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PREPARATION OF COMPOSITE BASED ON CAFFEIC ACID AND FUMED SILICA AND EVALUATION OF ITS ANTIOXIDANT AND ANTIMICROBIAL PROPERTIES

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Abstract. The aim of this work was the preparation of a composite comprising caffeic acid (CA) and fumed silica (A300), and comparison of antioxidant and antimicrobial properties of CA in solution and in composite. The CA+A300 composite with CA content of about 25 mg/g was obtained using the sorptive modification of silica with CA solution under fluidized bed conditions. Antioxidant properties of the CA solution and the CA+A300 composite were studied using $DPPH^{\bullet}$ and Folin-Ciocalteu assays, in addition $OH^{\bullet}$ and $NO^{\bullet}$ scavenging activity and antimicrobial properties against *Staphylococcus aureus* 209 strain were estimated. The results have shown that CA is very effective in the reaction with $DPPH^{\bullet}$ radicals and that the inclusion of CA in the composite results in the slowing down of this reaction. The CA solution and the CA+A300 composite had a similar activity as $NO^{\bullet}$ radicals' scavengers and as antimicrobial agents, whereas the CA solution was more effective in inhibition of $OH^{\bullet}$ radicals. It has been assumed that the difference in activity between the CA+A300 composite and the CA solution may be due to the gradual release of CA from the composite into reaction mixtures and by the increase in this release as CA is consumed in the reactions.

Keywords: caffeic acid, fumed silica, composite, antioxidant, radical scavenger, antimicrobial activity.

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Introduction

Fumed silica is a biocompatible and bioactive powder used as an auxiliary ingredient for preparation of the medicines and dietary supplements. While silica itself can adsorb a large number of various toxic molecules, acting as a detoxifying or wound healing agent [1], its function in the formulations may be to improve the stability of the active components against oxidation, to reduce the drugs hygroscopicity, to introduce hydrophobic compounds into aqueous solutions or hydrophilic compounds into lipophilic media, *etc.* [2-4].

The most common ways to prepare bioactive composites based on silica and bioactive compounds are the following: 1) co-milling the silica powder together with active ingredients, 2) chemical immobilization of the active molecules involving silica silanol groups, 3) adsorption/deposition of bioactive compounds on silica surface from the solutions [5-8]. In contrast to the previously described case of adsorption/deposition from excess solutions [6,9,10], adsorption/deposition under fluidized bed conditions was shown to preserve the high dispersion of silica nanoparticles, thus allowing silica to further act as an adsorbent and a detoxifying agent [9]. The technique also allows depositing of a high amount of active substances on silica surface, which is not restricted by the value of their equilibrium adsorption.

One of the main reasons for the inclusion of bioactive compounds, in particular antioxidants, in the composites is to provide their gradual release into solution or reaction medium. This slows the consumption of the compounds and ensures their prolonged action. For the case of silica-based composite, the rate of the active substances release apparently depends on the interaction of these substances with silica surface. Unfortunately, the most common antioxidants such as ascorbic acid, caffeic acid (CA), most polyphenols have a low affinity to silica, with free energies of adsorption being usually less than

20-40 kJ/mol [11], so one can expect that such substances will be readily released from the composite into appropriate solution or reaction medium.

The aim of the work was to prepare the composite comprising the antioxidant CA and fumed silica *via* the adsorption/deposition under fluidized bed conditions, and to compare the antioxidant and antimicrobial properties of CA in solution and in composite. The paper also includes the results on the release of CA from the composite into aqueous and ethanol solutions/mixtures. The results of the study will be useful for the preparation of silica-based formulations that possess both the biological activity of adsorbed molecules and the adsorption properties of silica powder.

Experimental

Materials

The following reagents and solvents were used in this study: caffeic acid, 2,2-diphenyl-1-picrylhydrazyl radical (DPPH$^{\bullet}$), Folin-Ciocalteu reagent, Greiss reagent, sodium nitroprusside, ferrous sulphate, brilliant green, ethanol (96%), phosphate buffered saline, hydrogen peroxide (all from Merck, Germany). Fumed silica (A-300, 99.7% purity) was obtained from State Enterprise "Kalush Test Experimental Plant of the Institute of Surface Chemistry of NAS of Ukraine" (Kalush, Ukraine).

