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Formulation and antioxidant properties of curcumin gum Arabic nanoparticles for delivery to cancer cells

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Abstract. Curcumin nanoparticles (Cur/GANPs) were formulated based on gum arabic (GA) as a stabilizer coatings for nanoparticles through efficient synthesis approach. The current study investigated the antioxidant properties and antihypertensive activity of curcumin (Cur) using various established in vitro assays, such as 1,1-diphenyl-2-picrylhydrazyl (DPPH) as well as angiotensin converting enzyme (ACE) inhibitory activity. The in vitro cytotoxicity of Cur/GANPs against human liver cancer (HepG2), and colon cancer (HT29) was investigated. The exposure of human cancer cells to Cur/GANPs (1.56-100 µg/ml) using MTT (3-(4,5-dimethylthiazol-2-yl)2,5-diphenyl tetrazolium bromide) has revealed that the Cur/GANPs inhibited the growth of cell lines examined in a dose dependent manner. Hence, Cur/GANPs nanoparticles may have great potential to be applied for cancer treatment.

1. Introduction

Nanomedicine has potentials to develop cancer therapies and diagnostics [1]. Nanoparticles made of chemotherapeutic hydrophobic drugs like curcumin have potential application in the treatment of solid tumors such as liver cancer and breast cancer [2-3]. Curcumin therapeutic efficacy towards several diseases is challenged with its poor solubility, rapid elimination, and low bioavailability [4-5]. The advancement in polymeric nanocarriers provides an effective approach to enhance the therapeutic efficiency of curcumin. The use of gum arabic as a polysaccharide in encapsulation process can play an important role in improving the antioxidant properties of curcumin due to its biodegradability, cost effectiveness, and biocompatibility with further modification in the presence of various functional groups. Previous studies mentioned that the incorporation of curcumin into nanoparticles systems improved its antioxidant properties and therapeutic viability [6].



Therefore, a novel nanoparticle system was developed using GA as a coating material to improve the therapeutic efficacy of curcumin (Cur/GANPs) against cancer cells. In this research, the Cur/GANPs have been prepared using the freeze-drying technique. The antioxidant activities of Cur/GANPs and GA were assessed by DPPH assays. The cytotoxicity of both pure curcumin and Cur/GANPs at various time intervals was individually determined based on the MTT assay. The main purpose of this research is to assess the antioxidant and antihypertensive properties of Cur encapsulated into GANPs. The *in vitro* cytotoxicity and therapeutic effect of Cur/GANPs against human cells was investigated.

2. Materials and methodology

2.1. Materials

Gum Arabic was purchased from ENNASR company (Sudan). Curcumin was bought from Biolutions Resources (China). HepG2 and HT29 cells were bought from American Type Culture Collection (ATCC). Dexamethasone, DPPH (1,1-diphenyl-2-picrylhydrazyl), TROLOX, Angiotensin-converting enzyme was purchased from R&M company (China.)

2.2. Preparation of Cur/GANPs

Cur/GANPs were prepared using the freeze-drying technique with slight modifications [7]. In the first step GA (0.70 g) was dissolved in 50 mL of deionized water. An aqueous solution of curcumin was prepared in ethanol at a concentration of 1 mg/mL then added to the dispersion in a ratio of 1:4 then mixed using a homogenizer. The mixture was kept under mild agitation at room temperature for 72 h. The final suspension was subjected to a high pressure homogenizer at a pressure of 1000 bar for 10 cycles, which was then frozen at -80°C . The final product was freeze-dried for 24 h at -55°C .

2.3. The DPPH scavenging activity of Cur/GANPs

This reaction has been related to the donating ability of the antioxidant occurred in the process [8]. Curcumin and Cur/GANPs nanoparticles were used as test samples. A serial dilution of 100 μg of trolox diluted in 1 mL of methanol was used in the range of 50- 200 $\mu\text{g}/\text{mL}$. 200 μL of DPPH solution was then added to each well of 96-well microplate. The absorbance was determined at 517 nm.

2.4. Antihypertensive activity

In this method 100 μL of curcumin and Cur/GANPs were reacted with ACE (25 μL , pH 8.3) for 5 min at 37°C . To evaluate the ACE inhibition capacity, an addition of 10 μL of hippuryl-histidyl-leucine (3.5 mM) to the assay mixture was then made followed by incubation for 30, 60, and 90 min. In order to stop the reaction, 50 μL of 3 M HCl was added to the mixture. Ethyl acetate (1 mL) was added to extract hippuric acid formed. Finally, the evaluation of hippuric acid was performed with a measurement of absorbance at 228 nm.

