

Calcium-Induced Loss of Antibacterial Activity in Catechol-Based Phytochemicals: Implications for Biomaterial Design

Nora ABDELLAOUI

nora.abdellaoui@uca.fr

Laboratoire de Physique de Clermont Auvergne

Cedric BOSSARD

Laboratoire de Physique de Clermont Auvergne

Nicolas CHARBONNEL

Laboratoire Microorganismes Génome et Environnement

Roman AGUAY

Laboratoire de Physique de Clermont Auvergne

Edouard JALLOT

Laboratoire de Physique de Clermont Auvergne

Aela LE BRUN

Laboratoire de Physique de Clermont Auvergne

Philippe BOUCHARD

Laboratoire Microorganismes Génome et Environnement

Jonathan LAO

Laboratoire de Physique de Clermont Auvergne

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Abstract

Phytochemical compounds are increasingly considered as bioactive dopants in biomaterials intended for bone and dental applications, where calcium ions are naturally abundant. However, the impact of Ca^{2+} chelation on the biological activity of these molecules remains largely overlooked. In this study, we investigate how Ca^{2+} interactions affect the molecular stability and antibacterial activity of selected phytochemicals – some bearing catechol groups (e.g.: caffeic acid, chlorogenic acid) and others without (e.g. : magnolol, thymoquinone) – under Ca^{2+} concentrations representative of calcium-rich biomaterials. UV-Vis spectroscopy, HPLC, and MIC/MBC assays reveal that Ca^{2+} significantly impairs the antibacterial performance and alters the optical properties of catechol-containing polyphenols, while non-catechol compounds remain unaffected. These results are corroborated in glass-polymer hybrid matrices (SiO_2 –PCL and SiO_2 –CaO–PCL), where calcium content selectively affects catechol-bearing molecules. These findings underscore the necessity of accounting for calcium chelation when selecting antibacterial phytochemicals for calcium-rich biomaterial design.

1. Introduction

Phytochemical compounds (PC) are increasingly being used in biomaterial design as alternatives to antibiotics^[1, 2], offering multifunctional therapeutic properties^[3] beyond simple antimicrobial activity, including anti-inflammatory^[4], anticancer^[5], and osteogenic activities^[6]. Examples include microparticle systems for drug delivery^[7], as well as thin films and scaffolds functionalized with PC for tissue engineering applications^[8, 9], highlighting the versatility of polyphenols as building blocks or doping agents in functional material engineering. For example, Dziadek *et al.* incorporated sage-derived polyphenols into polymeric matrices and bioactive glass (BG) composites, achieving significant antibiofilm and anti-inflammatory properties alongside enhanced osteoblast differentiation^[10]. Moreover, polyphenols promote and accelerate the formation of the apatite layer on BG-containing films^[11] or BGs grafted polyphenols^[12, 13]. This enhanced bioactivity is likely attributable to the hydroxyl groups of polyphenols exposed at the composite surface, which can interact with calcium ions and act as nucleation sites for apatite crystallization^[14, 15].

These studies exemplify a growing trend in biomaterials science: exploiting the inherent bioactivity of plant-derived PC to create multifunctional therapeutic platforms. However, the chelating properties of PC present a critical and underexplored challenge for their integration into calcium-containing biomaterials^[8, 16, 17]. Catechol groups, often present in plant-derived PC, are potent chelating agents whose bioactivity is modified upon metal binding^[18]. Palierse *et al.* investigated the interaction in solution between PC and Ca^{2+} , demonstrating that calcium chelation reduces the antioxidant activity of chlorogenic and rosmarinic acids, as evidenced by a decrease in 2,2-Diphenyl-1-picrylhydrazyl (DPPH) scavenging activity in the presence of Ca^{2+} . This effect was more pronounced for rosmarinic acid, which the authors attributed to the catechol ring of this molecule. In a material synthesis study of bioactive glasses (BGs) loaded with PC and prepared by different techniques (sol-gel or melt-quenching), Dziadek

et al. showed that BGs exhibiting higher polyphenol-binding affinity – which varies depending on the synthesis route – reduced both the overall release level of PC and the burst effect ^[11]. Beyond BGs, calcium is a dominant constituent of widely used bone substitutes including calcium phosphate ceramics such as hydroxyapatite and tricalcium phosphate ^[19, 20], as well as an endogenous physiological cation^[21], making PC-Ca²⁺ interactions a highly relevant topic across a broad range of biomaterials and applications.

