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Quercetin conjugated silica particles as novel biofunctional hybrid materials for biological applications

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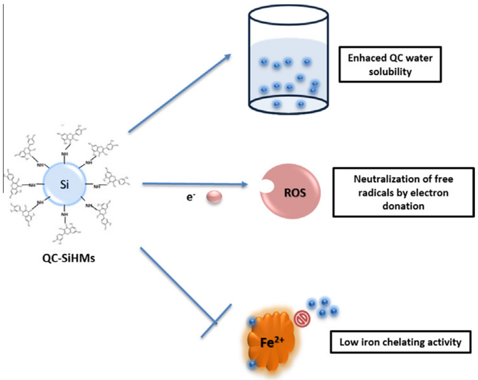
GRAPHICAL ABSTRACT

Quercetin-conjugated silica hybrid materials and their biological properties.



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ABSTRACT

The aim of this work is to formulate biofunctional hybrid materials (HMs) with quercetin (QC) and silica particles (SiPs) by simple methods such as sol–gel and QC conjugation. Physicochemical characterization included particle size, zeta potential (ζ), FTIR and SEM imaging. Spherical particles with *ca.* 115 nm in diameter were produced, ζ and FTIR demonstrated that QC conjugation was successfully achieved. Electrochemical analyses performed by cyclic voltammetry (CV) suggested that potential binding sites between QC and SiPs may be at functional groups from A ring or C ring, affecting the transfer electron

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Abbreviations: HMs, hybrid materials; QC, quercetin; SiPs, silica particles; QC-SiHMs, quercetin conjugated silica hybrid materials; Ps, particles; AOX, antioxidant compounds; TEOS, tetraethyl orthosilicate; APTES, (3-Aminopropyl) triethoxysilane; APTES-SiPs, APTES functionalized silica particles; KBr, potassium bromide; EDTA, ethylenediaminetetraacetic acid; ferrozine, 3-(2-pyridyl)-5,6-diphenyl-1,2,4-triazine-*p*,*p*′-disulfonic acid monosodium salt hydrate; $FeCl_2$, iron (II) chloride; TBA, 2-Thiobarbituric acid; EtOH, ethanol 40B denatured; H_2O_2, peroxide hydrogen; $FeSO_4$-7 H_2O, ferrous sulfate heptahydrate; CH_3-COOH, glacial acetic acid; H_3PO_4, phosphoric acid; H_3BO_3, boric acid; HCl, hydrochloric acid; Na_2HPO_4, sodium phosphate dibasic; KH_2PO_4, monobasic potassium phosphate; KCl, potassium chloride; NH_4OH, ammonium hydroxide; NaCl, sodium chloride; PC, L-α-phosphatidylcholine; diH_2O, deionized water; PBS, phosphate buffer solution; DMSO, dimethyl sulfoxide; SiOH, silanol groups; PI, polydispersity index; DLS, dynamic light scattering; ζ, zeta potential; SEM, scanning electron microscopy; DRIFT, Diffuse Reflectance of Infrared by Fourier Transform; CV, cyclic voltammetry; DPV, differential pulse voltammetry; N_2, nitrogen; $HOO^{\cdot}$, hydroperoxyl radicals; TBARS, lipidic peroxidation; MDA, malondialdehyde; BHT, butylated hydroxytoluene; TBA, thiobarbituric acid; TEP, tetraethoxypropane.

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of resorcinol moiety. Iron chelating activity and lipid peroxidation assays showed that after conjugation to SiPs, QC decreased its metal chelating activity, but anti-radical properties is maintained. Our results demonstrated that our proposed method is simple and effective to obtain bio-functional HMs. Our findings prove to be useful in the design of protective approaches against lipid oxidation in food, pharmaceutical, and cosmetics fields.

