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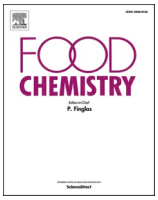

Rapid determination of phenolic composition in chamomile (*Matricaria recutita L.*) using surface-enhanced Raman spectroscopy

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ABSTRACT

Flavonoids and hydroxycinnamic acids are the main responsible of the antioxidant activity of chamomile (*Matricaria recutita L.*). Traditional methods for the analysis of the phenolic content in vegetables often suffer from limitations such as being expensive, time-consuming, and complex. In this study, we propose, for the first time, the use of surface-enhanced Raman spectroscopy (SERS) for the rapid determination of the main components of the polyphenolic fraction in chamomile. Results demonstrate that SERS can serve as an alternative or complementary technique to main analytical strategies for qualitative and quantitative determination of polyphenol compounds in plant extracts. The method can be proposed for quasi real-time analysis of herbal teas and infusions, facilitating rapid screening of their main antioxidant components.

1. Introduction

Chamomile (*Matricaria recutita* L.) is a medicinal plant featuring analgesic, anti-allergic, anti-spasmodic, antibacterial, anti-inflammatory and sedative properties. Its essential oil, that is rich in terpenoids, is among those most commonly used for anti-inflammatory and anti-stress purposes (Akram et al., 2024). Recently, much attention has been paid also to the phenolic fraction of chamomile extracts, containing several bioactive compounds belonging to the phenylpropanoid class (Ekiert et al., 2022; Mailänder et al., 2022; Sentkowska et al., 2016). In particular, the main responsible of the antioxidant activity of chamomile are flavonoids and hydroxycinnamic acids, which also constitute the dominant fraction of chamomile extracts (Foss et al., 2022; Liu et al., 2023).

Flavonoids are secondary metabolites widely present in the plant kingdom, representing a large class of phenolic compounds comprising more than 6000 different molecules. They are able to exert various beneficial biological activities, which justify the importance they have assumed for human health. Among the properties attributed to the flavonoids that arouse greater interest are their antioxidant (Panche et al., 2016) and anti-inflammatory actions (Comalada et al., 2005; Maleki et al., 2019). In the field of pharmaceutical research, the interest is focused on the potential anticancer properties (Kim & Choi, 2013) and the preventive / beneficial role that these compounds are able to exert in the presence of different disorders (Hasnat et al., 2024) such as Alzheimer's disease, atherosclerosis, etc. (Castañeda-Ovando et al., 2009; Lee et al., 2009; Panche et al., 2016). The most common hydroxycinnamic acids present in fruits, grains, and dietary supplements are caffeic acid and chlorogenic acid. Specifically, caffeic acid and its esters are well known for their several medicinal and pharmacological properties such as anti-Alzheimer, antidiabetic, antitumor, anti-inflammatory, and antihypertension (Agunloye & Oboh, 2018).

Parallel to the importance that phenylpropanoid compounds hold in the pharmaceutical, nutraceutical industry, there is growing interest in exploring new analytical techniques for their determination (Ignat et al., 2013; Khoddami et al., 2013). Different traditional methods like UV/Vis absorption spectroscopy and separation techniques like thin-layer chromatography (TLC) were used for their determination (Birk et al., 2005; Patle et al., 2020; Yılmazer Keskin et al., 2024). Recent scientific literature is instead mainly focused on qualitative and quantitative determination of these compounds by the use of capillary electrophoresis (CE) and high-performance liquid chromatography (HPLC) coupled with mass spectrometry (LC-MS) or nuclear magnetic resonance (LC-NMR) (Andrade et al., 2002; Yan et al., 2015; Yang et al., 2023).

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Although the above methods can provide a sensitive and effective analysis, often they suffer from some limitations such as being expensive, time-consuming and complex. In the last decades, great efforts were made in the development of simple, accurate and fast analytical techniques, which require no or minimal sample preparation. Examples include the use of NIR spectral data often coupled with chemometrics to offer an estimate of the total phenolic content or of specific phenolic compounds (Arslan et al., 2018; He et al., 2018; Wang et al., 2015; C. Zhang et al., 2020). Recently, special attention is given to the use of Raman spectroscopy techniques as an effective optical tool for the analysis of agri-foods due to its rapid, low-cost, informative and non-destructive nature (Wang et al., 2021). Standard Raman-based works initially focused on characterizing isolated flavonoids especially in relation to their metal chelation radical scavenging properties (Cornard et al., 2001; Cornard & Merlin, 2002; Torreggiani et al., 2005) and then on detecting flavonoids in complex matrices (Baranska et al., 2006; Gamsjaeger et al., 2011). In 2006, Jurasekova et al. proposed for the first time the use of surface-enhanced Raman spectroscopy (SERS) in the characterization of some flavonoids representative of the flavone and flavonol families (Jurasekova et al., 2006). In spite of the considerable interest in these polyphenolic compounds, the efficacy of SERS in their determination (Corredor et al., 2009; Dendisová et al., 2019; Jurasekova et al., 2014; Ricci et al., 2023), especially when applied to real samples (Li et al., 2021), has been scarcely investigated so far.

