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Gallic Acid: Review of the Methods of Determination and Quantification

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ABSTRACT

Gallic acid (3,4,5 trihydroxybenzoic acid) is a secondary metabolite present in most plants. This metabolite is known to exhibit a range of bioactivities including antioxidant, antimicrobial, anti-inflammatory, and anticancer. There are various methods to analyze gallic acid including spectrometry, chromatography, and capillary electrophoresis, among others. They have been developed to identify and quantify this active ingredient in most biological matrices. The aim of this article is to review the available information on analytical methods for gallic acid, as well as presenting the advantages and limitations of each technique.

KEYWORDS

Analytical methods; gallic acid; polyphenol

Introduction

Considered one of the major phenolic acids, gallic acid (or gallate) is a benzoic acid of great importance for the formation of a so-called galatotanin-hydrolyzable tannins group formed by a unit of sugar and a variable number of phenol acid molecules. Its distribution covers different families of the vegetable kingdom, such as Anacardiaceae, Fabaceae, and Myrtaceae (Battestin et al., 2004; Santos and Mello, 2010) as well as in fungi of the genus *Termitomyces* (Puttaraju et al., 2006).

The scientist Carl Wilhelm Scheele in 1786 was the first to identify gallic acid in plants (Fischer, 1914). However, this molecule attracts the interest of researchers mainly for its antioxidant capacity (Kim et al., 2007). Other pharmacological activities described in the literature are anticancer (Chia et al, 2010; Liang et al., 2012), anti-HIV (Kratz et al., 2008), antiulcerogenic (Jung et al., 2013), anti-inflammatory (Couto et al., 2013), antimicrobial (Kubo et al., 2003), and antifungal (Kubo et al., 2001), among others. Recently, some studies have been published relating the effect of gallic acid before the formation of amyloid plaques, considered to be the initial step in Alzheimer's disease (Jayamani and Shanmugam, 2014; Liu et al., 2013, 2014).

In addition to medicinal aspects, gallic acid is applied in other areas. Its first application was in the skin and leather industry, as a chelating agent (Costa et al., 2013). The first photographs used gallic acid as a developer (Beniwal et al., 2013). Gallic acid is used for the synthesis of trimethopim, an antimicrobial agent, and also as a preservative in food and beverages, primarily because of its power to kidnap to free radicals (Bajpai and Patil, 2008).

Chemical aspects, biogenesis, and synthetic production

Gallic acid (3,4,5 trihydroxybenzoin acid) is a crystalline solid, slightly colorless or slightly yellow. Its molecular weight is 170.11954 g/mol and its molecular formula is $C_7H_6O_5$. The melting point is 210°C with decomposition between 235° and 240°C, producing carbon dioxide and carbon monoxide. Its density is 1.69 kg/L (20°C), its pKa is 4.40, and the Log P of 0.70 (20°C). It is soluble in water, alcohol, ether, and glycerol and practically insoluble in benzene, chloroform, and ether petroleum (National Institutes of Health [NIH], 2015). The chemical structure of gallic acid is shown in Figure 1.

Although its biogenesis has not been completely defined, it is known that gallic acid has its origin in the shikimic acid pathway, an important route in the production of secondary metabolites of aromatic structure, existing in plants and certain microorganisms. This route starts with some amino acids, in particular l-phenylalanine, and produces an important class of compounds, such as coumarins, alkaloids, lignans, and polyphenols (Dewick and Haslam, 1969).

Three possible routes are described for its production (Figure 2). The first suggests an initial conversion of phenylalanine in caffeic acid, then in acid 3,4,5 trihydroxycinnamic, and finally in gallic acid. Another route suggests that it comes directly from the production of the acid 3,4,5 trihydroxycinnamic, considering that this has never been found in nature. Thus, the production of side chain occurs by the formation of protocatechuic acid, from caffeic acid (Santos and Mello, 2010). A third route suggests that the formation of 3-dehydroshikimic acid occurs by the action of dehydrogenase on shikimic acid. This follows from a spontaneous aromatization, resulting in the production of gallic acid (Kambourakis et al., 2000).

