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ORIGINAL PAPERS

# EXPLORING THE NANOSTRUCTURE OF COMPOSITES MADE OF NATURAL POLYPHENOLIC COMPOUNDS AND PEG6000 AS WELL GOLD NANOPARTICLES FUNCTIONALIZED WITH DOXORUBICIN FOR MEDICAL APPLICATIONS

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**Abstract.** *Natural polyphenolic compounds, such as curcumin, CCM, trans resveratrol, RES or R, and silymarin, SIL, have beneficial effects on human health due to their pharmacological activities and protective role against many diseases. They are recognized as antioxidants that possess bone tissue regenerative properties, metabolic regulation effects, anticancer activity, as well as hepatoprotective and cardioprotective effects. Whey protein concentrate (WPC) is often used to enhance and stabilize various foods for medical diet. It helps curcumin improve its water solubility, poor bioavailability, low stability in aqueous media and enhance the efficacy of CMC. This work provides insights into the nanostructure of several composites based on natural polyphenolic compounds, whey protein concentrate and PEG6000, namely: CCM-PEG6000, CCM-WPC-PEG6000, CCM-WPC-RES-PEG6000 and CCM-WPC-SIL-PEG6000. These advanced composites could possess a wide range of metabolic regulatory effects and tissue regenerative properties. This research paper also provides insights into the natural compounds used to generate innovative gold nanoparticles based on advanced composites prepared using resveratrol, R, denoted GNP_R1. The natural compounds used are: resveratrol, R, piperine, P and icariin, Ic. R, P and Ic and have demonstrated anticancer effects, inducing apoptosis, inhibiting cell migration and proliferation.*

*In addition, R, P, Ic and doxorubicin, D, which is an anticancer drug, have recently been used jointly to functionalize gold nanoparticles, denoted GNP-R1, to develop new innovative composites, such as GNP_R1@R/P/Ic/D compared to GNP_R1@D. These innovative composites demonstrated an enhanced effect against cancer, compared to doxorubicin administered alone.*

**Keywords**: curcumin, resveratrol, silymarin, whey protein concentrate, PEG6000, doxorubicin, piperine, icariin, gold nanoparticles

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## INTRODUCTION

Natural bioactive compounds derived from plants have gained increasing scientific attention due to their broad pharmacological potential and favorable safety profiles. These substances, often belonging to classes such as polyphenols, flavonoids, and terpenoids, exhibit antioxidant, anti-inflammatory, and metabolic regulatory properties that contribute to the prevention and management of chronic diseases, including cardiovascular, metabolic, and hepatic disorders. Their multitargeted mechanisms of action, combined with relatively low toxicity compared to synthetic drugs, position natural compounds as promising adjuncts or alternatives in evidence-based therapeutic strategies [1-12].

Curcumin, the principal curcuminoid of *Curcuma longa*, exerts multifaceted hepatoprotective and metabolic effects [13-18], including the reduction of hepatic steatosis, serum transaminases (ALT, AST), triglycerides, fasting glucose, insulin resistance (HOMA-IR), and body mass index (BMI), as demonstrated in randomized controlled trials and meta-analyses [19-27].

Resveratrol, a natural stilbenoid polyphenol, has shown modest clinical efficacy in decreasing hepatic steatosis and diastolic blood pressure, while also contributing to improved glycemic regulation in patients with metabolic disorders [19,28-32].

Silymarin, a standardized flavonolignan extract from *Silybum marianum*, has consistently been associated with significant reductions in aminotransferases and enhanced hepatoprotection, primarily through its antioxidant properties and modulation of enzymatic defense systems such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) [19,33].

Taken together, these natural polyphenolic compounds demonstrate distinct yet complementary mechanisms, positioning them as promising therapeutic agents in the management of metabolic dysfunction-associated steatotic liver disease (MASLD).

Resveratrol, piperine, and icariin are natural bioactive compounds with significant pharmacological potential, particularly in the context of chronic and degenerative diseases [34-68].

Whey protein concentrate (WPC) is a heterogeneous mixture of globular proteins derived from the liquid by-product of cheese manufacturing and is widely recognized for its high nutritional and functional value [69]. It contains a rich profile of essential amino acids, particularly branched-chain amino acids (BCAAs), which play a crucial role in muscle protein synthesis and metabolic regulation [70].

Polyethylene glycol 6000 (PEG6000) is a high–molecular weight, water-soluble, and biocompatible polymer widely applied in pharmaceutical, biomedical, and biotechnological fields [14]. Due to its hydrophilic nature and low toxicity, PEG6000 is commonly used as a solubilizing agent, stabilizer, and excipient in drug formulations [71]. It has also been employed in the modification of therapeutic proteins and nanoparticles to enhance circulation time, reduce immunogenicity, and improve pharmacokinetic profiles through a process known as PEGylation [72].

The integration of doxorubicin with biocompatible carriers and natural bioactives such as PEG 6000, whey protein concentrate (WPC), curcumin, silymarin, resveratrol [73], piperine, icariin, and gold nanoparticles (GNPs) [74-90] has emerged as a multifunctional approach to enhance therapeutic efficacy and reduce systemic toxicity. PEG 6000–doxorubicin conjugates improve circulation half-life and reduce cardiotoxicity through controlled release [71], while WPC-based nanocarriers enable encapsulation and co-delivery with phytochemicals, adding intrinsic antioxidant activity [91].