The present study investigates the influence of Ca²⁺ ions on an array of PC and derivatives, encompassing both catechol-bearing molecules – caffeic acid, chlorogenic acid, epigallocatechin gallate, and quercetin – and non-catechol compounds – honokiol, magnolol, thymol, and thymoquinone. This structural diversity allows us to dissect the specific contribution of catechol-mediated chelation to the observed effects. In the first part, we evaluate the impact of Ca²⁺ ions in solution on the antibacterial properties of these phytochemicals in controlled aqueous systems. Spectroscopic and chromatographic analyses are further conducted to probe their optical properties in the presence of Ca²⁺. Together, these approaches establish fundamental relationships between Ca²⁺ interaction and bioactivity. In the second part, we evaluate the integrity of PC when incorporated into a calcium-containing biomaterial, determining whether the interactions observed in solution also occur in solid matrices. This dual approach provides insights for designing PC-enriched biomaterials with preserved antibacterial activity.

2. Materials and methods

2.1. Bioactive molecules

Thymoquinone (TQ, 98% purity) was purchased from Sigma-Aldrich. Caffeic acid (CA, 99% purity), chlorogenic acid (CH, 99% purity), epigallocatechin gallate (EGCG, 98% purity), magnolol (MA, 99% purity), honokiol (HO, 99% purity), quercetin dihydrate (QU, 99% purity) and thymol (TH, 99% purity) were purchased from Extrasynthese (Lyon, France). All the compounds were obtained through synthesis.

2.2. Ultraviolet–visible spectrophotometry (UV–vis) and High-Performance Liquid Chromatography (HPLC)

Solutions containing 50 µM of bioactive molecules were prepared in absolute ethanol without or with CaCl₂ ($n_{Ca}/n_{molecule} = 100$). The absorbance of these solutions was measured in 1 cm quartz cells over the range of 800 to 200 nm using a Cary 50 UV-Vis spectrophotometer (Varian, USA) and HPLC. Analytical HPLC experiments were carried out on a Shimadzu Prominence LC system equipped with a degasser (DGU-20A5R), quaternary pumps (LC-20AR), an autosampler (SIL-20AHT), a photodiode array detector (DAD SPD-M20A). The Shimadzu LabSolutions software (Shimadzu, France) was used to acquire and analyze chromatograms and spectra. Gradient elution was performed using acetonitrile (A) and distilled water (B). For HO, MA, QU, TH, and TQ, the following gradient was applied: 0–5 min, 15–85% A; 5–15 min, 85% A. For CA and CH, the gradient was: 0–5 min, 15–85% B; 5–15 min, 85% B. The flow

rate is set to 1.0 mL/min and the sample volumes of 5 μ L were injected through a reversed-phase Zorbax® Eclipse Plus 3.5 μ m C18 column (150 $\times$ 4.6 mm; Agilent Technologies, France).

2.3. Solubility

The solubility of bioactive molecules was determined using the shake-flask method. Briefly, the studied molecule was added to an aqueous solution (2000 μ g/mL) of 10 mM tris(hydroxymethyl)aminomethane (TRIS) buffer at pH 7.4 and 37°C. After 24 h under vigorous orbital shaking, the supernatant was filtered, diluted in absolute ethanol and analysed by UV-Vis ($n = 3$). One sample was left for 48 h in order to make sure an equilibrium was reached. Concentrations were deduced from absorbance spectra using Beer Lambert's law. Calibration curves were prepared from known concentrations of molecules.