On an industrial scale, gallic acid is produced by the breakdown of tannic acid by tannase, a glycoprotein esterase. This enzyme is produced by different microorganisms, in particular, fungi in the genera *Aspergillus* and *Penicillium*, mostly by the fermentation process (Belmares et al., 2004; Macedo et al., 2005). Costa et al. (2013) obtained tannase and gallic acid from *Aspergillus tamarii* in solid medium and submerged. Better results in obtaining tannase and gallic acid from *Aspergillus*

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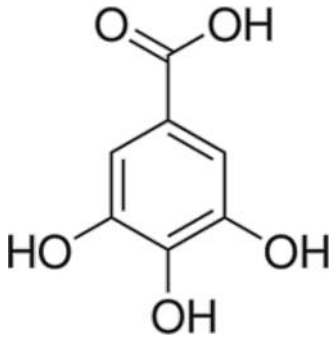

Figure 1. Chemical structure of gallic acid.

tamarii, along with *Aspergillus japonicus*, have been presented in the studies of Melo et al. (2013), in search of tannase-producing fungi in caves of the Brazilian regions Caatinga and Cerrado.

Analytical methods

The analytical methods used include spectroscopy, chromatography, capillary electrophoresis, thermal analysis, and chemiluminescence analysis.

Spectroscopy

Gallic acid offers maximum absorption at 272.5 nm with log ε 4.06 (NIH, 2015). This absorption is a result of the sum of the absorptions of the main chromophore group (cluster benzoil), added to the three substitutions-OH (two *goal* and one *for*), for which theoretical calculations result in absorption of 269 nm (Pavia et al., 2013). However, it is possible to observe slight variations around that value. Pawar and Salunkhe (2013), using UV-Vis spectrophotometry, quantified and validated a method for determination of gallic acid in hydroalcoholic extract of *Thipala churna* in 273 nm. Vijayalakshmi and Ravindhran (2012) obtained fingerprints of *Diospyrus ferrea* Willd., obtained in different solvents, that verified that the maximum absorption of gallic acid occurs between 270 and 275 nm, with better results for the ethanolic extract.

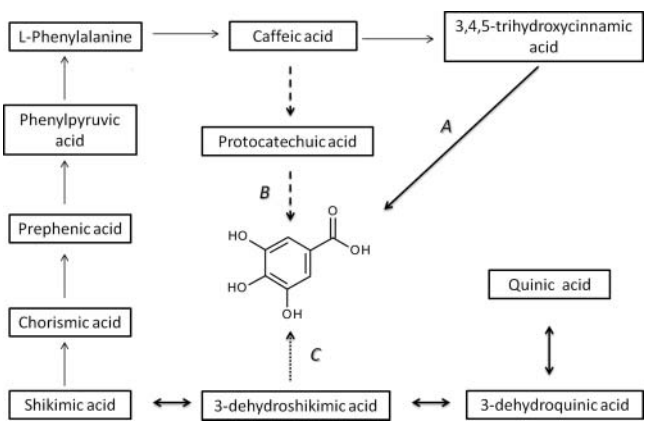

Figure 2. Three possible routes for gallic acid production.

A great part of the application of spectroscopy in the UV-Vis region is in the determination of total polyphenols. Folin-Ciocalteu's method (FC) is a colorimetric method based on transfer of electrons between reagents and polyphenols. In this essay, gallic acid is used as the default and the results are expressed as gallic acid equivalents (Balan et al., 2015; Sánchez-Rangel et al., 2013; Stalikas, 2007). Chaves et al. (2013) developed and validated a method for *Guapira graciliflora* and *Pseudobombax marginatum*, aimed at evaluating the production of metabolites during periods of rain and drought. A variation of this technique is the use of the Folin-Denis method, which was an improvement over the previous method (Monteiro et al., 2005).