Combination with curcumin augments doxorubicin-induced apoptosis by synergistic inhibition of NF-κB and Akt signaling and by suppressing multidrug resistance [92]. Silymarin confers hepatoprotective and antioxidant activity, attenuating doxorubicin-induced hepatic injury and improving tumor selectivity [93].

Resveratrol potentiates doxorubicin efficacy by enhancing ROS-mediated apoptosis, inhibiting angiogenesis, and downregulating P-glycoprotein expression [94]. Piperine, as a bioenhancer, increases intracellular doxorubicin accumulation by inhibiting efflux transporters, while also sensitizing tumor cells through cell cycle arrest and pro-apoptotic signaling [95-99]. Icariin synergizes with doxorubicin by modulating PI3K/Akt and MAPK pathways, inducing caspase-dependent apoptosis, and attenuating angiogenesis [100-102].

Gold nanoparticles (GNPs) provide a versatile delivery platform for doxorubicin and phytochemicals, enabling targeted release, enhanced cellular uptake, and additional cytotoxicity via photothermal and ROS-mediated mechanisms [103-110]. Collectively, these composite systems exemplify a nanomedicine-based strategy where polymers, proteins, phytochemicals, and metallic nanocarriers act synergistically to improve pharmacokinetics, overcome drug resistance, and amplify the anticancer potential of doxorubicin.

This research paper provides insights into the natural compounds used to generate innovative gold nanoparticle-based biocomposites prepared using RES, denoted GNP_R1. The natural compounds used are: resveratrol, RES, piperine, P and icariin, Ic. R, P, Ic and doxorubicin, D, which is an anticancer drug, have recently been jointly used to functionalize gold nanoparticles, denoted GNP-R1, to develop new innovative biocomposites, such as GNP_R1@R/P/Ic/D compared to GNP_R1@D.

In addition, this work provides insight into the nanostructure of several biocomposites based on natural polyphenolic compounds, whey protein concentrate and PEG6000, namely: CCM-PEG6000, CCM-WPC-PEG6000, CCM-WPC-RES-PEG6000 and CCM-WPC-SIL-PEG6000. These biocomposites could possess a wide range of metabolic regulation effects and tissue regenerative properties.

## MATERIAL AND METHODS

### Materials for composites with PEG6000

Curcumin powder extracted from Curcuma longa having a purity (HPLC) ≥ 95% was purchased from Sigma-Aldrich, Darmstadt, Germany; Whey protein concentrate (WPC) with a content of minimum 80% protein (Fat content maximum 11.5% and water 6.5%) was acquired from Foodcom S.A. Warsaw, Poland. PEG 6000 was purchased from Merck (Darmstadt, Germany). Silymarin (80.6% purity) was purchased from Nanjing Hua Cheng Pharmaceuticals, Liaoning, China having the following natural phenolic content: silybin 40.93%, isosilybin 11.65%, silychristin 17.08%, and silydianin 4.51%. Trans-resveratrol (99% purity) was purchased from Sigma-Aldrich (Saint Louis, USA). Ultrapure water (resistivity of 18.2 MΩ x cm) was employed in every experiment.

### Materials for composites with GNP_R1

For the synthesis of gold nanoparticles, there were used trans-resveratrol ≥ 99% (HPLC assay, from Sigma-Aldrich, Buchs, Switzerland), tetrachloroauric acid trihydrate ($HAuCl_4 \cdot 3H_2O$) 99.5% (Merck, Darmstadt, Germany) and NaOH reagent grade ≥ 98% (Merck KGaA, Darmstadt, Germany) in aqueous solutions prepared with bi-distilled deionized water.

For the functionalization of GNPs there were used doxorubicin hydrochloride (about 98%) from Sigma-Aldrich Chemie GmbH (Munich, Germany), piperine ≥ 98% (HPLC assay) from AlfaAesar (Karlsruhe, Germany), and icariin, analytical standard (≥94%), from Sigma-Aldrich (Steinheim, Germany). Dimethyl sulfoxide (DMSO) was purchased from Sigma-Aldrich (Schnelldorf, Germany). Dulbecco's phosphate-buffered saline (PBS), without $CaCl_2$ and $MgCl_2$, (pH 7.4), was purchased from Alfa Aesar (Karlsruhe, Germany). MTT tetrazolium salt (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) ≥ 98% was acquired from Sigma-Aldrich (Buchs, Switzerland).

### Preparation of some CCM and PEG6000 composites

Four solid CCM-PEG6000 composites were prepared by physically mixing the melted PEG6000 (m.p. 60-65°C) with the appropriate biologically active compounds as shown in Table 1. All materials were used in solid form. The content of CCM was constant in each composite.

**Table 1** Curcumin and PEG6000 composites

| Composites | Mole ratio to CCM | | | | |
|---|---|---|---|---|---|
| | CCM | PEG | WPC | RES | SIL |
| CCM - PEG6000 | 1 | 8 | – | – | – |
| CCM - WPC- PEG6000 | | 10 | 0.5 | – | – |
| CCM - WPC- RES-PEG6000 | | 10 | 0.4 | 2.5 | – |
| CCM - WPC - SIL PEG6000 | | 10 | 0.4 | – | 2.5 |

CCM: curcumin; WPC: whey protein concentrate; RES: trans-resveratrol; SIL: silymarin

**Synthesis of GNP_R1, GNP_R1@D/Ic, GNP_R1@D/R/P/Ic nanocarriers/ nanocomposites**

GNPs were synthesized by the green reduction of $HAuCl_4$ with resveratrol, similar to the method we used in Mocanu at al. 2025 [111]. In short, a solution of 50 mg resveratrol in 20 mL 0.02 M NaOH was added to 200 mL $10^{-3}$ M $HAuCl_4$ in bi-distilled water, under steady stirring at 500 RPM for 10 min at room temperature. The gold nanoparticles, formed by reducing $HAuCl_4$ with resveratrol and noted as GNP_R, were obtained in the initial gold concentration of 0.91 mM (179 mg/L Au) in colloidal solution.