2.4. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC)

MIC is the minimal inhibitory concentration that impairs the growth of bacteria. MBC is the minimal bactericidal concentration that kills the bacteria. MIC and MBC were determined using the broth microdilution method in Mueller-Hinton (MH) medium. For TQ, MA, HO we also add 5% DMSO to help solubilize the molecules. Three relevant bacterial strains were considered: *Staphylococcus aureus* (API : 1307131 clinical strain isolated from osteoarticular infection), *Pseudomonas aeruginosa* (ATC 27853) and *Escherichia coli* (ATCC® 25922™). Isolated colonies of each strain were cultured overnight in LB broth at 37°C under agitation (100 rpm) then diluted to reach a bacterial of 10^6 CFU/mL. A starting PC concentration is considered at 2048 μ g·mL⁻¹ followed by twofold serial dilution that give the following range dilution 2048, 1024, 512, 256, 128, 64, 32 to 8 μ g/mL. To study the influence of Ca²⁺ we add in the first step (where [PC] = 2048 μ g/mL) CaCl₂ solution to reach a concentration of [Ca²⁺] = 2.56 mg/mL. When twofold serial dilutions were performed on this mixture, both PC and Ca²⁺ concentrations decreased proportionally across the dilution range, maintaining a constant Ca²⁺/PC molar ratio throughout. Under these conditions, Ca²⁺ was present in a 4.7- to 11-fold molar excess relative to the PC, depending on its molar mass, consistent with the Ca²⁺ concentrations encountered during biomaterial synthesis. All experiments were performed in triplicate ($n = 3$).

2.5. Integrity of the molecules after synthesis

PC were incorporated into glass-polymer hybrids through a sol-gel synthesis that was described in a previous work^[6]. Two hybrid compositions were prepared: one with calcium (SiO₂-CaO-PCL) and one without calcium (SiO₂-PCL). In order to check the integrity of PC after synthesis, PC were extracted from hybrids by immersion in ethanol (10 mg/mL) for 24 h in orbital stirring at room temperature. Then, the extracts were analysed by UV-Vis spectrophotometry and the spectra were compared to those of PC alone.

3. Results and discussion

Table 1

MIC/MBC of CA, CH, EG, HO, MA, QU, TH, TQ and solubility measurements in distilled water for each phytochemical compounds. The * is for MIC or MBC > 1024 µg/mL.

Compound (solubility at 37°C, pH 7.4)	Bacteria	Compound		Compound + Ca ²⁺		MIC of the compound in the literature (µg/mL)
		MIC (µg/mL)	MBC (µg/mL)	MIC (µg/mL)	MBC (µg/mL)	
Caffeic acid (CA) (> 2000 µg/mL)	E. coli	∞	∞	∞	∞	N/A
	P. aeruginosa	∞	∞	∞	∞	N/A
	S. aureus	256	∞	∞	∞	256–1024 [22]
Chlorogenic acid (CH) (> 2000 µg/mL)	E. coli	∞	∞	∞	∞	N/A
	P. aeruginosa	∞	∞	∞	∞	N/A
	S. aureus	256	1024	∞	∞	500 ^[23] , 2500– 5000 ^[24]
Epigallocatechin gallate (EGCG) (> 2000 µg/mL)	E. coli	∞	∞	∞	∞	400 ^[25] , ≥ 800 ^[26]
	P. aeruginosa	256	256	1024	1024	200–400 ^[25] , 400– 800 ^[26]
	S. aureus	64	64	∞	∞	50–100 [26]
Honokiol (HO) (88 ± 3 µg/mL)	E. coli	∞	∞	∞	∞	> 100 ^[4] ,
	P. aeruginosa	∞	∞	∞	∞	> 100 ^[27]
	S. aureus	16	16	16	16	10–90 ^[4] , 50 ^[27]
Magnolol (MA) (29 ± 1 µg/mL)	E. coli	∞	∞	∞	∞	> 100 ^[4]
	P. aeruginosa	∞	∞	∞	∞	> 100 ^[27]
	S. aureus	256	256	128	128	20–90 ^[4] , 38 ^[27]

Quercetine (QU)	E. coli	∞	∞	∞	∞	
	P. aeruginosa	∞	∞	∞	∞	
	S. aureus	∞	∞	∞	∞	512–1024 ^[28] , 260 ^[29]
Thymol (TH) (1657 ± 53 µg/mL)	E. coli	128	128	512	512	400 ^[30] , 125 ^[31]
	P. aeruginosa	1024	∞	∞	∞	400 ^[30] , > 1000 ^[32]
	S. aureus	128	128	128	128	200 ^[30] , 250 ^[31]
Thymoquinone (TQ) (1055 ± 37 µg/mL)	E. coli	512	512	1024	1024	> 512 ^[33]
	P. aeruginosa	∞	∞	1024	∞	> 512 ^[33]
	S. aureus	8	128	8	128	8 ^[33]

Table 1 reports MIC, MBC and solubility for several PC with or without the presence of Ca²⁺.