Another possibility for quantification of total polyphenols is using near-infrared (NIR) spectroscopy, which corresponds to the spectrum between 4000 and 10,000 cm^{-1}. However, for the best viewing and interpretation of data, chemometrics tools were applied as the minimum partial least squares (PLS) or principal component regression (PCR) (Chen et al., 2008; Moncada et al., 2013). NIR was used in the prediction of total polyphenols in green tea (*Camellia simensis* L.), also using PLS; when comparing the data obtained with HPLC, the method using NIR proved faster and economical and allowed for the simultaneous quantification of different compounds (Schulz et al., 1999).

In infrared spectroscopy, gallic acid presents specific regions of absorption. Vijayalakshmi and Ravindhran (2012) identified eight major peaks at 1022, 1234, 1448, 1622, 1714, 3043, 3280, and 3365 cm^{-1}; the peak at 1714 cm^{-1} is considered the most important because it is specific to polyphenols. Lam and collaborators (2012) found: characteristic peaks at 3492, 3370, and 3282 cm^{-1} (related to different forms of hydroxyl); peaks at 2920 and 2850 cm^{-1} corresponding to the stretching of C-H in aromatics; a peak at 1701 cm^{-1} corresponding to the carbonyl absorption in carboxylic acid and at 1615 cm^{-1} corresponding to stretching-related carbon-carbon in alkenes.

Chromatography

Chromatographic methods are the most used for identification and quantification of gallic acid in different matrices. Among the methods are thin-layer chromatography, gas chromatography, and high-performance liquid chromatography.

Thin-layer chromatography (TLC)

TLC is widely used as a fast, low-cost method that allows a first "fingerprint" of the chemical composition of extracts of medicinal plants (Sonowane et al.., 2012; Tótoli & Salgado, 2014). As it is a technique in which the separation stems from migration of compounds against the stationary and mobile phases' affinity, perhaps the most crucial step in the development of methods for TLC is optimization (Pedroso and Salgado, 2013).

Sharma et al. (1998) used TLC for the identification of gallic acid and other phenolic compounds, using silica gel plates. Among all stages tested, the mobile phase, consisting of chloroform:ethyl acetate:acetic acid (50:50:1), was the one that best separated compounds. To visualize the plates, ferric chloride, sulfuric acid, and vanillin were used. Gallic acid was also identified in *Schinus terebinthifolius* Raddi and *Arctostaphylos*

uva-ursi (L.) Spreng. In both species the mobile phase used was toluene:ethyl acetate:methanol:formic acid (75:25:10:6) and as visualizing solution 1% $FeCl_2$ (Braz et al., 2012).

Dhralwal et al. (2008) developed and validated a method of quantification for *Bergenia ciliata* and *Bergenia ligulata* by TLC. The chosen mobile phase was toluene:ethyl acetate:formic acid (40:60:10). However, instead of a visualizing solution, the reading was made using an automated system called high-performance thin-layer chromatography (HPTLC) or TLC densitometric. This technique was also used for quantification in *Hygrophila auriculata* (K. Schum) (Hussain et al., 2012), *Terminalia chebula* (Kumar et al., 2010), *Acacia leucophloea* (Leela and Saraswathy, 2013), and *Syzygium aromaticum* (L.) Merr. & Perry (Pathak et al., 2004). The main difference among these works is the variation of the composition of the mobile phase. However, in all of them is the presence of an acid (glacial acetic acid or formic acid) causing the pH of the stage to be more acid. Thus, there is a suppression of ions for gallic acid (Arapitsas, 2012).

Gas chromatography (GC)

Although gas chromatography is a technique that allows the identification and quantification of various compounds, GC analysis requires that the compound have good volatility and does not boil above 300°C, such as essential oils, or volatilizability. Moreover, it is a technique that has high sensitivity and delectability (Penteado et al., 2008).