The GNP_R initially obtained was centrifuged to eliminate the secondary reaction products obtained during their synthesis. The working method is described in the previous work [112].

The obtained nanoparticles were characterized by the following methods: UV-VIS; TEM; high-resolution TEM (HR-TEM); atomic Force Microscopy, AFM; zeta (ξ-) potential; dynamic light scattering (DLS) and X-Ray Diffraction (XRD) [74,111].

Identification of surface functional group coating of GNPs was performed by Fourier transform infrared spectroscopy (FTIR) [74].

The GNP_R1 colloidal solution was further used in the functionalization of GNP_R1 particles with selected natural compounds: resveratrol, piperine, and icariin (see Table 1 in the previous work) [112]. GNP_R1 was functionalized with R, P, D, and Ic, resulting in GNP_R1@R/P/D/Ic.

**Analysis methods for the nanostructure of these innovative composites**

***Atomic force microscope*:** AFM, JEOL JSPM 4210 model (Tokyo, Japan) was used to determine the morphology of these innovative composites (Figs.1-3) for various compositions. They were hydrated in ultrapure water under magnetic stirring (900 rpm for 30 min, in dark conditions) to assure preparation of homogeneous aqueous dispersions. Then, the adsorption of nanoparticles, NPs, on optically polished glass is realized, and the adsorbed layer was dried naturally, in dark conditions. The surface of each sample is scanned with a sharp tip (cantilever), using silicon nitride cantilevers (NSC 15 Hard, purchased from MikroMasch, Sofia, Bulgaria), with a resonant frequency of 325 kHz and a force constant of 40 N/m. Accordingly, AFM images are obtained by monitoring the changes in amplitude of the cantilever oscillation during scanning. The measurements were achieved in tapping mode to obtain the surface morphology. The topography, phase and amplitude images were obtained simultaneously and their processing was performed with Win SPM2.0 Processing software, JEOL, Japan.

***Transmission electron microscope:*** TEM images were taken with a transmission electron microscope, JEOL - JEM 1010. The composite colloidal solutions were deposited on carbon-coated copper grids and investigated by TEM, as given in Figs 4 and 5.

### Cell lines and MTT test

Certified cell lines of HeLa and CaSki cervical carcinoma cells were used in this study. Cell lines were provided by the European Collection of Authenticated Cell Cultures (ECACC) and purchased from Sigma-Aldrich. HeLa cells were cultivated with Dulbecco's modified Eagle (DMEM) medium, low glucose, supplemented with 10% fetal calf serum (FCS), 2 mM L-glutamine, 1% antibiotic, and 1% non-essential aminoacids (NEAs) at 37°C in 5% $CO_2$ humidified air; for CaSki cells, the cultivation medium was RPMI-1640 medium supplemented with 10% fetal calf serum (FCS), 2 mM L-glutamine, and 1%antibiotic; all Sigma-Aldrich reagents, all Sigma-Aldrich reagents. To perform the MTT test, the cells were trypsinized and counted with a hemocytometer and seeded on 96-well plates at a density of 1 × 104 in 200 µL complete medium/well. After 24 h, during which HeLa and CaSki cells adhered to the surface of the plates, treatments with functionalized gold nanoparticles and biocompounds and/or doxorubicin were applied, with a dilution of 1/20. The viability of cells was evaluated after 24h and 48h by an MTT assay that uses a tetrazolium salt (3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide).

After 24 and 48 h of exposure to treatments, the medium was extracted from the wells, 100 µL of MTT solution was added, and the plates were incubated for 1 h at 37°C in the dark. The MTT solution was discarded from the wells, and 150 µL of DMSO/well was added to solubilize the formazan crystals from the cells. Optical density readings were performed at 492 nm using a BioTek Synergy 2 microplate reader (Winooski, VT, USA). The cytotoxic effect of doxorubicin and/or of biomolecules, such as resveratrol, was expressed as the relative viability (% control) [111,112].

### Statistical analysis

The data are presented, from triplicate experiments, as mean ± standard deviation. Statistical analysis was performed with the GraphPad Prism 5 program, using two statistical analysis methods: one-way ANOVA followed by the "Dunnett's Multiple Comparison Test" posttest for the comparison of the treated cells with the control sample without treatment, setting the p-value at $p < 0.05$ (statistically significant).

## RESULTS AND DISCUSSIONS

### 1. Composites with PEG6000

Beyond its nutritional value, WPC exhibits multiple biological activities, including antioxidant, antihypertensive, antimicrobial, and immunomodulatory effects, attributed to bioactive peptides released during gastrointestinal digestion or enzymatic hydrolysis [91,113]. Additionally, WPC supplementation has been associated with improvements in body composition, exercise recovery, and satiety regulation, supporting its application in sports nutrition and clinical settings [114].

Recent studies also highlight its potential role in metabolic health, as WPC may improve insulin sensitivity and lipid metabolism [115]. It helps curcumin improve its water solubility, poor bioavailability, low stability in aqueous media, and enhance the efficacy of CCM [13,14]. Overall, WPC represents not only a high-quality protein source but also a functional ingredient with promising applications in health promotion and disease prevention.