Methods and instruments

Composite preparation was done as follows: 10 g of the silica powder was placed in the reaction vessel equipped with a stirrer and then 5 mL of the 270 mM CA solution in 96% ethanol were gradually dropped to the vessel under permanent intensive stirring; then the mixture was stirred for one more hour to provide good distribution of CA over the silica surface. The obtained powder was heated for 5 hours under reduced pressure at 40°C to remove the solvent. The calculated content of CA in the resulted composite was 24.4 mg per 1 g of silica or ~2.4 wt. %.

Thermogravimetric and differential thermogravimetric analysis (TG-DTG) was performed using a Q-1500D Derivatograph (MOM, Hungary) in air with the heating rate of 10°/min within the 20–800°C range.

DPPH$^{\bullet}$ radical scavenging evaluation of CA solutions and CA+A300 composite was performed by using 2,2-diphenyl-1-picrylhydrazyl (DPPH$^{\bullet}$) radical scavenging method as described by Brand-Williams W. *et al.* [12]. Briefly, 1 mL of CA solutions of various concentrations was poured into glasses and 2 mL of 70% ethanol and 2 mL of 0.15 mM DPPH$^{\bullet}$ solution were consecutively added. A quantity of 7.5 mg of composite was weighted into glass, and 60 mL of 70% ethanol and 40 mL of 0.15 mM DPPH$^{\bullet}$ solution were added. The solution/suspension was shaken at 25°C for 5÷120 min; then, in the case of the composite, the supernatant was separated from the solid phase. The change in concentration of stable radicals in the mixtures during the reaction was determined from the change in absorption at the maximum of 520 nm for tested solutions as compared to absorption value for blank solution. The blank solution was prepared by mixing 3 mL of 70% ethanol with 2 mL of 0.15 mM DPPH$^{\bullet}$ solution. The stoichiometry of the reaction of CA with DPPH$^{\bullet}$ radicals was investigated as follows. The course of the reaction at different [CA]/[DPPH$^{\bullet}$] molar ratios was studied and the $([CA]/[DPPH^{\bullet}])_{50}$ ratio corresponding to the inhibition of 50% of the original amount of DPPH$^{\bullet}$ was found. The doubled value of $([CA]/[DPPH^{\bullet}])_{50}$ gives the theoretical effective concentration of the antioxidant required to reduce 100% of the radicals, and the value inverse to this concentration determines the stoichiometry of the reaction [12].

Folin-Ciocalteu assay on CA solutions and the CA+A300 composite was done according to a previously described method [13]. Briefly, to measure the total phenolic content for CA solutions of various concentrations, 45 mL of distilled water, 5 mL of Folin-Ciocalteu reagent, 20 mL of 20% sodium carbonate solution and 25 mL of water were consecutively added to 5 mL of tested solution. The solution was stirred for various time periods, the absorbance at 750 nm (D_{750}) was measured and the dependence of D_{750} value on CA concentration was determined. In the case of CA+A300 composite, 7.5 mg of the composite was placed into glasses, followed by addition of 50 mL of distilled water, 5 mL of Folin-Ciocalteu reagent, 20 mL of 20% sodium carbonate solution and 25 mL of water.

NO$^{\bullet}$ and OH$^{\bullet}$ radicals scavenging assays for CA solution and the CA+A300 composite were performed by Griess-Ilosvay reaction and Fenton reaction, respectively [14,15]. To carry out the tests, a CA solution of about 4.5 mM/L and a suspension of composite in distilled water with the composite content of 0.035 g per 1 mL were used. The antioxidant quantities in solution and in suspension were equal.

The antimicrobial activity of CA solution and CA+A300 composite was studied using the

"wells" method. A volume of 0.1 mL of a 24-hour suspension of *Staphylococcus aureus* 209 strain was applied on the surface of the agar medium [16]. "Wells" with a diameter of 8 mm were made with a sterile drill, into which 0.015 μL of a CA solution (with concentration of about 4.5 mM/L) or a CA+A300 composite suspension (with the composite content of 0.035 g per 1 mL) was added. The cups were placed in a thermostat at 28°C for 48÷72 hours. The diameter of the zone of bacterial growth inhibition under the action of the solution/suspension was determined.