Taken together, MIC and MBC results reveal an inhibition of *S. aureus* proliferation at lower concentrations of CA (from 256 µg/mL to over 1024 µg/mL), CH (from 256 µg/mL to 1024 µg/mL) and TQ (from 8 µg/mL to 128 µg/mL). Otherwise, the compounds were bactericidal with no inhibitory effect involved beforehand. As observed in literature, few MIC were found against *E. coli* or *P. aeruginosa*. MIC was found for all compounds (except quercetin) against *S. aureus*. For quercetin, no antimicrobial activity was observed below 1024 µg/mL on either bacterial strain. This contrasts with studies from Kyaw et al. who reported a MIC of 512 to 1024 µg/mL against *S. aureus* (methicillin resistant strains)^[28] and Amin et al. who reported a MIC of 260 µg/mL against *S. aureus* (strain ATCC 43300)^[29]. For the other molecules, obtained MIC are quite consistent with the literature, the largest discrepancy being with magnolol (256 µg/mL against *S. aureus* compared to 20–90 µg/mL according to Chiu et al.^[4]).

When adding CaCl₂, the antimicrobial potential of the compounds either declined or remained unchanged. The MIC and MBC of magnolol improved from 256 µg/mL to 128 µg/mL against *S. aureus*, however these concentrations are not considered significantly different since a single dilution sets them apart. Likewise, HO, TH and TQ kept similar antimicrobial properties in the presence of Ca²⁺ ions, with the exception of thymol against *E. coli* for which the MIC and MBC increased from 128 µg/mL to 512 µg/mL. CA, CH and EGCG (highlighted in grey in Table 1) suffered a heavy loss of their antimicrobial properties, with MIC and MBC values all ≥ 1024 µg·mL⁻¹. This decrease in antibacterial activity concurs with a change in their UV-VIS and/or HPLC-UV spectrum in the presence of Ca²⁺ ions (Fig. 1).

UV-VIS analysis (Fig. 1) showed no spectral modification for non-catechol compounds (HO, MA, TQ) upon Ca^{2+} exposure, consistent with the absence of chelating moieties, and HPLC retention times remained unchanged (Fig. 2). For CA and CH, no UV-VIS spectral changes were detected, however HPLC analysis revealed shifts in retention times upon Ca^{2+} exposure (Fig. 2). EGCG and QU exhibited new absorbance shoulders at 325 nm and 450 nm respectively (Fig. 1) and HPLC retention time shifts (Fig. 2). The minor spectroscopic changes observed for PC with catechol groups suggest that Ca^{2+} interaction does not alter the molecular backbone but rather affects the electronic structure of the catechol moiety, consistent with the formation of a coordination complex. All polyphenols exhibiting spectroscopic modifications upon Ca^{2+} exposure also showed a decrease in antibacterial activity (Table 1).

The decreasing of antibacterial activity upon Ca^{2+} complexation is likely due to multiple interconnected mechanisms. First, as evidenced by UV-Vis and HPLC analyses, Ca^{2+} coordinates at the catechol moiety, occupying the hydroxyl groups that are central to the antibacterial mechanism of PC. Since the antibacterial activity of flavonoids relies on their ability to form complexes with bacterial proteins through hydrogen bonding, hydrophobic effects, and covalent bond formation, such prior occupation of these sites directly competes with protein-binding interactions, thereby undermining the primary molecular basis for antimicrobial action^[34]. Second, complexation may reduce the generation of reactive oxygen species (ROS)—a key antimicrobial mechanism of PC—thereby decreasing oxidative damage to bacterial cell walls, proteins, lipids, and DNA^[35]. Collectively, these factors compromise the capacity of PC (with catechol) to disrupt bacterial cell walls, damage intracellular organelles, and ultimately cause cell death^[2]. Our results demonstrate that Ca^{2+} cation can significantly impair PC bioactivity, a result with direct implications for PC-functionalized bone biomaterials.