In biotechnology, PEG6000 is extensively utilized in macromolecule crowding studies, protein crystallization, and cell fusion protocols, where its ability to modulate osmotic pressure and molecular interactions is advantageous [116]. Furthermore, PEG6000 has demonstrated applications in controlled drug release systems and as a cryoprotectant in cell preservation, underscoring its versatility as a multifunctional polymer in biomedical sciences.

Composites incorporating polyethylene glycol 6000 (PEG6000), whey protein concentrate (WPC), curcumin, silymarin, and resveratrol have attracted increasing attention in pharmaceutical and biomedical research due to their synergistic potential in improving drug delivery and therapeutic efficacy. PEG6000, a biocompatible polymer, serves as a stabilizer and carrier matrix that enhances solubility, prolongs circulation time, and controls drug release [71].

WPC, a protein-rich biopolymer, contributes not only structural integrity but also functional bioactivity, providing antioxidant and immunomodulatory effects that complement therapeutic outcomes [91]. When combined with curcumin, silymarin, and resveratrol—three polyphenolic compounds with well-documented antioxidant, anti-inflammatory, and anticancer properties—the resulting formulations demonstrate improved stability, bioavailability, and cellular uptake, thereby amplifying their pharmacological actions [36,92]. Such multifunctional composites are of particular interest for applications in cancer nanomedicine, metabolic disorders, and nutraceutical formulations, where both polymeric carriers and bioactive phytochemicals act in concert to enhance therapeutic performance [117].

In dentistry, the integration of natural bioactive compounds and nanomaterials into biomaterials offers promising therapeutic and regenerative applications [118-127]. Whey protein concentrate (WPC) serves as a biocompatible matrix that enhances remineralization and supports tissue regeneration, while polyethylene glycol (PEG) is widely used as a stabilizer and carrier to improve the delivery and controlled release of therapeutic molecules. Natural polyphenolic compounds such as curcumin, silymarin, and resveratrol exhibit potent antioxidant, anti-inflammatory, and antimicrobial properties, which are highly relevant for managing oral infections, reducing oxidative stress, and promoting periodontal health [128-131].

### *Morphology of composites investigated by AFM*

AFM is already confirmed to be used to analyze the CCM, WPC and their CCM/WPC mixtures for different mole ratios [13,14,113]. Certainly, AFM investigation on composite layers can show their nanostructure revealing the interaction between various molecules within these composites at nanoscale.

Figure 1 displays the 2D- and 3D-topographies as well as the phase images by AFM investigation at nanometer resolution for the four composites.