In this paper we explore the possibility to use SERS for determination of the main phenylpropanoids in chamomile including apigenin and quercetin derivatives as well as chlorogenic and ferulic acids. These are among the most abundant flavonoid and hydroxycinnamic compounds in chamomile, as well as represent the main antioxidant fraction among the phenolic species in this plant (Catani et al., 2021; European Medicines Agency, 2015; Gupta et al., 2010). Particularly, we propose a rapid and sensitive SERS assay, which takes advantage of a drop-on method that we previously developed (Banchelli et al., 2019) and that was adapted for the analysis of nanogram amounts of compounds. This method is applied to various commercial chamomile infusions to determine the composition of the main polyphenols present.

2. Materials and methods

2.1. Chemicals

Flavonoid and hydroxycinnamic compounds were purchased from Extrasynthèse (Genay, France). Standard solutions of phenolic compounds at 1×10^{-5} M were obtained by aqueous dilution of concentrated ethanolic stock solutions. Silver nanowires (AgNWs) PVP-stabilized suspension in isopropanol was home-made produced according to Amicucci et al. (2021) (**Fig. S1**). All solvents used were HPLC grade.

2.2. Methanolic extracts and tea infusions of chamomile

Dry chamomile whole flowers (containing both white ligulate and yellow tubular flowers) obtained from a local herbal medicine store were ground and 2 g of them were weighed into a 100 mL volumetric flask. 60 mL of methanol were then added to the flask, which was then shacked for 30 min in a Stuart rotator SB3 apparatus. The mixture was left to stand for 5 days in the dark and afterwards it was adjusted to 100 mL with methanol and filtered (0.20 μm PTFE) for the subsequent analyses (Tsivelika et al., 2021).

Chamomile infusion samples were prepared from three different commercially available chamomile tea products. Briefly, each preparation for infusion was steeped in 100 mL of distilled water at 90 °C for 10 min according to Harbourne et al. (2009). After heating, the extract was cooled rapidly and filtered (0.20 μm PTFE) before analysis.

2.3. HPLC analysis of phenolic compounds

The analysis of phenolic compounds in chamomile extracts was conducted on both methanolic extracts and aqueous infusions. Aliquots of methanolic extracts were subjected to defatting using n-hexane to remove chlorophylls and carotenoids before analysis. Qualitative and quantitative analyses were conducted using HPLC-DAD-Q-ToF. The HPLC-DAD system consisted of an Agilent 1260 Series (Agilent, Santa Clara, CA, USA) LC system equipped with a binary pump, an online degasser, an auto plate-sampler, a thermostatically controlled column compartment and a diode array detector (DAD). The chromatographic separation was carried out on a column Poroshell 120 EC-C18 column (100 × 2.1 mm, 2.7 mm; Agilent, CA, USA), preceded by a C18 guard column (4.00 × 2.00 mm; Agilent, CA, USA). The column was maintained at 40 °C and the injection volume was 1 μL. The following gradient of solvents was applied: 0–1 min (97 % A), 1–46 min (97–60 % A), 46–72 min (60–3 % A), over a 72-min run and a flow of 0.3 mL min^{-1}. The composition was then returned to initial conditions and maintained 15 min for equilibration. The UV–vis spectra were recorded between 200 and 600 nm.

Mass spectrometry profiling was performed using an Agilent 6530 Q-TOF mass spectrometer (Agilent, Santa Clara, CA, USA) equipped with an electrospray ionization (ESI) interface, and was operated in negative ion mode with the following parameters: capillary voltage, 4000 V; fragmentor, 180 V; skimmer, 60 V; OCT 1 RF Vpp, 750 V; pressure of nebulizer, 20 psi; drying gas temperature, 325 °C; sheath gas temperature, 400 °C. Nitrogen was used as sheath and drying gas at a flow rate of 10.0 and 12.0 L/min, respectively. Data were collected in centroid mode and the mass range was set at *m/z* 50–1100 using the extended dynamic range. The accurate-mass capability of the TOF analyzer was maintained by continuously spraying an external calibration solution (Agilent calibration solution A) to recalibrate the mass axis, ensuring mass accuracy and reproducibility throughout the chromatographic run. Agilent MassHunter Workstation Acquisition Software Version B.05.01 and Qualitative Analysis Software Version B.07.00 were utilized for system control, data acquisition, and data processing.

Quantitative analyses were performed on the basis of DAD signal using authentic standards for the calibration curves: chlorogenic acid, ferulic acid, coumaric acid, quercetagetin 7-O-glucoside, quercetin 3-O-glucoside, apigenin 7-O-glucoside, luteolin 7-O-glucoside (all from Sigma–Aldrich®–Merck®KGaA, Darmstadt, Germany and Extrasynthese, Genay, France). If a commercial standard was not available, the quantification was performed using the calibration curve of standards from the same phenolic class. The linearity of the curves was determined by the coefficient of determination (R^2), being higher than 0.99 for all standards.

2.4. Fabrication of SERS substrates

SERS substrates were fabricated by microfiltration under pressure of an AgNWs / isopropyl alcohol suspension as previously reported with minor modifications (Banchelli et al., 2019; Barucci et al., 2021). Specifically, an amount of 2 mL of solution was passed through the PTFE membrane by using an Amicon Stirred cell Model 8003, 3 mL (Merk Millipore, Milan, Italy) cell. The as-fabricated substrates were finally patterned in the form of dot arrays by using a laser engraver (NEJE, $\lambda =$ 405 nm, max power 3 W, spatial resolution 0.45 μm) to form 10 spots of 1.3 mm diameter (**Fig. S2**) on the sample plane.