The release of the CA from the composite into solutions/reaction mixtures was studied under constant solution volume conditions. Fixed volumes (100 mL) of water or 70% ethanol solution were added to 7.5 mg of the composite; the glasses with the suspensions were placed into a shaking water bath (Jeio Tech BS-11, UK) and shaken at 25°C for 1÷120 min. The concentration of CA in the solutions after various time intervals was evaluated from the changes in absorbance of the solution at a wavelength of 312-315 nm. The degree of the antioxidant release was determined as the percentage of CA released regarding to its total amount in the composite.

The CA release under given conditions, when the antioxidant reacts with dissolved substances, was examined according to the procedure described above, with the Folin-Ciocalteu assay or DPPH test reaction mixtures being used instead of pure water or 70% ethanol solution, respectively. The amount of CA transferred from the composite into water-based and ethanol-based reaction mixtures during Folin-Ciocalteu and DPPH tests was estimated using the calibration data obtained during the assays performed for CA solutions of various concentrations (0.01÷0.10 mM).

The UV-Vis spectra of solutions and reaction mixtures were recorded using a Lambda 35 spectrophotometer (Perkin Elmer, USA) at 25°C in the wavelength range of 200–800 nm.

Results and discussion

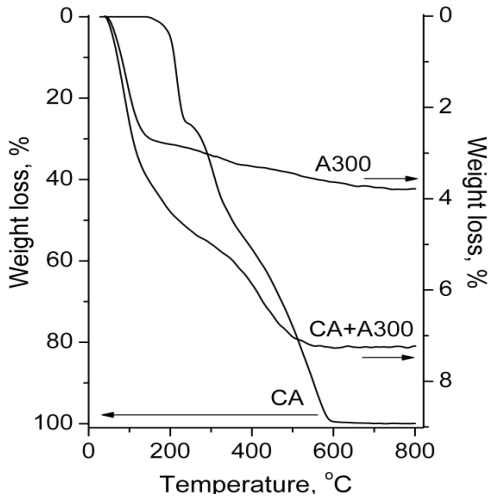
In order to confirm that after sorptive modification of silica A300 with CA and subsequent solvent removal the modifying agent remains in the composite, TG-DTG studies have been carried out. TG-DTG data on the weight loss of the bulk CA, original silica, and CA+A300 composite upon the temperature increase is given in Figure 1.

For the bulk CA sample, above 99% of the weight loss occurs within the temperature interval of 150–600°C (Table 1) as a result of the thermal decomposition and thermal-oxidative degradation processes. For the A300 sample, about three quarters of its total weight loss is in the region of 20–150°C and is mainly due to removal of physically adsorbed water; the further weight loss of ~1% in the temperature range of 150–600°C may be related to removal of strongly bound water or water formed as a result of silanol groups dehydroxylation. As to the CA+A300 composite, the weight loss in the region of 20–150°C is about 1% higher than in the case of A300, suggesting that ~1 wt.% of ethanol still remains in the composite after its drying.

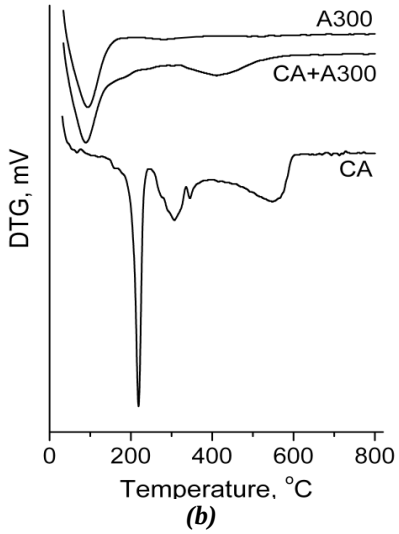
Table 1

Parameters derived from TG-DTG studies.

Sample	*Weight loss, %*		*Total weight loss, %*
	20-150, ℃	*150-600, ℃*	
A300	2.7	1.0	3.8
CA	0.2	99.3	100.0
CA+A300	3.6	3.6	7.2



(a)



(b)

Figure 1.TG (*a*) and DTG (*b*) curves for A300, CA, and CA+A300 composite.

In the temperature range of 150–600°C, corresponding to the CA degradation, the weight loss for the composite is by 2.6% higher than in the case of the A300 sample. This value is close to the calculated CA content in the composite (~2.4%, see the Experimental part), with additional 0.2% being attributed to the further loss of the solvent and/or the products of its interaction with silica surface (thermal decomposition of ethoxysilyl groups). Thus, the TGA data confirms that the quantity of CA in the composite is about 25 mg/g.