2.5. Cell viability

200 μL of a 1×10^4 cells/mL suspension were seeded into each well of 96-well plate for 24 h. The cells were treated with Cur and Cur/GANPs of concentrations of (15.6 - 100 $\mu\text{g}/\text{mL}$) for 72 h. 20 μL of MTT solution (5 $\mu\text{g}/\text{mL}$) was added into each 96-well with fresh media then mixed gently and incubation for 4 hours at 37°C with 5% CO_2 . The MTT-including culture medium was replaced with 200 μL / well of DMSO in order to dissolve the formazan crystals formed. The absorbance was determined at 570 nm.

3. Results and discussions

The role of gum Arabic nanoparticles in drug delivery applications can be related to their unique properties, particularly high stability and low toxicity [2, 9]. Cur/GANPs displayed a particle size over the range of 20-260 nm as shown in Figure 1. The Cur/GANPs exhibited more DPPH scavenging activity due to its hydrogen-donating ability (Figure 2). Therefore, ACE inhibition activity of Cur/GANPs appeared to be higher than that of free curcumin due to the antihypertensive effect of gum

arabic under specific *in vitro* conditions (Figure 3). As a result, the encapsulation of curcumin in gum Arabic could improve the antihypertensive capacity of curcumin.

The results denoted that the anticancer activity of curcumin loaded into gum Arabic nanoparticles (Cur/GANPs) was higher than that of free curcumin. Cur/GANPs have exhibited improved cytotoxicity and tumour targeting against HepG2 cells (Figure 4) [8,10]. These results were similar to the data from the literature, which suggest that curcumin might be a potential antitumor compound [11]. In a previous study, the mechanism of GA nanoparticles targeted to the liver has been explained based on the interactions between asialoglycoprotein receptors, the function of receptor-mediated endocytosis, and nanocarriers [8]. The role of gum Arabic nanoparticles in drug delivery applications can be related to their unique properties, particularly high stability and low toxicity. Consequently, the presence of the asialoglycoprotein receptors on the surface of hepatocytes, which interact with galactose moiety on gum Arabic have increased the anticancer activity of the Cur/GANPs. In a previous study, gum Arabic nanoparticles have also showed increased uptake caused by the malignant liver cancer cells [8]. Thus, this study indicates that Cur/GANPs have promising future to further develop a nanocarrier for cancer therapy.

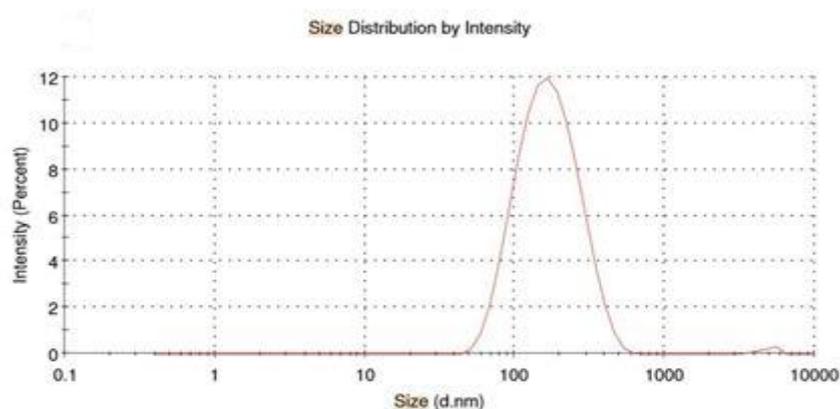


Figure 1. Particle size of Cur/GANPs.

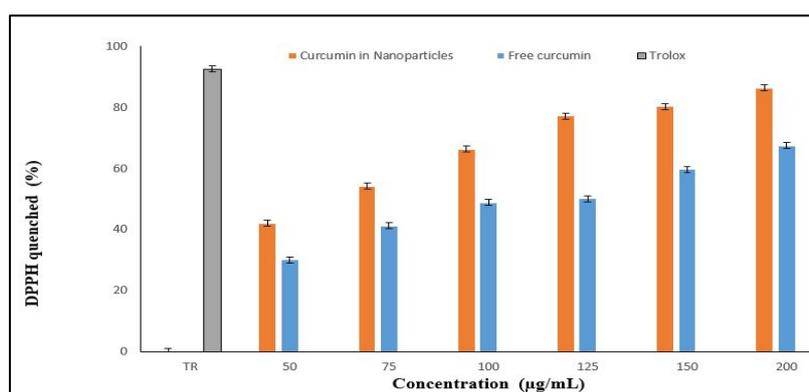


Figure 2. DPPH scavenging of free curcumin and Cur/GANPs.