2.5. SERS measurements

SERS analysis was performed using a micro-Raman spectrometer (Horiba LabRam HR-Evo, France) working at 785 nm to reduce the risk of fluorescence interference (D. Li et al., 2018; McNay et al., 2011; Rao et al., 2018; Zhang et al., 2019), a 600 grooves/mm grating, a 50× objective with 0.25 NA (7 μm waist), a laser power at the sample of 0.5

mW. SERS spectra were obtained by pouring 3 μL of each compound onto a single spot of the SERS substrate and let to dry. SERS spectra represent an average of 20 spectra (5 s acquisition time, 1 accumulation). Spectra were background subtracted, cropped in the 450–1740 cm^{-1} range, and baselined by arPLS in MatLab (MathWorks, USA). Fresh samples from methanolic extracts were preliminarily 1:100 diluted in water and immediately analyzed by SERS. A maximum relative standard deviation (RSD) in the SERS signal (peak ~1480 cm^{-1}) not exceeding 10 % was observed. The correlation model of SERS spectra was built under MatLab.

3. Results and discussion

3.1. HPLC analysis

An HPLC analysis was initially conducted on dry chamomile flowers to determine the polyphenolic composition qualitatively and quantitatively. Our focus was on compounds previously documented in the literature and recognized for their prevalence in organic chamomile extracts (Mulinacci et al., 2000; Nováková et al., 2010). These included hydroxycinnamic acids (p-coumaric, ferulic and caffeic acid derivatives), flavones (apigenin, luteolin and their glucosides), and flavonols (quercetin and quercetagetin and their glucosides).

The HPLC chromatograms of the extract exhibited approximately eleven main peaks (Fig. 1). We identified the polyphenolic compounds by UV/MS results and, for some compounds, by comparing the retention times of peaks with those of authentic standards, as summarized in Table 1.

Ferulic acid derivatives, namely 1-O-glucoside and 7-O-glucoside, were the predominant phenolic acid species (2.66 mg/g DW), followed by chlorogenic acid derivatives (i.e. chlorogenic acid and dicaffeoylquinic acid derivative, 1.32 mg/g DW) and p-coumaroyl derivatives (i.e. tetra-p-coumaroyl spermine, 0.42 mg/g DW). Quercetagetin glycosides (comprising quercetagetin 7-O-glucoside and patuletin 7-O-glucoside represented the highest flavonoid fraction (2.71 mg/g DW) followed by apigenin 7-O-glucoside, luteolin 7-O-rutinoside and quercetin 3-O-hexoside (2.03 mg/g DW, 1.50 mg/g DW and 1.43 mg/g DW, respectively). Total concentration as well as composition and concentration of individual compounds are consistent with previous findings (Nováková et al., 2010; Temerdashev et al., 2023), which support the prevalence of chlorogenic and ferulic acid derivatives and of quercetin derivatives and apigenin glucosides in alcoholic extracts of chamomile flowers. All these compounds mostly dominate the phenolic fraction of chamomile extracts (Catani et al., 2021; Haghi et al., 2014). Apart from apigenin, all of them contain a catechol moiety (carrying the orto-hydroxy substitution 3OH,4OH of phenolic acids and 3'OH,4'OH of flavonoids), which plays a fundamental role in plants as both a scavenger of reactive oxygen species and a chelator of transition metal ions (Agati et al., 2007; Agati & Tattini, 2010; Wang et al., 2018).

Table 1
List of phenolic compounds identified in methanolic and aqueous extracts of Matricaria recutitia L. flowers (value ±SD, $n = 3$).

	t_R (min)	Compound	$m/z(-)$ negative mode	Amount (mg/g DW)
1	23.58	chlorogenic acid	191.0, 353,09 $[M-H]^-$, 707,2 $[2\ M-H]^-$	0.735 ± 0.0391
2	26.26	ferulic acid 1-O-glucoside	193.1, 355.1$[M-H]^-$, 711.2 $[2\ M-H]^-$	1.1853 ± 0.0562
3	29.04	quercetagetin 7-O-glucoside	479.1 $[M-H]^-$	1.3918 ± 0.0790
4	31.08	ferulic acid 7-O-glucoside	193.1, 355.1$[M-H]^-$, 711.2 $[2\ M-H]^-$	1.4756 ± 0.0756
5	32.90	quercetin 3-O-hexoside	463.1 $[M-H]^-$	1.4304 ± 0.0719
6	33.22	patuletin 7-O-glucoside	493.1 $[M-H]^-$	1.3156 ± 0.0710
7	33.79	dicaffeoylquinic acid derivative	191.1, 515.1 $[M-H]^-$	0.5883 ± 0.0345
8	36.06	apigenin 7-O-glucoside	269.1, 431.1 $[M-H]^-$	1.4190 ± 0.0891
9	39.79	apigenin 7-acetylhexoside	473.1 $[M-H]^-$	0.6085 ± 0.0198
10	51.07	luteolin 7-O-rutinoside	593.4 $[M-H]^-$	1.4954 ± 0.0486
11	67.69	tetra-p-coumaroyl spermine	785.3 $[M-H]^-$	0.4185 ± 0.0323