Hybrid matrices were synthesized by incorporating 1 wt% PC with (CA, CH) or without catechol groups (MA, HO) into glass-polycaprolactone composites with two compositions: SiO_2 –CaO–PCL (calcium-containing) and SiO_2 –PCL (calcium-free). Catechol-containing PC showed marked sensitivity to calcium presence. Indeed, extracts from calcium-containing matrices (SiO_2 –CaO–PCL) show no detectable CA and CH signatures after extraction (Fig. 3a,b), suggesting that both polyphenols are retained within the material rather than released. This is likely attributable to chelation of their catechol moieties by Ca^{2+} ions from the bioactive glass matrix. Given that the release of PC from the matrix and their binding conditions are key determinants of bioavailability and biological activity^[34], the retention of PC within the matrix through Ca^{2+} chelation could therefore limit their antibacterial potential, which remains to be assessed in future release studies. In contrast, extracts from calcium-free matrices (SiO_2 –PCL) exhibited absorption spectra identical to those of pure CA and CH, with no color changes during synthesis, confirming PC released is not affected by the materials. For MA and HO, the characteristic absorption band at 290 nm was unchanged regardless of calcium presence (Fig. 3c,d), consistent with its preserved antibacterial activity in solution experiments. MA and HO were readily released from both matrix types, consistent with the absence of Ca^{2+} chelation.

Previous studies corroborate our observations: Chirdon *et al.* reported strong adsorption of catechol and pyrogallol on hydroxyapatite^[36], Palierse *et al.* attributed baicalein binding to hydroxyapatite to pyrogallol-calcium complexation with concomitant loss of antimicrobial efficacy^[18], and Dziadek *et al.* showed strong binding of rosmarinic acid (containing catechol groups) to CaO–SiO₂–P₂O₅ bioactive glass, which reduced both release kinetics and antioxidant activity^[10]. PC affinity with materials not only reduces their release^[10, 37], but may also impede their antimicrobial activity as observed in the present study with calcium chelates. For instance, the aforementioned baicalein-loaded hydroxyapatite showed very little to no effect against *S. aureus*^[37]. Reduced bioavailability resulting from binding to calcium-containing surfaces^[38] limits the concentration of free, active PC molecules available to exert antibacterial effects.

Our findings demonstrate that not all PC are suitable for incorporation into calcium-rich scaffolds as delivery agents, since catechol-containing compounds may be retained within the matrix through Ca²⁺ chelation. However, such immobilization does not necessarily preclude biological activity, as surface-bound PC may still exert local effects upon direct contact with bacteria^[39–41]. More broadly, Ca²⁺–PC interactions should not be considered inherently detrimental, as the biological outcome of metal–PC complexation is highly context-dependent. Depending on the specific metal ion, PC structure, and targeted bioactivity, complexation has been shown to enhance antioxidant activity^[42, 43], improve the stability of encapsulated compounds^[44], or strengthen interfacial interactions in assembled materials^[45]. Indeed, flavonoids forming chelate complexes with other metal ions (Ni²⁺, Co²⁺, Cu²⁺) have been shown to exhibit enhanced biological activity compared to their free form^[46, 47].

This highlights the importance of careful molecule selection and thorough investigation of their interaction with the matrix when designing drug delivery systems. In this light, our results suggest that Ca²⁺ chelation of catechol may immobilize PC within the matrix, compromising their release and therefore their bioavailability at the target. It should be noted that the Ca²⁺ concentrations used in this study represent a simplified model system and may differ from local ion concentrations in physiological or biomaterial microenvironments. Additionally, the study focuses on antibacterial activity, while other biofunctions of PC, such as antioxidant or osteogenic effects, may be differently affected by metal complexation.

4. Conclusion

This study demonstrates that Ca²⁺ ions strongly impair the antibacterial activity of catechol-containing PC, likely through chelation-induced structural modifications as evidenced by UV–Vis and HPLC analyses. CA, CH, and ECGC exhibited a marked loss of antimicrobial efficacy in the presence of Ca²⁺, whereas non-catechol compounds (HO, MA, TH, TQ) retained their activity and their spectroscopic properties upon Ca²⁺ exposure. Incorporation of PC into calcium-containing hybrid matrices (SiO₂–CaO–PCL) resulted in chemical adsorption of catechol-based phytochemicals, whereas calcium-free matrices (SiO₂–PCL) show release of the molecule when the material is in solution.