In the case of gallic acid, sample derivatization is possible. This procedure results in a better response of the detector front of the chromatographic system, allowing the analysis of gallic acid by GC (Frias et al., 2014). Tor et al. (1996) when determining gallic acid and pirrogalol in biological matrices by gas chromatography coupled to mass spectrometry (GC/MS) derivatized the sample prior to injection. The column used was a J & W Scientific 15 m × 0.53 mm × 0.1 μm DB-1, with helium gas drag and flow rate of 7 mL/min, operating at 60°C and oven temperature gradient system up to 275°C. Sample derivatization was also adopted by Kuskoski et al. (2012) in analyzing phenolic compounds by GC/MS ion trap in guarana (*Paullinia cupana*). To this end, the research used a fused silica capillary column (Phenomenex Zebron ZB-5ms 30 m × 0.25 mm × 0.25 mm), with a temperature of 300°C of injection and helium gas drag with flow rate of 1 mL/min.

Phenolic compounds, free sugars, and polyols were determined in mango (*Mangifera indica* L.) by means of GC/MS, with sample derivatization (Núñes Sellés et al., 2012). Initially the sample was diluted in pyridine, then it was silylated to 80°C for 30 min in *N,O*-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA) containing 1% of trimethilclorosilane (TMS) as a catalyst. The derived TMS was kept in iso-octane prior to analysis. The column used was a J & W Scientific DB1, 25 m × 0.2 mm × 0.33 μm, with helium as drag gas (flow of 1 μL/min) and oven temperature gradient system up to 290°C.

High-performance liquid chromatography (HPLC)

Of all the techniques, high-performance liquid chromatography is the most applied in the identification and quantification of gallic acid. Its great power and resolution, resulting in better separation of compounds, make this technique the gold standard in the analysis of gallic acid (Stalikas, 2007). As phenolic compounds present high molecular weight and high polarity, the use of a separation technique becomes applicable, considering these compounds to be the training framework of hydrolyzable tannins (Araptisas, 2012).

Another great advantage of liquid chromatography is the application in different arrays, mainly herbal extracts. Thus, the correct choice of the method and solvent extraction is the first critical point of analysis of gallic acid by HPLC. Different techniques such as turbo-extraction, ultrasonication, maceration, and infusion can be used, the last two being the most used (Table 1). Generally, the extraction methods can be classified into conventional (reflux, infusion, and steeping, for example) and nonconventional or modern (turbo-extraction and ultrasonication). However, there is not yet a general method, making necessary the use of optimizations in the extractive process (Brusotti et al., 2014).

One class of the solvents used, hydroalcoholic solutions, is the most applied, although methanol, acetone, and water may also be used. In the case of water, its application is mainly in hot or cold infusion, chiefly focused on production of teas. According to Azmir et al. (2013) methanol and ethanol are the most suitable solvents for extraction of phenolic compounds. Since acetone is more suitable for extraction of flavonoids, water is more used in the extraction of tannins.

For chromatographic columns most of the work used a reversed-phase column (C-18 and C-8). The most applied were the columns of 250 mm. However, smaller columns, such as 150 and 100 mm, are used in analysis by ultraperformance liquid chromatography (UPLC). Although the time of analysis with the use of larger columns is a little longer, their use is justified when there is a large number of compounds present in the array (He et al., 2015).

Stationary reverse phases allow the retention of ionizable compounds, in the case of gallic acid, since their ionization is supressed. Thus, it is necessary to use a mobile phase ion-pair, aiming to maintain the pH of the mobile phase just below the pKa of gallic acid (Lopes et al., 2009; Róses et al., 2009). Formic acid, TFA, and acetic acid orthophosphoric were employed for mobile phase acidifying (Table 1). De Souza et al. (2002) suggest that for analysis using detection in the UV-Vis range, orthophosphoric acid is the most suitable, due to good resolution in the chromatogram. Formic acid, in addition to reducing the effect of the tail of the chromatogram, allows an increase in ionization in the case of MS/MS (Mahfoudhi et al., 2014). In some cases it is necessary to use the acidification of two phases (aqueous and organic) due to structural similarities of the compounds (Wang et al., 2000).

The organic phase modifiers complement the mobile phase used in analyses by HPLC. The most used are methanol and acetonitrile (Table 1), usually in a gradient system with the aqueous phase. Although it does not upgrade a protection of the column protection in analysis, the acetonitrile promotes a better resolution of the peaks (Stakilas, 2007).