3.2. SERS characterization

A SERS spectrum of chamomile extract is reported in Fig. 2 (blue line). Our choice of SERS substrate was about a nanosilver-spotted PTFE membrane previously showing effective signal enhancement (Banchelli et al., 2023; D'Andrea et al., 2023) and supporting the deposition and analysis of microliter drops of analyte corresponding to the amount of nanograms or subnanograms of phenolic compounds in the mixture (see **Fig. S3** for further details on the detection sensitivity). These substrates

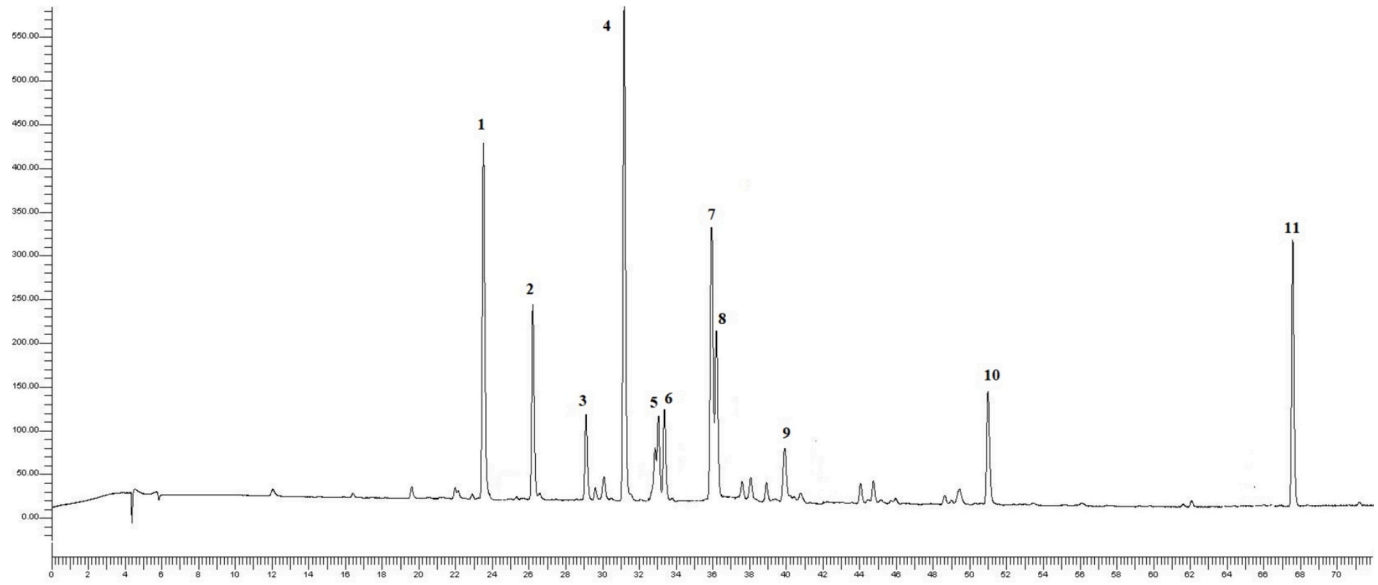

Fig. 1. Representative HPLC-DAD chromatogram at 320 nm of *Matricaria recutitia* L. flowers methanolic extract. Peaks identification is reported in Table 1.

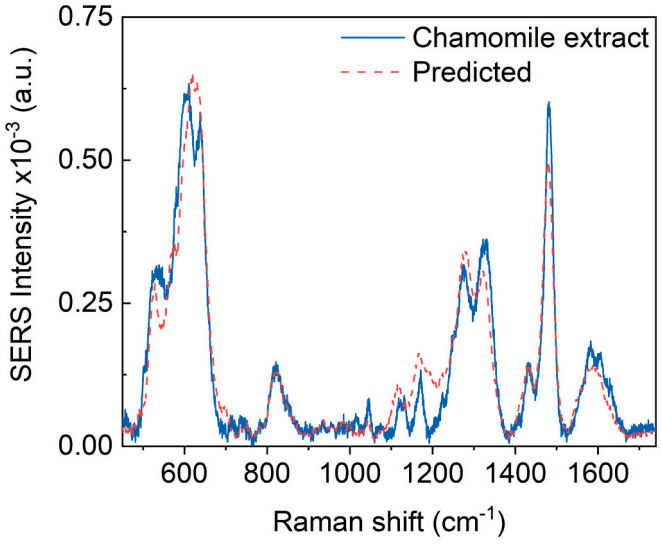

Fig. 2. SERS spectrum of a methanolic extract of *Matricaria recutitia* L. flowers (blue line). Predicted spectrum by the LS model (red dashed line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