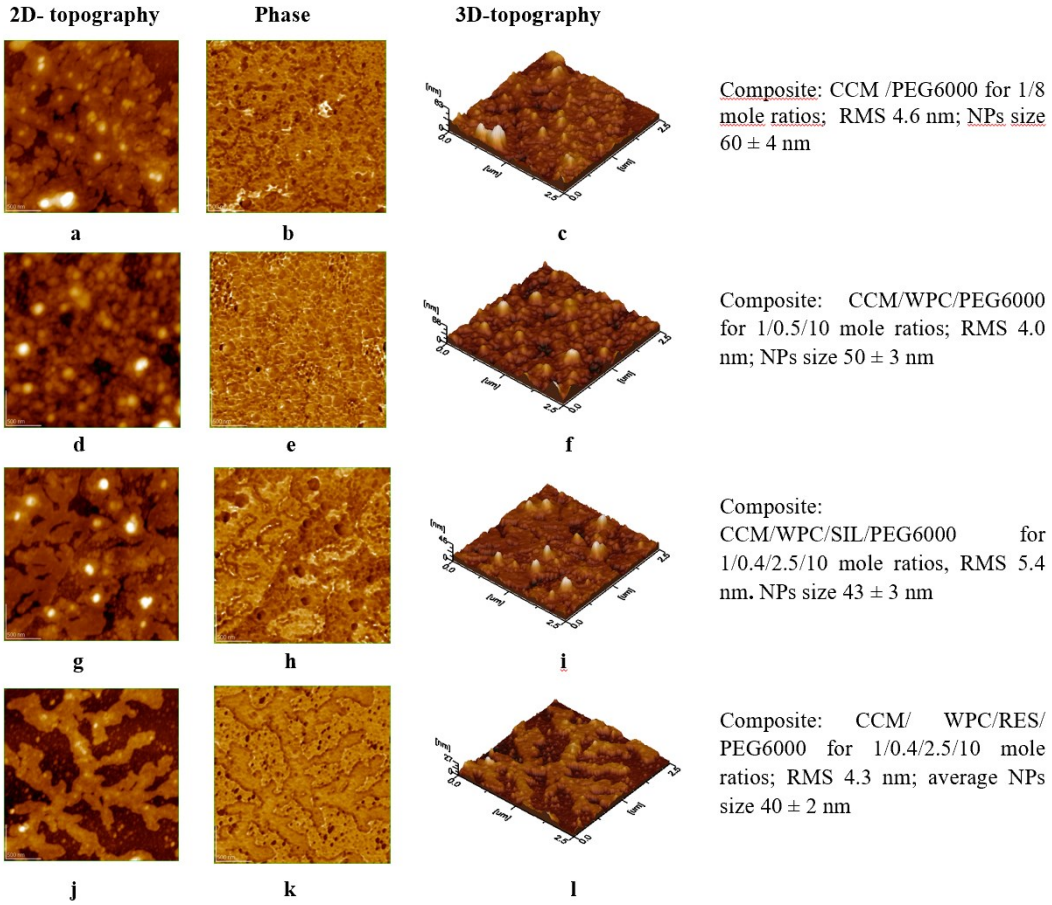


**Figure 1.** AFM images of the morphology of advanced composites, made of curcumin (CCM), whey protein concentrate (WPC) and silymarin (SIL) or trans-resveratrol (RES) and PEG6000, for the four specified composites: CCM/PEG6000, CCM/WPC/PEG6000, CCM/WPC/SIL/PEG6000 and CCM/WPC/RES/PEG6000, shown above near each composite, adsorbed from aqueous dispersion on glass plate: 2D-topographic image; phase image; 3D-topographic image; scanned area of 2.5 μm x 2.5 μm; roughness expressed as root mean square, RMS, is given near the investigated composite. The height of the composite layer is given on each 3D- topography. The estimated average size of nanoparticles is also given for each composite.

The shape of particles within these composites is similar to spherical shape as assessed by using AFM images and analysis of cross section profiles as exemplified in Figure 2.

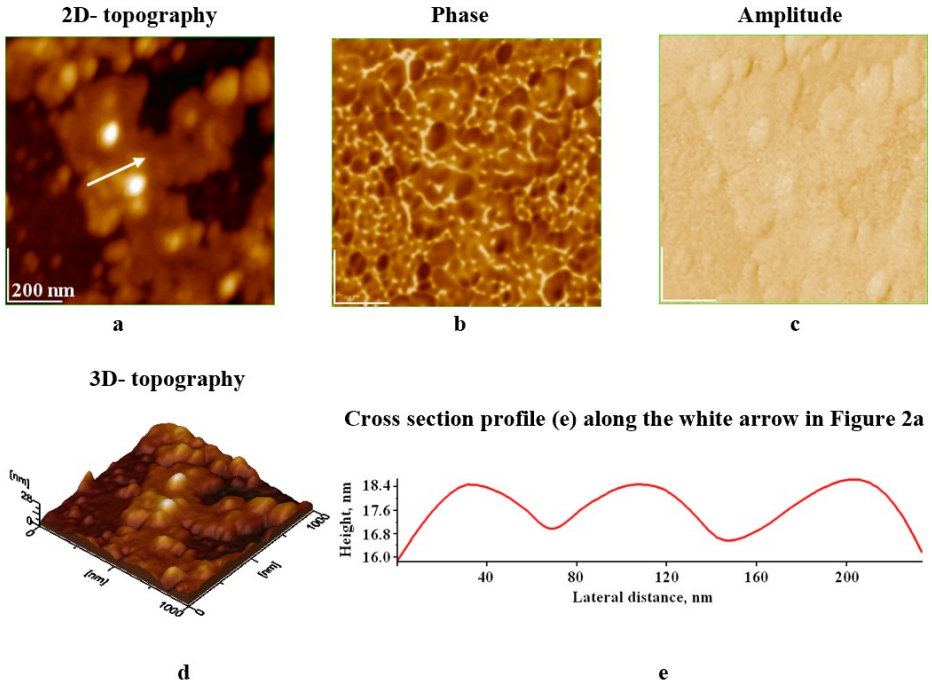


**Figure 2** displays the 2D-topography (a) and 3D-topography (d) as well as the phase (b) and the amplitude (c) images by AFM investigation at nanometer resolution for CCM and PEG6000 composite. Scanned area of 1μm x 1μm is presented. Cross section profile (e) is given along the white arrow showed in Figure 2a. Height is of 28 nm, and surface roughness, RMS, is of 4.6 nm, and the mean diameter of a particle is about 60 ± 4 nm. In phase image (b) is clearly shown that the nanoparticles are covered by PEG6000 layer.

The particle diameter is estimated as full width at half maximum of the profile peak height (e.g., Figure 2e), to eliminate the convolution effect of the AFM probe's tip shape with the sample features. By measuring the diameters of a statistical number of particles (about 20 particles) on numerous cross profiles (in the same scanned area), an average diameter (d) and standard deviation (SD) were estimated for particles of the CCM and PEG6000 composite (e.g., 60 ± 4 nm).

In addition, the surface roughness value is calculated as the root mean square (RMS) value. The roughness value was generated by the AFM software. The roughness RMS is 4.6 nm and indicates a well covering of the surface with the nanoparticles of this composite, as observed in AFM images in Figure 2a, b, c, and d. The smallest roughness of 4.0 nm is recorded for CCM/WPC/PEG6000 composite, very close to RMS of 4.3 nm obtained for CCM/WPC/RES/PEG6000 composite. The

RMS of 5.4 nm was evidenced for the CCM/WPC/ SIL/PEG6000 composite rather close to the other RMS values for the four composites studied.

Accordingly, using the cross profiles (Figure 2e) along the various arrows taken in 2D AFM images, as in example given in Figure 2a, the average diameter of nanoparticles was evaluated with its standard deviation, 60 ± 4 nm, as indicated in Figure 1 (a, b, c) for average nanoparticles size. The same procedure was applied for all composites given in Figure 1 and the average size of nanoparticles is given near the investigated composite. The smallest average size of nanoparticles is recorded for CCM/WPC/SIL/PEG6000 composite as 43± 3 nm which is practically identical with 40 ± 2 nm for CCM/WPC/RES/PEG6000 composite.