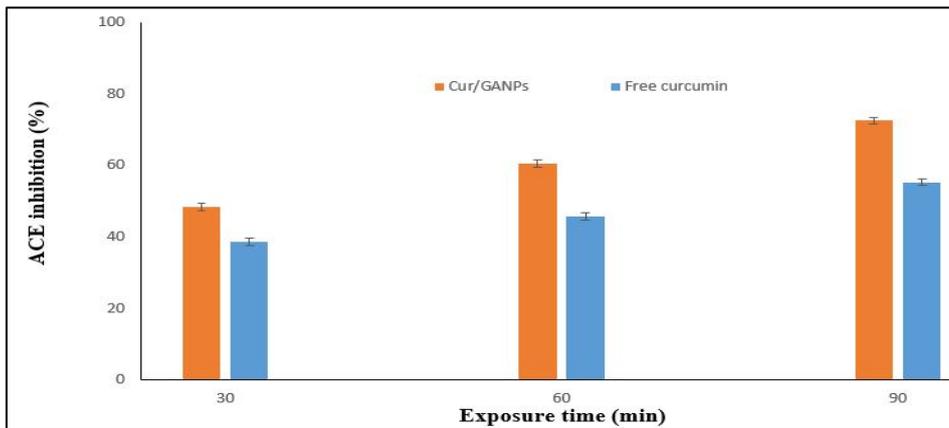
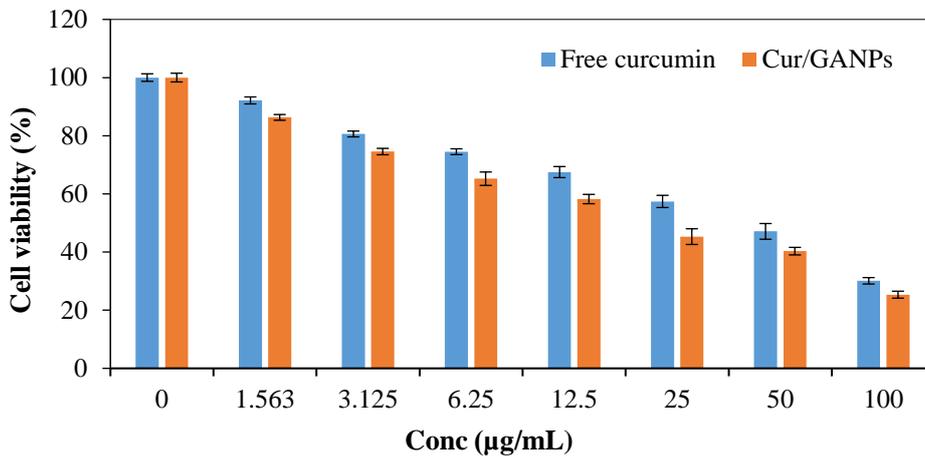
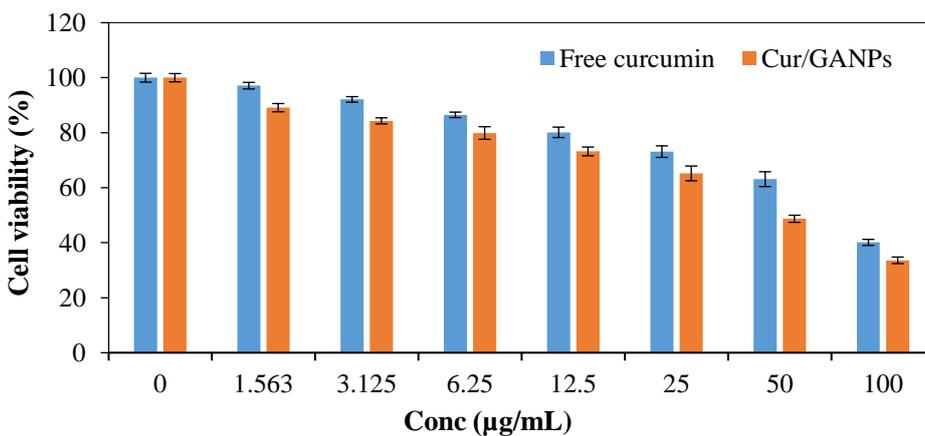


Figure 3. ACE inhibition (%) for free curcumin and Cur/GANPs after 30, 60, and 90 minutes.



(a)



(b)

Figure 4. Cytotoxicity effect of curcumin, Cur/GANPs at different treatment concentrations on cancer cell lines (a) HepG2; and (b) HT-29

4. Conclusion

The purpose of this present study is to enhance the therapeutic efficacy and the antioxidant properties of curcumin encapsulated into gum arabic polymer. As a result of the antioxidant activity on DPPH, Cur encapsulated into gum Arabic nanoparticle had been considerably higher than its free counterpart. This study reveals that Cur/GANPs are a potential candidate compound for the evaluation of prevention and treatment of cancer cells. Extrapolation of the *in vitro* cytotoxicity effects of Cur/GANPs to *in vivo* anticancer effects demands further investigation in light of its application as a cancer chemotherapeutic agent.

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