represent a convenient SERS system due to the combination of low manufacturing costs, stability, disposable characteristics, and simplicity for routine use (Amicucci et al., 2022; Banchelli et al., 2020; D'Andrea et al., 2024). The SERS profile appears as a convolution of spectra reflecting a complex phenolic mixture as assessed above by chromatography analysis. Therefore, a comparison of the chamomile spectrum with those of isolated compounds was carried out, by focusing on classes of compounds, as identified by HPLC. Specifically, we considered a simplified grouping (Fig. 3) of standard solutions at 10^{-5} M consisting of caffeic (CAA), ferulic (FEA) and p-coumaric (COU) acid, apigenin 7-O-glucoside (AP7), luteolin 7-O-glucoside (LU7), quercetin 3-O glucoside (QU3) and quercetagetin 7-O-glucoside (QG7). Furthermore, although under the instrumental detection sensitivity (0.05 mg/g DW) of HPLC in the chamomile extract, the apigenin aglycone (APG) was added to the analysis due to its detection in chamomile preparations, as reported in previous studies (Catani et al., 2021; Temerdashev et al., 2023). SERS spectra (Fig. 4) of the reference compounds featured characteristic profiles whose tentative peak assignments are reported in **Table S1**. Briefly, main observed peaks are: CAA (605 cm^{-1}; 641 cm^{-1}; 1270 cm^{-1}; 1329 cm^{-1}; 1479 cm^{-1}), FEA (615 cm^{-1}; 1269 cm^{-1}; 1477 cm^{-1}; 1602 cm^{-1}), COU (1169 cm^{-1}; 1202 cm^{-1}; 1264 cm^{-1}), APG (580 cm^{-1}; 1170 cm^{-1}; 1243 cm^{-1}; 1573 cm^{-1}), AP7 (569 cm^{-1}; 1175 cm^{-1}; 1247 cm^{-1}; 1573 cm^{-1}; 1606 cm^{-1}), LU7 (637 cm^{-1}; 1250 cm^{-1}; 1298 cm^{-1}; 1480 cm^{-1}; 1570 cm^{-1}), QU3 (631 cm^{-1}; 1285 cm^{-1}; 1325 cm^{-1}; 1480 cm^{-1}), QG7 (560 cm^{-1}; 636 cm^{-1}; 1328 cm^{-1}; 1478 cm^{-1}; 1548 cm^{-1}; 1593 cm^{-1}). We can note that all the compounds featuring a catechol moiety show a common peak ~1480 cm^{-1}, which is lacking in the SERS profile of apigenins (APG and AP7) and COU. Very strong bands at around 630 cm^{-1}, 1327 cm^{-1} and 1480 cm^{-1} for LU7, QU3, QG7, which include modes originated by the ortho-dihydroxylated B ring (Aguilar-Hernández et al., 2017; Corredor et al., 2009; Jurasekova et al., 2014; Li et al., 2021; Teslova et al., 2007), could suggest a preferential interaction of these compounds on the silver surface of the SERS substrate through the OH groups of catechol. On the other hand, enhanced bands of CAA and FEA ascribed to both the carboxylic and the ortho-dihydroxy phenolic groups (at around 610 cm^{-1} and 1480 cm^{-1}), and of COU ascribed to ring vibrations (at 1169 and 1602 cm^{-1}) (Aguilar-Hernández

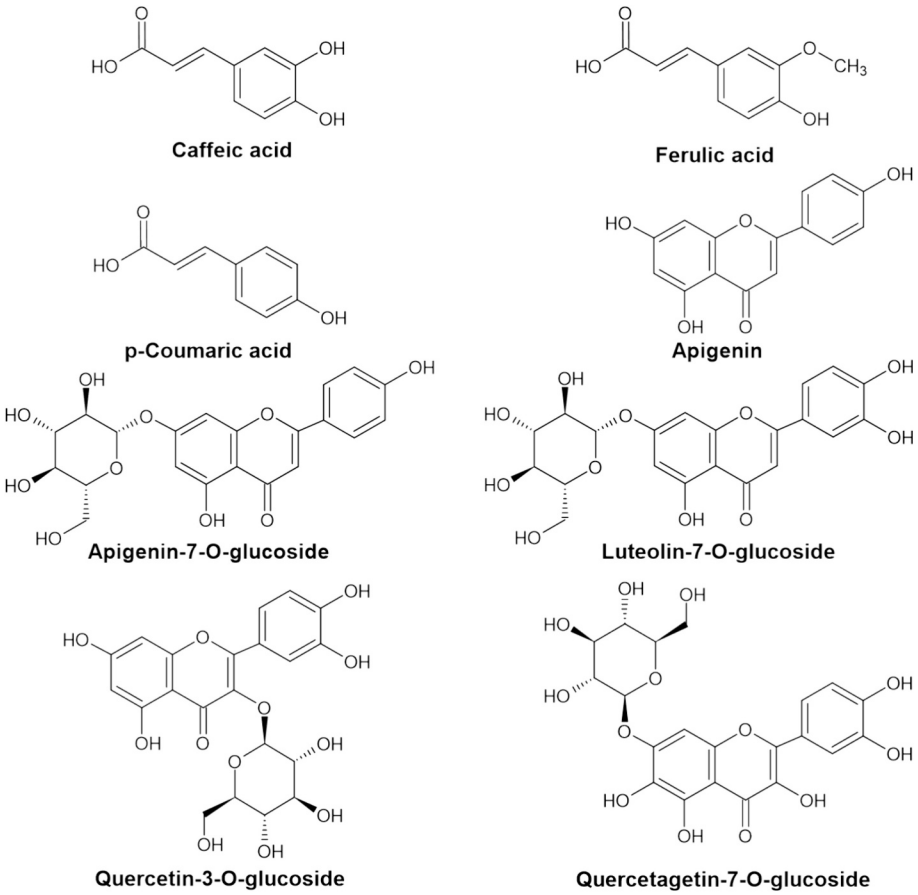

Fig. 3. Chemical structure of phenolic compounds selected for SERS analysis.

