin-AgNPs, respectively (25).

Quercetin isolated from methanolic extract of *Clitoria ternatea* plant species was able to synthesize AgNPs with spherical shape and the mean size of 65 nm, which revealed ~70% inhibition of exopolysaccharide synthesis at 100 ppm against *S. aureus* with ~4.5% hemolytic activity at 120 ppm (26). It should be noted that, synergistically, modification of AgNPs by plant secondary metabolite of quercetin may be more efficient than a green synthesis of AgNPs using plant extract. For example, MBC amounts for AgNPs-quercetin towards ESbL (+) *E. coli*, ESbL (+) *P. aeruginosa*, methicillin-sensitive *S. aureus*, and methicillin-resistant *S. aureus* strains were 60, 60, 70, 70 ppm compared to AgNPs phyto-synthesized by yellow bell pepper extract with MBCs of 80, 80, 100, 100 ppm, respectively (27). In a lower diameter, AgNPs can inhibit bacteria more efficient than larger ones, as quercetin-synthesized AgNPs with a size of 8 nm displayed a minimum inhibitory concentration (MIC) value of 1 ppm toward *E. coli* in comparison with AgNPs (size of 20 nm) by the MIC of 2.5 ppm (28). Small interference RNA (siRNA) or silencing RNA is non-coding double-stranded RNA with 19-25 base pairs (29). siRNA was employed for surface modification of AgNPs-quercetin to prepare siRNA/AgNPs-quercetin with a mean size of ~ 40 nm in a spherical shape, which exhibited significant bacterial inactivation as MIC value of 2.1 ppm compared to AgNPs and AgNPs-quercetin by MIC amounts of 16.4 and 13.2 ppm, respectively against antibiotic-resistant *B. subtilis*. Moreover, this nanoformulation showed reduced bacteremia symptoms in mice specimens after 7 days of treatment (30).

Conclusions

Pathogenic bacterial strain with obtaining antibiotic resistance can sidestep the plethora of conventional antibiotics. Recently, metal or metal oxide nanoparticles specifically silver nanoparticles (AgNPs) have been used efficiently to inhibit antibiotic-resistant Gram-negative and Gram-positive bacteria. AgNPs at high concentrations is toxic for eukaryotic cells, application of other biocompatible materials such as natural phenolic compounds of curcumin and quercetin to reduce cytotoxicity is an indispensable affair. These phenolic compounds can contribute to the synthesis of AgNPs by reduction of Ag^+ ions in the redox reaction. In addition to synergistic antibacterial activity against Gram-negative and Gram-positive bacteria, increased antioxidant property is expected for combination of AgNPs with curcumin and quercetin bioactive metabolites. As a critical point, curcumin-AgNPs complex can stimulate mutagenic in TA98 and TA100 strains of *S. typhimurium* at the presence of S9 by the recovered abilities to fabricate histidine. Finally, future investigations should meet the increased biocompatibility of AgNPs by other phenolic compounds similar to curcumin for an efficient formulation, suitable for physiological conditions.

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Interest conflict

The authors declare no conflict of interest.

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