The morphology of the first three composites given in Figure 1, CCM/PEG6000 (AFM images: a, b, and c), CCM/WPC/PEG6000 (AFM images: d, e, and f), and CCM/WPC/SIL/PEG6000 (AFM images g, h, and i) for various compositions given as mole ratios (in Table 1 and Figure 1) is similar with spherical nanoparticles of composites randomly packed in the composite layers. The interaction among these molecules is very strong particularly for CCM/WPC/SIL/PEG6000 composite, where the nanoparticle average size is about 43 nm. As observed in phase images these nanoparticles are covered by PEG6000.

The morphology of the surface composite layer made of CCM/WPC/RES/PEG6000 for 1/0.4/2.5/10 mole ratio is different (AFM images j, k, and l) and shows two domains, one domain with nanoparticles very well visualized and a high-level domain with nanoparticles very well packed forming a special type of surface nano structure similar with fractal structure. The height of these domains is very well observed in the 3D topography image, Figure 1 (l). Clearly, the interaction among these molecules is very strong and the particles are rather small with an average diameter of around 40 nm.

Gold nanoparticles (GNPs) have emerged as highly promising biomaterials due to their unique physicochemical properties, including biocompatibility, surface plasmon resonance, and ease of functionalization [132,133]. These nanostructures can be engineered with various surface coatings or biomolecule conjugations to enhance stability, targeting ability, and therapeutic efficiency [134]. In biomedical applications, GNPs are extensively investigated for drug delivery, photothermal therapy, bioimaging, and biosensing, offering a versatile platform for diagnostics and treatment [135-147]. Furthermore, their ability to penetrate cells [148-151] and modulate biological pathways positions them as valuable tools in cancer therapy and regenerative medicine [152-160]. The ongoing development of GNP-based biomaterials highlights their potential to revolutionize personalized medicine by enabling precise, minimally invasive, and multifunctional therapeutic strategies [161-171].

Resveratrol, a polyphenolic stilbene found in grapes and berries, exhibits antioxidant [34], anti-inflammatory [35], and cardioprotective activities, and has been widely

studied for its ability to modulate cellular signaling pathways involved in aging and cancer [36-43]. Its anticancer effects are mediated through the induction of apoptosis, inhibition of angiogenesis, and suppression of tumor cell proliferation by targeting pathways such as NF-κB, STAT3, and PI3K/Akt/mTOR [44-49]. Piperine, the principal alkaloid of Piper nigrum (black pepper), enhances the bioavailability of various drugs and phytochemicals by inhibiting cytochrome P450 enzymes and P-glycoprotein, while also displaying anti-inflammatory and neuroprotective effects [50-56]. Importantly, piperine exhibits anticancer potential by inducing cell cycle arrest, triggering apoptosis, and inhibiting metastasis in multiple cancer models, partly via modulation of Wnt/β-catenin and MAPK signaling [57-59].

Icariin, a prenylated flavonol glycoside derived from Epimedium species, is known for its osteogenic, neuroprotective, and cardioprotective properties, mediated through the activation of the PI3K/Akt and MAPK pathways [60-63]. In oncology research, icariin has demonstrated anticancer activity by inhibiting proliferation, promoting apoptosis, and reducing tumor angiogenesis, with reported effects on the regulation of Bcl-2 family proteins, caspases, and VEGF expression [64-66]. Collectively, these natural compounds not only contribute to health maintenance but also represent promising candidates for integrative anticancer strategies, either as adjuvants to conventional chemotherapy or as lead structures for novel therapeutic agents [67,68].

Gold nanoparticle (GNP)–based conjugates of curcumin, silymarin, resveratrol, piperine, and icariin potentiate anticancer activity primarily through improved intracellular delivery, redox modulation, and targeted interference with oncogenic signaling [172-186]. Curcumin–GNPs induce enhanced reactive oxygen species (ROS) accumulation, leading to mitochondrial depolarization, cytochrome c release, and caspase-3 activation, while also downregulating NF-κB and PI3K/Akt/mTOR signaling [187-189]. Silymarin–GNPs augment cytotoxicity in hepatocellular carcinoma by enhancing apoptosis via p53 upregulation, Bax/Bcl-2 ratio modulation, and caspase cascade activation, coupled with suppression of VEGF-driven angiogenesis [190]. Resveratrol–GNPs exhibit prolonged bioactivity, enabling sustained inhibition of NF-κB, STAT3, and Akt phosphorylation, thereby attenuating tumor cell survival, proliferation, and inflammatory crosstalk within the tumor microenvironment [191,192]. Piperine–GNPs enhance bioavailability and induce G1 phase arrest through p21 upregulation and cyclin D1 suppression, while simultaneously inhibiting epithelial-to-mesenchymal transition (EMT) via downregulation of MMP-9 and vimentin [193-197]. Icariin–GNPs activate intrinsic apoptotic pathways by modulating Bax/Bcl-2 expression and caspase-9 activation, while also impairing angiogenesis through downregulation of VEGF and HIF-1α, alongside suppression of MAPK/ERK and PI3K/Akt signaling [198]. These mechanistic insights highlight that GNP-mediated delivery not only improves pharmacokinetics but also amplifies pathway-specific anticancer responses,

positioning such composites as promising candidates for nanomedicine-based oncology [199-202].