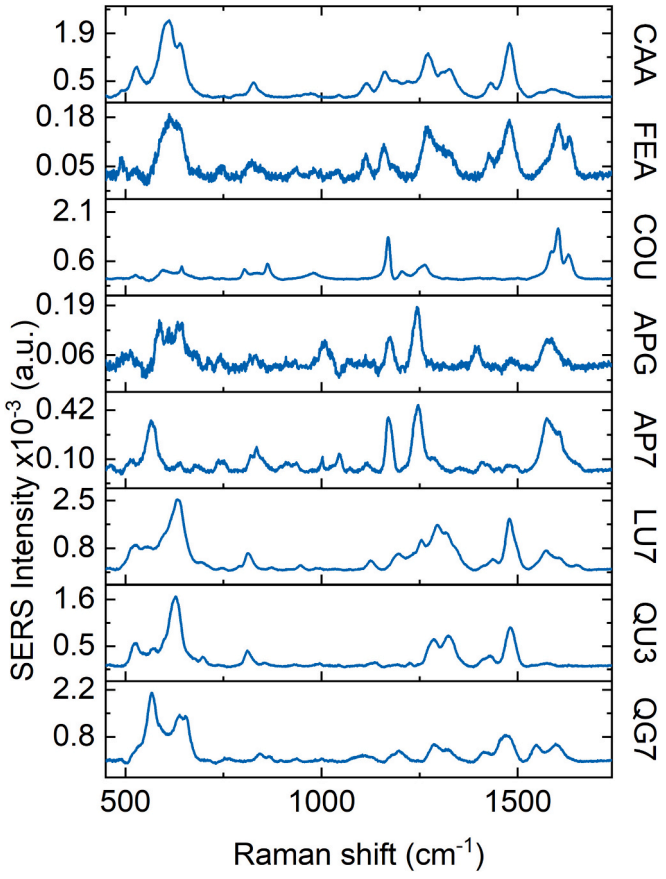

Fig. 4. SERS spectra of phenolic standards at 1×10^{-5} M concentration. CAA: caffeic acid; FEA: ferulic acid; COU: p-Coumaric acid; APG: apigenin; AP7: apigenin 7-O glucoside; LU7: luteolin 7-O glucoside; QU3: quercetin 3-O glucoside; QG7: quercetagetin 7-O glucoside.

et al., 2017; Eravuchira et al., 2012), can be explained by a plan orientation of the caffeic or coumaroyl moiety of these molecules toward the silver plane, although through different adsorption mechanisms. Instead, in the case of APG and AP7, we can observe an intense bands at around 1245 cm^{-1}, which suggests an interaction of these species through the OH group in C(7).

3.3. Least-squares (LS) model

Once assumed that the compounds listed in Table 1 represent a comprehensive composition of chamomile, we can attempt to derive the SERS spectrum of chamomile from a rough linear combination of the measured equimolar standard spectra, which thus can be described as follows:

$$S_0 = S_1c_1 + S_2c_2 + \ldots + S_mc_m \quad (1)$$

where c_i are the amount of the m reference compounds as derived by HPLC analysis (m = 8 in our case, Table 2) and represent the mass fraction of the compound i in the mixture, S_i are their spectra (Fig. 4), and S_0 is the calculated spectrum resulting from their combination (red line in **Fig. S4)**. In this case, the unbalance in the linear dependence of SERS on concentration among different species leads to profile discrepancies between HPLC-derived and original spectra. Specifically, underestimate of the peaks at 528 cm^{-1}, 610 cm^{-1}, 1327 cm^{-1} and 1480 cm^{-1}, and overestimate of the peaks at 1195 cm^{-1} and 1600 cm^{-1} can be explained by different SERS cross sections values of the chamomile components and their specific chemical affinity toward the silver substrate. Immediate feedback of such intrinsic behavior of the various components is provided by their SERS response profile at fixed concentration (Fig. 4), showing average signals that differ among species by up to about one order of magnitude.

Table 2
c_i amounts from HPLC, a_i coefficients from the LS method on SERS spectra of equimolar reference compounds, and calculated w_i weights of the phenols from extracted chamomile. Note: APG was included in the LS calculation although under the instrumental detection sensitivity of HPLC in the chamomile extract (0.05 mg/g DW); tabulated w_i values are derived from Eq. 3 considering the original significant digits for a_i values as reported in **Table S2** and then approximated to 4 significant digits for more clarity. ND = not detectable.

Reference	c_i	a_i	w_i
CAA	1.3233	0.1467	9.0184
FEA	2.6609	0.0957	27.8142
COU	0.4185	~0	ND
APG	< 0.05	ND	ND
AP7	2.0275	0.1071	18.9365
LU7	1.4954	0.0300	49.8247
QU3	1.4304	0.1455	9.8306
QG7	2.7074	0.0578	46.8297

The SERS spectrum of chamomile as a spectrum of a mixture of the m reference coumpounds can be also mathematically described as linear combination of the SERS equimolar spectra (Fig. 2, red line) of the single compounds:

$$S_a = S_1a_1 + S_2a_2 + \ldots + S_ma_m \quad (2)$$

where a_i are regression coefficients able to maximize the covariance between original and predicted spectra obtained by computing a nonnegative solution via a linear least-squares problem under the lsqnonneg MATLAB routine. The least-squares estimated concentration values a_i can then be related to actual concentration (c_i) of the compounds via a calibration as shown below.