The data on the inhibition of DPPH$^{\bullet}$ radicals by the CA solutions of various concentrations is given in Figure 2, and the data that allow determining the stoichiometry of this reaction is presented in Figure 3 indicating that $([CA]/[DPPH^{\bullet}])_{50}$ value, corresponding to the inhibition of 50% of the original amount of DPPH$^{\bullet}$ radicals, is about 0.11. Thus, the doubled $([CA]/[DPPH^{\bullet}])_{50}$ value is ~0.22, and the value reciprocal to 0.22 (~4.5) gives the stoichiometry of the reaction. This result is in agreement with literature data, indicating that each molecule of CA can reduce in average 4.5 molecules of DPPH$^{\bullet}$ [12].

The data on the inhibition of DPPH$^{\bullet}$ radicals by the CA+A300 composite is given in Figure 4; for comparison, curve *2* also shows the inhibition of DPPH$^{\bullet}$ radicals by the CA solution with the equivalent amount of antioxidant. In the case of the composite, scavenging of the radicals during the first hour of the reaction occurs much more slowly than in the case of the CA solution. This appears to be caused by gradual desorption of CA from silica surface. The final percentage of radicals inhibited by the composite and by the solution during two hours is ~57% and ~65%, respectively; thus, one can conclude that, during 2 hours, the main portion of antioxidant was released from the composite into solution and participated in the reaction.

Figure 5 presents similar data on the interaction of CA, both individual and included in the composite, with the Folin-Ciocalteu reagent in aqueous medium.

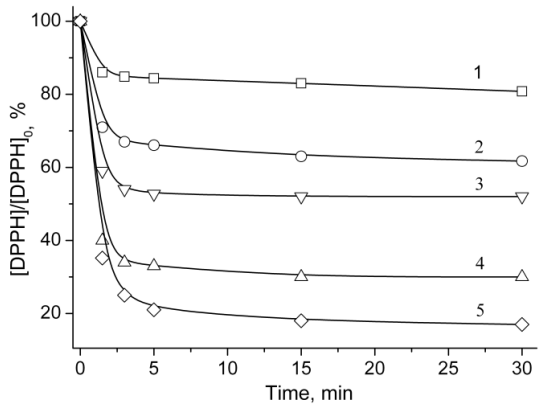


Figure 2. Inhibition of DPPH$^{\bullet}$ radicals in the reaction with CA solutions at a molar [CA]/[DPPH$^{\bullet}$] ratio of 0.05; 0.075; 0.10; 0.15; 0.30 (curves *1*-*5*, respectively).

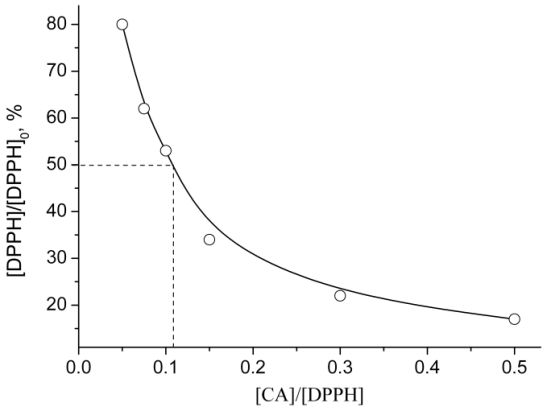


Figure 3. Percentage of residual DPPH$^{\bullet}$ radicals in the reaction mixture versus the [CA]/[DPPH$^{\bullet}$] molar ratio.

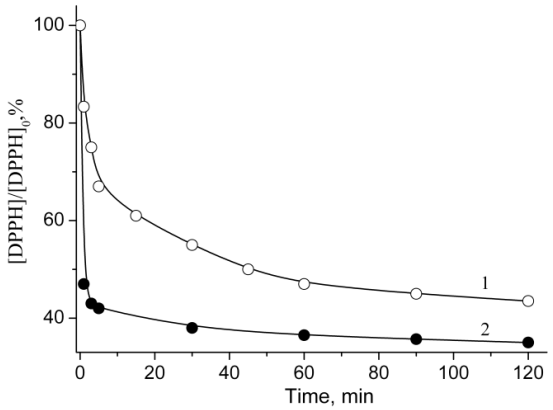


Figure 4. Inhibition of DPPH$^{\bullet}$ radicals in the reaction with the CA+A300 composite (curve *1*) and with an equivalent quantity of individual CA (curve *2*).