Model membranes, such as supported lipid bilayers and liposomes [203-213], play a crucial role in elucidating the interactions of nanomaterials with biological systems, particularly in the context of therapeutic applications [214-226]. The use of gold nanoparticles (GNPs), often functionalized with polyethylene glycol (PEG) to enhance circulation time and reduce immunogenicity, has been extensively studied in combination with bioactive carriers like whey protein concentrate (WPC) to improve biocompatibility and drug-loading capacity [227-239]. By employing model membranes, researchers can investigate nanoparticle adsorption, penetration, and potential disruption of lipid bilayers [240-248], providing valuable insights into their cellular uptake and safety profiles [249-259]. These systems allow for controlled evaluation of how GNP–PEG–WPC complexes interact with membrane components, thereby offering predictive data on their stability, bio-distribution, and therapeutic efficacy in vivo [260-275].

In dentistry, gold nanoparticles (GNPs), due to their favorable surface chemistry and plasmonic properties [276-282], provide additional advantages in antimicrobial coatings, diagnostic imaging, and targeted drug delivery within the oral cavity [283,284]. The synergistic application of these components in dental biomaterials and therapeutic formulations holds significant potential to enhance oral health care, improve implant integration, and accelerate the healing of oral tissues [285-302].

The surface morphology of GNP_R1 spread on solid support is investigated by AFM and is shown in Figure 3.

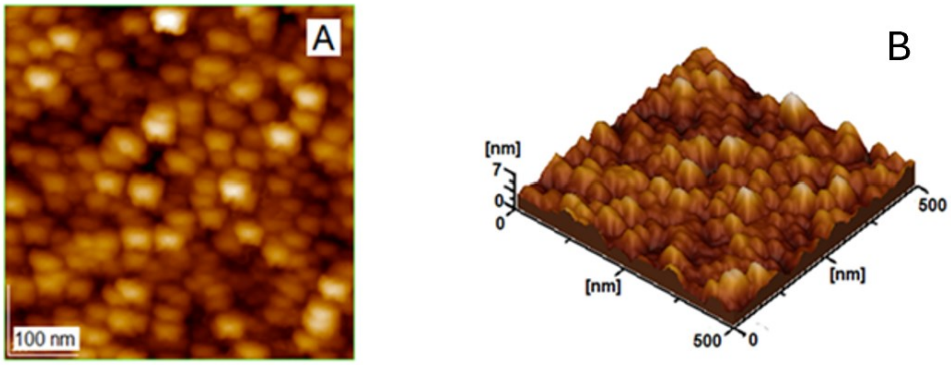


**Figure 3** displays 2D topography (A) and 3D topography (B) for almost spherical nanoparticles of GNP_R1. These nanoparticles were purified by centrifugation and washing and stabilized by a resveratrol, RES, shell adsorbed on their surface.

The particle diameter is estimated as the full width at half maximum of the profile peak height, to eliminate the convolution effect of the AFM probe's tip shape with the surface characteristics of the shell layer, as shown by us previously [72,301]. An average diameter (d) of the nanoparticles of GNP_R1 can be estimated by measuring

a statistical number of approximately 30 particle sizes. Figure 3A shows the nanoparticles for GNP_R1 and the average diameter is 24.9 ± 4.1 nm.
The root mean square (RMS) value is used to compute the surface roughness value [303-305]. The 3D image is given in panel B of Figure 3. The roughness value of 3.5 ± 1.3 nm was generated by AFM software and shows that the adsorbed layer of GNP_R1 nanoparticles, which are spread on the glass plate, is very well self-assembled and has a low RMS value. Thus, AFM topographies revealed that these gold nanoparticles are very well spread within the adsorbed layer on the glass surface, showing directly that they were also very well dispersed in highly stabilized colloidal solution.

### *Nanostructure characterization of GNP_R1@Ic/D and GNP_R1@R/P/Ic/D composites through TEM images*

The nanoparticles of GNP_R1 are functionalized with R, P, and/or Ic, as well as with doxorubicin, D, resulting composites GNP_R1@Ic/D and GNP_R1@R/P/Ic/D highly stabilized as shown in TEM images (Figures 4 and 5).

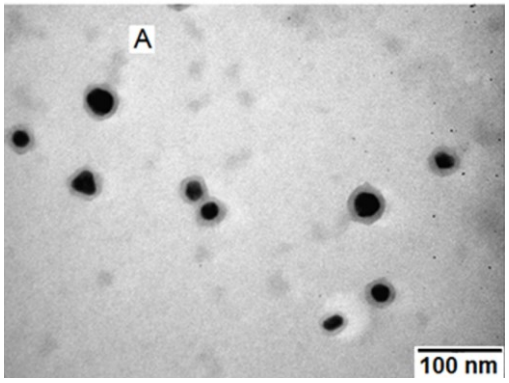


**Figure 4.** TEM image for functionalized GNP-R1, used in composition (**1**): GNP_R1 4.8 µg/mL, Ic 1.3 µg/mL, and D 2 µg/mL, noted GNP_R1@Ic/D, panel A; the bar is 100 nm. The averaged size, d, of multi-functionalized GNPs is about 19.4 ± 5.1 nm.

Figure 4 clearly shows that GNP-R1@D nanoparticles can be further stabilized by using biomolecules as capping agents, such as in composition 1, GNP-R1@D/Ic.

These coatings, made of D and Ic, prevent aggregation by keeping the nanoparticles separate from one another and in consequence, enhancing their stability. Definitely, through engineering strategy, the properties of GNPs can also be improved by molecular functionalities of these capping biomolecules, realizing that the shell morphology of these drug carriers have important roles in their interaction with biological membranes and targeting cancer cells.