Initially, the specific contribution a_i of each phenolic component to the overall chamomile SERS response is deduced (Table 2). In this case, a satisfactory match (R^2 = 0.93) of the resulting S_a spectrum (Fig. 2, red line) is obtained compared to the original chamomille profile as expected, ironing out almost all the discrepancies observed in the combination S_0 (**Fig. S4**, red line). Minor discrepancies include an overestimation of the 1195 cm^{-1} peak attributed to CAA (Fig. 4, **Table S1**), which may be explained by its favored behavior in the competition of the different chamomille components in the interaction with the silver surface, whose effect cannot be contemplated by a mathematical combination of contributions from isolated compounds.

Afterwards, the achievement of c_i by HPLC and the calculation of a_i by the SERS model allowed us to derive a calibration method of the SERS response based on the HPLC analysis, which compensates for the intersample nonlinearity with the concentration of the SERS technique. We note that the choice of calibrating our SERS system on an alcoholic maceration of chamomille flowers is convenient due to its slightly superior extraction yield and richness as compared to other popular extraction methods including hot water decoction, ultrasounds or microwave-based techniques (Temerdashev et al., 2023). Starting from the c_i and a_i datasets is thus possible to obtain the weights w_i (Table 2) that act as correction factors in the prediction of the real concentration values of an unknow batch of chamomile, where:

$$w_i = c_i/a_i \quad (3)$$

APG is not detected by our model in the chamomile extract, consistent with the HPLC analysis. Therefore, its presence was excluded from the model when applied to commercial samples. COU also appears as a non-contributing species in the LS model ($a_i \sim 0$), although it was detected in small amount by HPLC. This hindered the determination of a nonzero w_i coefficient, thus making it not applicable for prediction.

3.4. Application of the LS model to commercial products

Afterwards, the above model was tested for quantitatively characterize the polyphenol composition from three different commercial chamomile tea products (*P1, P2, P3*), commonly found on the italian market. Specifically, the presence of each phenolic compound in their infusions can be rapidly estimated by first collecting the relevant SERS spectrum, followed by extrapolation of the a_i coefficients (allowing a ± 30 % variability of the a_i coefficients around reference a_i values of Table 2) and calculation of the c_i values by means of Eq. 3 (see the sketch in **Fig. S5** displaying the workflow of the method).

A good match between the original and predicted SERS curves throughout the three chamomile formulations (displayed in Fig. 5), with R^2 ranging from 0.71 to 0.82, confirmed the robustness of the model when applied to unknown samples. Upon reviewing the predicted compositions (Table 3), variability in phenolic species was observed across different formulations compared to the alcoholic chamomile extract. This variation in phenolic profile is definitely expected due to differences in the extraction medium (Cvetanović et al., 2015; Haghi et al., 2014; Harbourne et al., 2009; Sotiropoulou et al., 2020; Temerdashev et al., 2023) and may also originate from variation in plant matrices used for making herbal preparations, influenced by factors such as primary production, manufacturing processes and geographical origin (Mekinić et al., 2014; Raal et al., 2012; Tsivelika et al., 2021; Viapiana et al., 2016).

As a final step, HPLC analysis of the three commercial batches was carried out to validate the SERS model. The HPLC results are shown in Table 4 (see **Table S3** for detailed HPLC analysis). There was a congruous agreement between SERS-predicted concentration index (c_i) and analytical values, with an average deviation of 37 %. Notably, hydroxycinnamic acids exhibited a very precise prediction, with an average deviation of only 8 %, whereas flavonoids exhibited an average deviation of 65 %. This discrepancy can be attributed to the superior fit of the model within the spectral range of 400–1000 cm^{-1} (Fig. 5), which is predominantly influenced by hydroxycinnamic acids. Finally, it is noteworthy that coumaroyl species can be considered negligible in the infusions as revealed by HPLC (values ≤ the instrumental detection sensitivity of HPLC), in line with a low polarity of the specific coumaroyl derivative detected in chamomile (Table 1). This result minimizes previous concerns regarding the detectability of coumaroyl derivatives using SERS (Table 2) in future predictions of chamomile teas.

Therefore, the proposed method can be easily adapted for the rapid analysis and quantification of the polyphenol fraction in other tea products, as well as in fruit and vegetable-based beverages or extracts. Following a preliminary definition of the dataset of SERS spectra of phenolic standards, which can be extended as needed to describe the diverse composition of the target sample, the weights w_i are defined, enabling the model to extract the predicted concentration values c_i.

Table 3
a_i coefficients of three chamomile tea commercial formulations (*P1, P2, P3*) and the predicted c_i amounts of the phenolic species. A maximum error of ±0.2 can be estimated on c_i.