These results provide a framework for the selection of polyphenols in calcium-containing biomaterials, suggesting that non-catechol PC represent more suitable candidates for direct incorporation when simple release-based drug delivery is expected. The strong affinity of catechol-based PC for Ca^{2+} , however, may be deliberately exploited to design surface-active systems where immobilized PC exert their bioactivity through direct contact with the surrounding biological environment.

Declarations

Conflict of interest

The authors declare no competing financial interest.

Author Contribution

N.A. and C.B. conceptualized the study, designed the methodology, curated the data and conducted the formal analysis of the data. N.A. and C.B. synthesized and characterized the glass-polymer hybrid materials and prepared the calcium–phytochemical solutions. A.L., N.A. and C.B. performed the spectroscopic and chromatographic experiments. N.C., R.A. and P.B. carried out the microbiological assays and interpreted the results. N.A. wrote the original draft. J.L. and E.J. acquired the funding and supervised the project. All authors reviewed, edited and approved the final manuscript.

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Figures

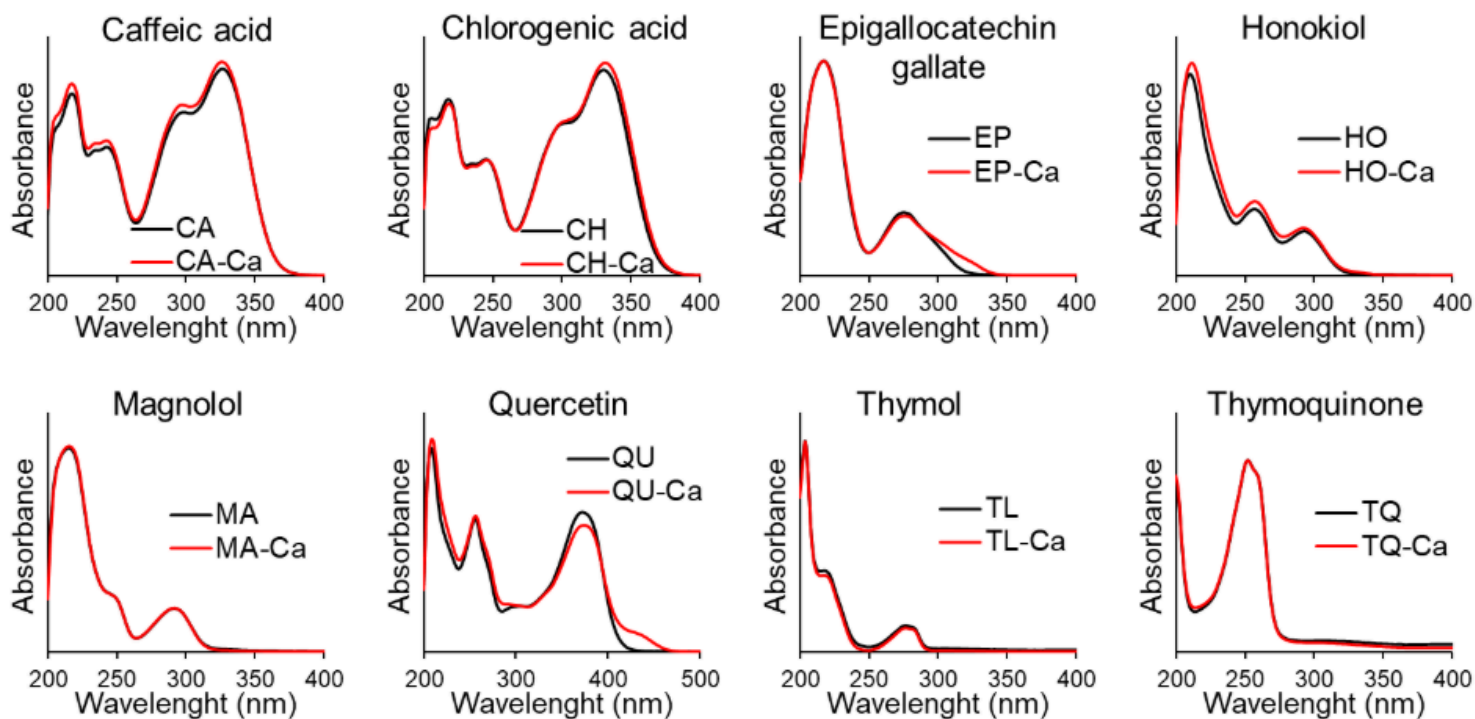


Figure 1

UV-Vis spectra of the molecule alone and in solution with Ca^{2+} .

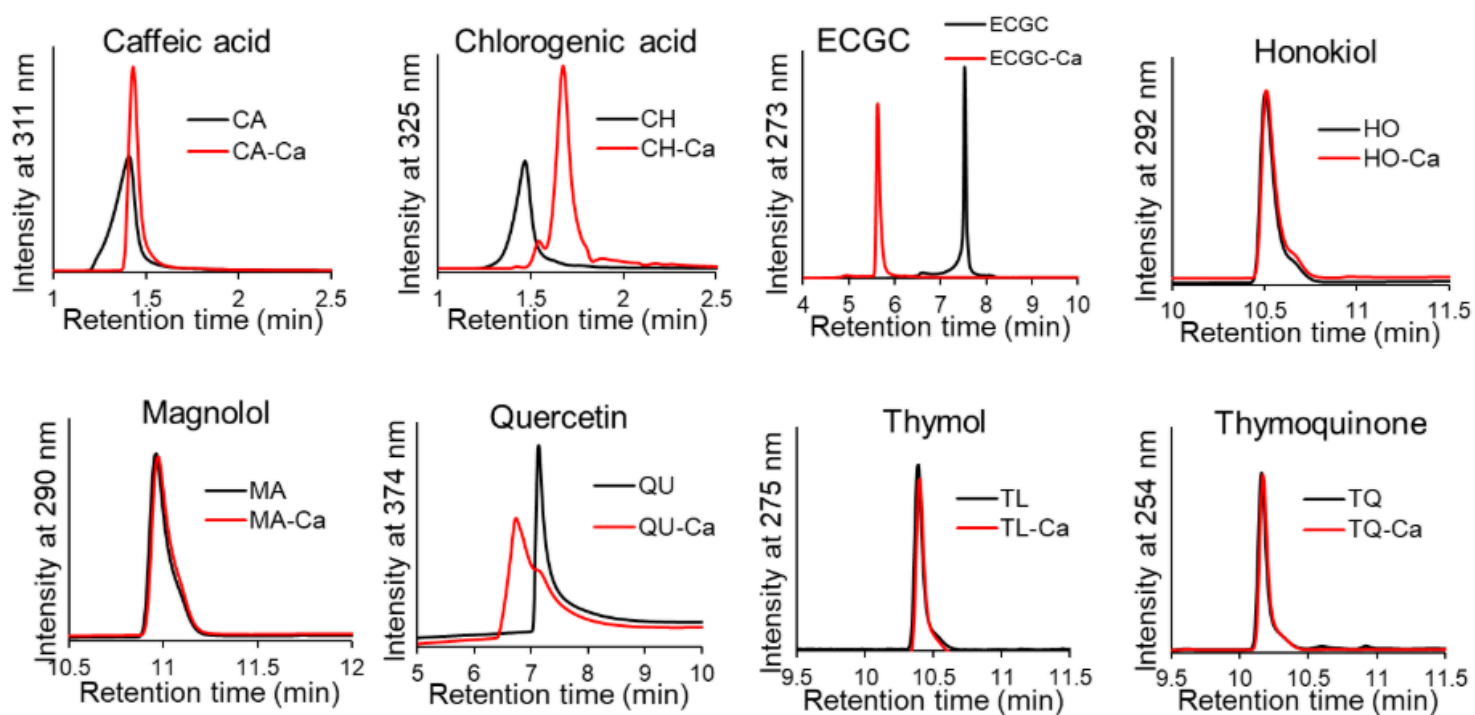


Figure 2

HPLC-UV-VIS retention time of the molecule alone and in solution with Ca^{2+} .