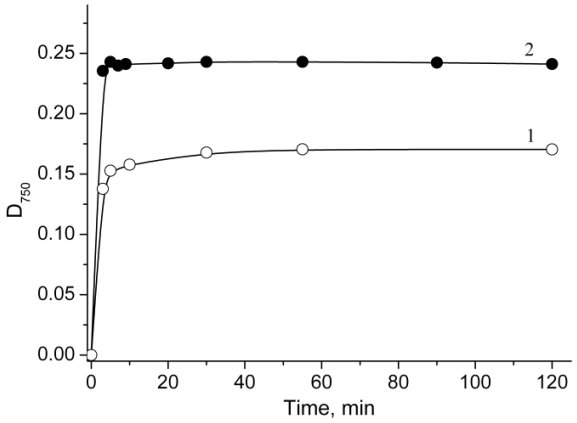


Figure 5. Change in D_{750} value during Folin-Ciocalteu test for the CA+A300 composite (curve *1*) and for an equivalent quantity of individual CA (curve *2*).

The data also shows that individual CA interacts with the reagent rapidly, with the changes in absorbance values at 750 nm during 2–120 min of the reaction being within 1÷2% of its average value. For the CA+A300 composite, during the same time interval an increase in D_{750} values by about 20% is observed, although only ~70% of the total quantity of antioxidant available in the composite appears to interact with the Folin-Ciocalteu reagent.

Figures 6 and 7 present the data on the release of CA into pure solvents and into the reaction mixtures containing DPPH$^{\bullet}$ radicals or Folin-Ciocalteu reagent. Curves *1* in the Figures 6 and 7 illustrate the release of CA from the composite into 70% ethanol and into pure water, respectively, with the composite-to-volume ratio being the same as in the DPPH$^{\bullet}$ and Folin-Ciocalteu tests. The data show quick, within 10-30 min, equilibration of CA concentration in the solutions, while the percentage of CA released into water and ethanol being about 55 and 60%, respectively.

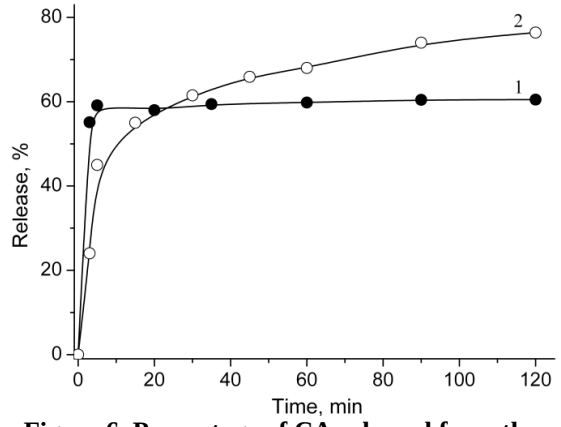


Figure 6. Percentage of CA released from the composite into 70 % ethanol (curve *1*) and into the reaction mixture of the DPPH$^{\bullet}$ test (curve *2*).

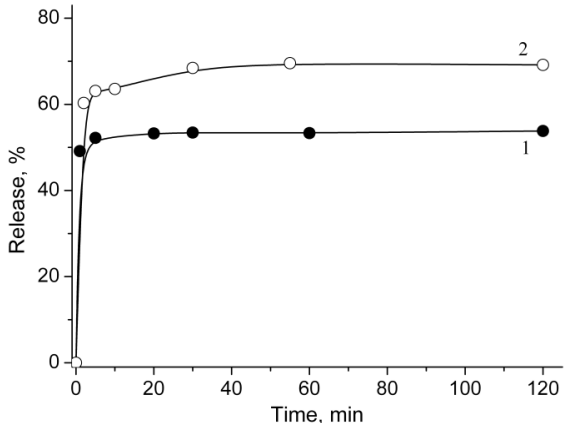


Figure 7. Percentage of CA released from the composite into pure water (curve *1*) and into the reaction mixture of the Folin-Ciocalteu test (curve *2*).