1. Introduction

In the recent years, within the biomedicine, food, pharmaceutical, and cosmetic fields, many efforts have been focused on the synthesis of novel micro and nanocarriers with different sizes, shapes and functions in order to protect and to control the release of bioactive compounds [1,2]. Among all carriers developed and studied, micro and nanoparticles have gained attention due to their unusual and multifunctional properties influenced by their size, morphology, structure and nature [3,4]. A key scientific question is how these approaches can carry out and to deliver bio-compounds in specific places to prevent or to treat undesirable diseases and/or degradation reactions in functional products [5–7]. In this regard, many studies have been focused in the creation of organic compounds–inorganic particles hybrid materials (HMs) that possess the biological activities of bio-compounds and the properties of inorganic particles (Ps) (including ease of fabrication, chemical inertness, negligible swelling in aqueous/organic solvents, tunable physical properties, and mechanical and thermal stability) [8–10]. In this regard, recent studies have demonstrated that creation of bio-hybrid materials is possible by trapping [11], impregnating [12], and functionalizing the inorganic Ps with organic compounds [13]. Organic compounds such polymeric ligands [14], oligonucleotides [15], proteins [16], and others, have been successfully conjugated in the surface of different Ps, demonstrating a wide variety of biological functions, such as sensing biomolecules [17], diagnosis of diseases [18], enhancing cell uptake [19], and controlled release [20]. These previous works suggest that regardless the strategy used to develop a bio-HMs, the process do not affect the biological properties of organic compounds, maintaining therefore, their chemical structure available and stable to exert its functions. However, there is a lack of information how these processes can improve or affect other biological activities of organic compounds. Additionally, information about the utilization of antioxidant compounds (AOX) for the creation of novel and functional AOX-inorganic Ps as HMs is minimal. Two studies performed by different research groups in 2012 [21] and 2014 [22], achieved the functionalization of inorganic nanoparticles with phenolic compounds (gallic acid and QC, respectively) using reflux and nanoprecipitation methods (respectively). However, there is a need to create new methodologies that allow in a simple way the conjugation of AOX or other bio-compounds in the surface of inorganic Ps. Therefore, the present study describes a simple method (based on modifications to the sol–gel) to obtain and to control the size distributions of SiPs, with combination of a methodology based in aqueous dispersion and heat to conjugate QC in the surface of SiPs. QC (3,5,7,3′,4′-pentahydroxyflavone), the most abundant flavonoid, was chosen due to it possess several and interesting biological properties for human being, such as anti-inflammatory, antiallergenic, antiviral, antibacterial and anticancer [23]. Those biological activities of the flavonoid are exert mainly by scavenging reactive oxygen species (ROS) [24], inhibition of lipid peroxidation [25], and chelating metal ions [26]. Therefore, it is of great interest in this work to evaluate how some of these properties are improved or affected after conjugation to SiPs. Additionally, SiPs were chosen due to their excellent properties such as easy manufacture and functionalization [27], high stability at different environments (temperature, pH) [28], biocompatibility [29], and low cytotoxicity [30].

The information obtained in this study will have great impact in the development of novel smart HMs formed by SiPs and flavonoids, as QC, using a simple method. Additionally, the findings of this work, it may be helpful to elucidate how conjugation of flavonoids on the surface of inorganic particles could decrease, maintain and/or enhance the biological activities of these molecules. Consequently, this information may have a remarkable influence for future innovative applications within the food, pharmaceutical, cosmetic, and biomedical fields of biofunctional HMs.

2. Material and methods

2.1. Materials

Quercetin dihydrate (QC), tetraethyl orthosilicate (TEOS, 98%), (3-Aminopropyl) triethoxysilane (APTES, 99%), potassium bromide (KBr), ethylenediaminetetraacetic acid (EDTA, ⩾98.5%), 3-(2-pyridyl)-5,6-diphenyl-1,2,4-triazine-*p*,*p*′-disulfonic acid monosodium salt hydrate (ferrozine, 97%), iron (II) chloride ($FeCl_2$, 98%), Triton X-100, and 2-Thiobarbituric acid (TBA) were purchased from Sigma Aldrich Co. (USA). Ethanol 40B denaturized (EtOH), peroxide hydrogen (H_2O_2, 30%), ferrous sulfate heptahydrate ($FeSO_4$-7 H_2O), glacial acetic acid (CH_3-COOH), phosphoric acid (H_3PO_4), boric acid (H_3BO_3), hydrochloric acid (HCl), sodium phosphate dibasic (Na_2HPO_4), monobasic potassium phosphate (KH_2PO_4), potassium chloride (KCl), ammonium hydroxide (NH_4OH, 28–30%), and sodium chloride (NaCl) were obtained from J.T. Baker (USA). L-α-phosphatidylcholine (PC 99%, egg, chicken,) was obtained from Avanti Polar Lipids Inc. (USA). Deionized water (dH_2O) was used in all experiments.

2.2. Methods

2.2.1. Synthesis of SiPs

SiPs were prepared following slightly modification reported by our work group to previous protocols [31–34]. Briefly, EtOH, diH_2O, NH_4OH, and TEOS (final molar ratios were 23:2.4:0.11:1, respectively) were magnetically stirring (500 rpm) during 2 h and then 2 h more at 40 °C. Then, samples were centrifuged during 15 min at 5000 rpm, room-temperature and washed with EtOH three times. Washed Ps were dispersed in EtOH 80% and dried at 80 °C an Imperial V Laboratory oven (Lab-Line Instruments Inc., USA) in order to maintain silanol groups (SiOH) in NPs. Finally, SiPs were pulverized in an agate mortar, placed in vials and stored in free humidity desiccators until further use.

2.2.2. Functionalization of SiPs

Samples of SiPs (0.2 g) were dispersed in diH_2O during 4 h, and 2 mL of APTES was added. This solution was kept in magnetically stirring at 60 °C/24 h. Sample were centrifuged