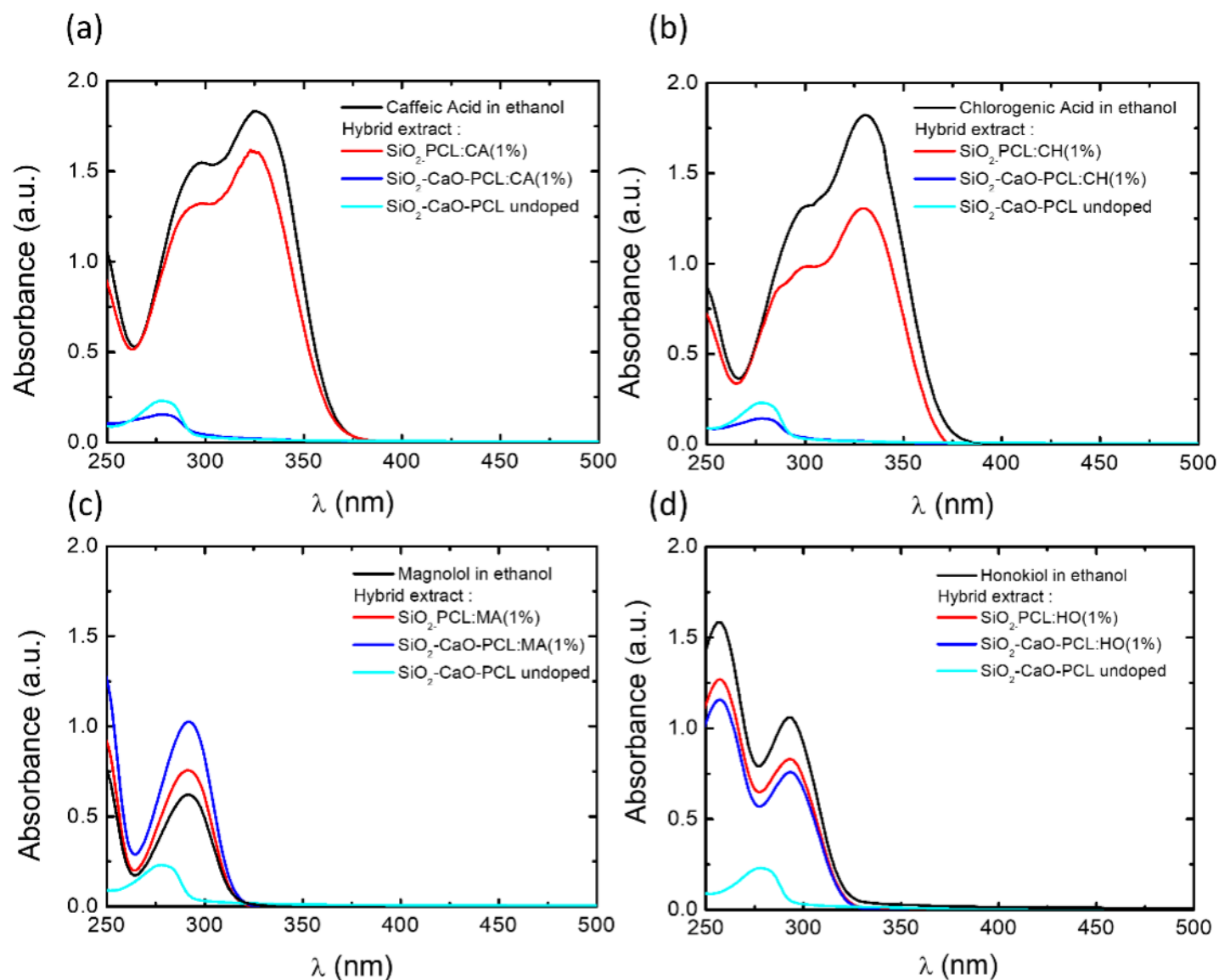


Figure 3

UV-Vis spectra of pure PC molecules diluted in ethanol and the release of caffeic acid (a), chlorogenic acid (b) magnolol (c) and honokiol (d) included in the hybrid materials with and without Ca.