The release of only about a half of the total amount of CA is not the expected result. For example, in the case of a composite comprising A300 silica and another antioxidant - ascorbic acid - that is also weakly bound to silica, the release of ~90% of this antioxidant into aqueous media during 30 min was observed [4]. The lower release of CA into both solvents may be caused by the lower affinity of the CA for the solvents and its higher affinity for silica surface [11,17-19]. Thus, according to [4,11,17], the free energy of adsorption on silica surface for CA and ascorbic acid is about -40 and -30 kJ/mol, respectively, while the solubility of these antioxidants in water (ethanol) is ~1 (15) g/L for CA and 330 (27) g/L for ascorbic acid [18-20].

Curve *2* in Figure 6 gives the calculated values on the CA release into reaction mixture during the DPPH$^{\bullet}$ test. (This data were derived from the data on the inhibition of DPPH$^{\bullet}$ radicals by the CA+A300 composite, curve *1* in Figure 4, taking into account the stoichiometry of the reaction and the data on the CA content in the composite.) As one can see from Figure 6, the percentage of CA released from the composite into the mixture gradually increases during the entire time of observation and after 2 h reaches a value approximately 25% higher than the amount of CA released into 70% ethanol. The similar increase in the CA release was observed for water-based solutions, when the reaction mixture of Folin-Ciocalteu assay was used instead of pure water (Figure 7, curve *2*). (This data, were derived from Figure 5, curve *1* data, using the preliminary found dependence of the D_{750} value on the concentration of CA in Folin-Ciocalteu reaction mixture.) Thus, for the case of reaction mixtures, the data obtained shows a prolongation of CA desorption and a noticeable increase in the overall amount of CA released. It can be assumed that the consumption of CA molecules in the reactions with DPPH$^{\bullet}$ radicals or with Folin-Ciocalteu reagent leads to a decrease in CA concentration in the mixtures and, therefore, to the release of additional amount of antioxidant from the composite.

The CA solution and the CA+A300 composite were also tested in the reactions with NO$^{\bullet}$ and OH$^{\bullet}$ radicals and as antimicrobial agents against *Staphylococcus aureus* 209 bacterial strain. The results (Table 2) show that the CA solution and the CA+A300 composite suspension have a similar activity as NO$^{\bullet}$ radicals scavengers and as antimicrobial agents; on the other hand, the CA solution was more effective in inhibition of OH$^{\bullet}$ radicals.

Table 2

Antiradical and antimicrobial activity of CA solution and CA+A300 composite.

Sample	*$OH^{\bullet}$ radical scavenging activity, %*	*$NO^{\bullet}$ radical scavenging activity, %*	*Diameter of the zone of bacterial growth inhibition, mm*
A300	-	-	-
CA solution	9.8	33.8	12÷14
CA+A300 composite	0.1	34.6	12÷14

These results agree with the above data on the CA release from the composite into solutions/ reaction mixtures. Indeed, in the case of very reactive $OH^{\bullet}$ radicals, the rate of CA release is not sufficient to scavenge $OH^{\bullet}$ radicals. In the case of the antimicrobial test or in the reaction with $NO^{\bullet}$ radicals, the tests duration is long enough (several days and 2.5 hours, respectively) for the main part of CA to be released into the reaction medium (Table 2).

Conclusions

The CA+A300 composite comprising CA and fumed silica A300 was obtained using the sorptive modification of silica with CA solution under fluidized bed conditions; antioxidant and antimicrobial properties of the CA solution and the CA+A300 composite were compared.

The results have shown that CA itself and the CA+A300 composite are effective antioxidants and antimicrobial agents. Under chosen experimental conditions, the CA+A300 composite and the equivalent amount of individual CA possessed the same antimicrobial properties against *Staphylococcus aureus* 209 bacterial strain and the same $NO^{\bullet}$ radicals scavenging activity. On the other hand, the CA solution was more effective in the reaction with $OH^{\bullet}$ radicals and inhibited $DPPH^{\bullet}$ radicals faster than the CA+A300 composite. The distinctions in activity of the CA solution and the CA+A300 composite are consistent with the data on the CA release. Although only 55÷60% of CA was desorbed from the composite into water and 70% ethanol until equilibrium was reached (within 10–30 min), a more complete and gradual release of the compound was observed when the media for desorption were reaction mixtures used for the Folin-Ciocalteu or $DPPH^{\bullet}$ tests. So, the results of this study demonstrated the prolonged CA release and its action as antioxidant and antimicrobial agent in real systems where CA consumption occurs due to the interaction with oxidants and free radicals.

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