Ref	$a_{i(P1)}$	$c_{i(P1)}$	$a_{i(P2)}$	$c_{i(P2)}$	$a_{i(P3)}$	$c_{i(P3)}$
CAA	0.1954	1.7623	0.2394	2.1591	0.1865	1.6817
FEA	0.1052	2.9270	0.1296	3.6055	0.1300	3.6153
COU	0.0012	ND	0.0021	ND	0.0021	ND
AP7	0.1178	2.2303	0.1001	1.8957	0.1121	2.1123
LU7	0.0150	0.7477	0.0099	0.4935	0.0052	0.2596
QU3	0.0918	0.9029	0.0702	0.6933	0.1200	1.1795
QG7	0.0290	1.3581	ND	ND	0.0289	1.3537

Table 4
Polyphenolic composition in chamomile tea commercial formulations (*P1, P2, P3*) as measured by HPLC analysis.

Ref	Amount P1 (mg/g DW)	Amount P2 (mg/g DW)	Amount P3 (mg/g DW)
CAA	2.0666	2.1064	1.8099
FEA	3.0016	3.1557	3.2069
COU	0.0545	0.0201	0.0192
AP7	1.8398	1.5903	2.0243
LU7	0.1141	0.0697	0.0592
QU3	0.9135	0.8922	0.6274
QG7	1.6624	1.2897	1.2491

4. Conclusion

In this study, our aim was to identify a rapid and convenient method for the qualitative and quantitative determination of the phenolic composition of chamomile flowers based on SERS analysis. To achieve this goal, we employed a silver spotted SERS substrate to generate a dataset of reference spectra from phenylpropanoid samples, designed to mimic the composition of a methanolic extract of chamomile flowers previously analyzed by HPLC. Subsequently, we built up a correlation model comprising a linear combination of these reference SERS spectra and calibrated it based on the HPLC analysis. This approach enabled us to predict the phenolic composition of unknow chamomile samples.

The effectiveness of the model was evaluated using commonly sold chamomile tea products. We successfully identified the relative compositions of flavonoids and hydroxycinnamic acids, which reflect the characteristic nutraceutical content of the different formulations.

Nowadays HPLC has become a powerful tool for quality control and has been internationally accepted for the evaluation and quality control of herbal medicines and preparations (European Medicinal Agency,

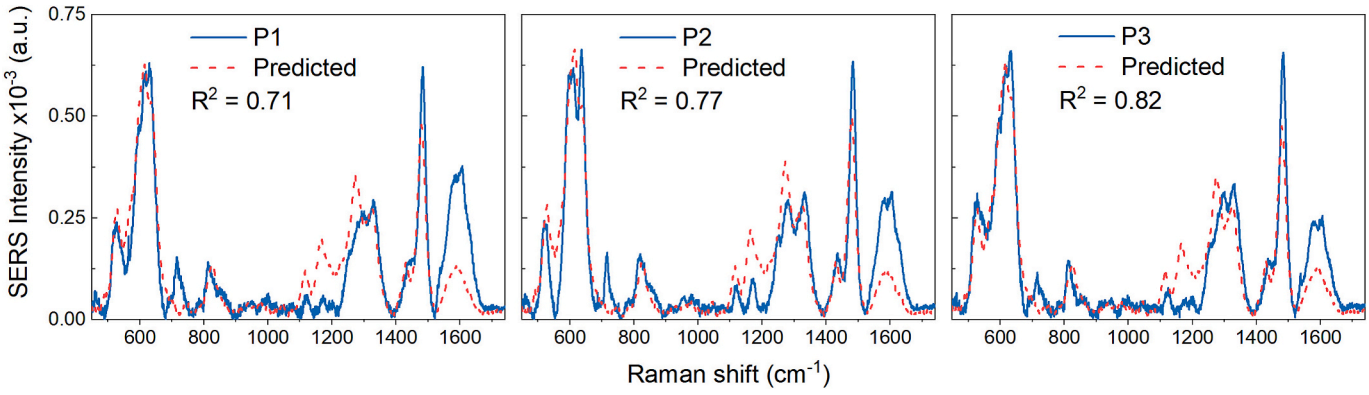

Fig. 5. SERS spectra of chamomile infusion samples of different commercial tea products (*P1, P2, P3,* blue line) and the SERS profiles predicted by the LS model (red dashed lines). The coefficient of determination (R^2) values estimating the accuracy of the least-squares calculation in approximating the real SERS profiles are also reported. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2011; WHO, 2007). Nonetheless here we suggest that SERS can become an alternative or complementary technique, overcoming some limits of HPLC, which is time-consuming and expensive. The use of silver spotted substrates, as those developed in our labs, is in line with a fast and effective analytical response, enabling the processing of trace (nanogram scale) amounts of sample on a multi-sample platform. Future steps will include adapting the proposed strategy to the quantification of other plant extracts. Overall, the method can be proposed for monitoring phenol concentration down to a submiligram /g DW scale in food and beverages and for the nutraceutical industry or for ensuring compliance with quality standards.

CRediT authorship contribution statement

Marella de Angelis: Validation, Methodology, Investigation, Data curation. **Chiara Amicucci:** Methodology, Investigation. **Martina Banchelli:** Writing – review & editing, Methodology, Investigation. **Cristiano D'Andrea:** Writing – review & editing, Methodology, Investigation. **Antonella Gori:** Writing – review & editing, Methodology, Investigation. **Giovanni Agati:** Writing – review & editing, Funding acquisition. **Cecilia Brunetti:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Data curation. **Paolo Matteini:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodchem.2024.141084.

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