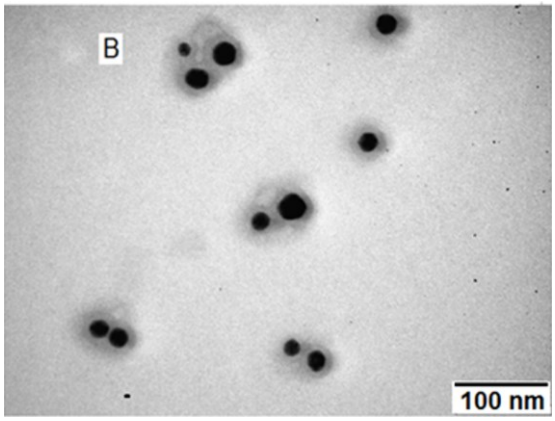


**Figure 5.** TEM image for functionalized GNP-R1, used in composition (2): GNP_R1 3.6 μg/mL, R 0.14 μg/mL, P 0.35 μg/mL, Ic 0.7 μg/mL, and D 2 μg/mL, noted GNP_R1@R/P/Ic/D, panel B; the bar is 100 nm. The averaged size, d, of multi-functionalized GNPs is about 19.4 ± 5.1 nm.

Figure 5 presents composition 2, containing advanced GNP_R1@R/P/Ic/D composite. This R/P/Ic/D coating prevents the aggregation of nanoparticles by keeping them separate from one another in colloidal solution and in consequence, enhancing their stability. Through engineering strategy, the properties of multi-functional GNPs can be improved by molecular functionalities of these capping biomolecules, realizing that the shell morphology of these drug carriers have important roles in their interaction with biological membranes and targeting cancer cells.

The general mechanism of GNPs stabilization involves charge stability on the nanoparticle surface achieved by adsorption of charged biomolecules as a function of medium pH, which can help nanoparticles repel each other from becoming aggregated or preventing them from touching each other by steric effects. The chosen natural molecules, R, P, and Ic, and their mixture revealed that they can be used, as an adsorbed layer on the GNP-R1@D surface, for protection from agglomeration (see Figures 4 and 5).

Compositions 1 and 2 are a result of comparing different compositions and various measurements to assess which is the best from the observed data for a particular cancer cell line. For this purpose, the MTT assay was used [111, 112].

For instance, many samples were prepared, characterized and tested on HeLa and CaSki cell lines [112] and the highly increased cytotoxic response for composition 1 (GNP-R1 4.8 μg/mL, Ic 1.0 μg/mL, D 2 μg/mL) and composition 2 (GNP-R1 3.6 μg/mL, R 0.14 μg/mL, P 0.35 μg/mL, Ic 0.7 μg/mL, D 2 μg/mL) are identified for HeLa and CaSki cell lines. The reduced viability of cancer cells can be explained by the increased stability of advanced gold nanoparticles by selecting appropriate concentrations of gold, doxorubicin, and biomolecules (e.g., composition 2, for GNP_

R1 3.6 μg/mL, R 0.14 μg/mL, P 0.35 μg/mL, Ic 0.7 μg/mL, D 2 μg/mL) assuring targeted delivery of D to cancer cells of HeLa and CaSki.
This specific coating with natural biomolecules and doxorubicin on the GNP_R1 core of functionalized nanoparticles can prevent their aggregation and enhance their stability and anticancer efficacy on HeLa and CaSki cells [306].

## CONCLUSIONS

This work provides insight into the nanostructure of several biocomposites based on natal polyphenolic compounds, whey protein and PEG6000, namely: CCM-PEG6000, CCM-WPC-PEG6000, CCM-WPC-RES-PEG6000 and CCM-WPC-SIL-PEG6000. These composites could possess a wide range of metabolic regulation effects and tissue regenerative properties. Prevention and cure of diseases using phytochemicals, as natural polyphenolic compounds, especially flavonoids are rather well known as biological active compounds. Medicinal efficacy of natural polyphenolic compounds as antibacterial, anticancer, anti-inflammatory, and antiviral agents is relatively well established. However, further achievements will provide novel insights leading to a new era of advanced biocomposites, based on polyphenolic compounds, especially curcumin, resveratrol and silymarin, as pharmaceutical agents complexed with protein and PEG6000, for the treatment of infectious, cancer and brain degenerative diseases or as dietary agents. Furthermore, the nanostructure of advanced composites jointly with vitamins can further modulate key signaling pathways involved in cancer development and treatment and in bone tissue regenerative properties [118].
Piperine, P, is a natural compound documented to increase the bioavailability of polyphenolic compounds, such as trans resveratrol, noted RES or R, with anticancer effect. Icariin, noted Ic, is a natural compound that suppresses the growth of human tumor cells by interfering with multiple signaling pathways critical for tumor cell growth. R, P and Ic demonstrated anticancer effects, inducing apoptosis, inhibiting cell migration and proliferation. The development of the advanced composites, based on gold nanoparticles functionalized with these natural compounds and doxorubicin, demonstrated an enhanced effect against cervical cancer, compared to doxorubicin, D, administered alone [306].
Moreover, their nanostructure and biophysical properties make these hybrid composites as promising candidates for the development of new cancer therapies with a focus for continued research on their potential applications in biomedicine [307], for the treatment of infectious and brain degenerative diseases or as dietary agents.

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