The UV-Vis/diode array detector (DAD) is undoubtedly the most widely used HPLC detection system, although mass

Table 1. Instrumental conditions used in liquid chromatography for the determination and quantification of gallic acid.

Sample	Matrix	Sample preparation	Column	Chromatography condition	Detection	Retention time (min)	Reference
Camellia sinensis	Infusion	Sample added to boiling water, then cooled, filtrated, diluted, and frozen until use	LiChroCART 250-4 LiChrospher 100 RP-8 (250 × 4 mm, 5 μm)	Gradient A: trifluoroacetic acid 0.05%; B: methanol Flow rate: 0.8 mL/min	DAD	7.89	Gil et al., 2011
Camellia sinensis, *Arctostaphylos uva-ursi*, *Corylus avellana*, *Oenothera biennis*, *Vitis vinifera*	Ethanol and acetone extract	Extraction with ethanol 95% and acetone 80%	LiChroCART 250-4 LiChrospher 100 RP-8 (250 × 4 mm, 5 μm)	Isocratic – water: acetonitrile:acetic acid (88:10:2) Flow rate: 1.0 mL/min	UV-Vis (280 and 350 nm)	3.23	Karamac et al., 2006
Cerasus avium	Maceration with shaking	Extraction with water and ethanol	Macherey-Nagel Nucleoder C18 Gravity column (125 × 2 mm, 5 μm)	Gradient A: methanol with formic acid 0.5%; B: formic acid 0.5% Flow rate: 0.3 mL/min	MS/MS (tandem gold triple quadripole)	2.50*	Bursal et al., 2013
Green tea	Infusion	Hot water extraction	Kingsorb C-18 (150 × 4.6 mm, 5 μm)	Isocratic – methanol/water/ phosphoric acid Flow rate: 1.0 mL/min	UV-Vis (210 nm)	2.60	Wang et al., 2000
Chinese hamster ovary (CHO) cell line	Cell lysate	Centrifugation	Gemini C-18 Phenomenex (100 × 2 mm, 5 μm)	Isocratic – formic acid 0.05% and acetonitrile Flow rate: 0.35 mL/min	MS/MS (hybrid triple quadrupole/ linear ion trap mass spectrometer)	0.98	Wang et al., 2013
Dendrophthoe falcate	Raw material	Extraction with methanol	Thermo MOS 2 Hypersil C18 column (250 cm × 4.6 mm, 5 μm ODS 3)	Isocratic – acetonitrile and water with 0.1% phosphoric acid (60:40%) Flow rate: 1.0 mL/min	UV-Vis (271 nm)	12.81	Deshmukh and Prabhu, 2011
Emblica officinale and *Glycyrrhiza glabra*	Hommade syrup	Dilution in methanol-water (1:1).	Inerstil ODS C-18 (4.6 × 250 mm, 5 μm)	Gradient A: acetonitrile; B: water with acid water (0.1% phosphoric acid) Flow rate: 1.0 mL/min	UV-Vis (251 nm)	NA	Deodhar et al., 2012
Hamamelis virginiana	Sonication	Extraction with water in ultrasound	Kingsorb C-18 (150 × 4.6 mm, 5 μm)	Gradient A: phosphoric acid 0.1%; B: methanol and phosphoric acid 0.1% Flow rate: 1.0 mL/min	UV-Vis (210 nm)	3.00*	Wang et al., 2003
Ilex paraguariensis	Infusion and maceration	Hot infusion; hydroethanolic extraction (70%)	Shimadzu RP C8 (4.5 × 150 mm, 5 μm)	Isocratic - methanol/water Flow rate: 0.5 mL/min	DAD (280 nm)	17.00*	Pereira et al., 2012
Juglans mandshuricae	Sonication	Hydroethanolic extraction (74%) with ultrasound	Venusil ASB C18 (100 × 2.1 mm, 5 μm)	Gradient A: formic acid 0.1%; B: acetonitrile Flow rate: 0.2 mL/min	UHPLC MS/MS (triple-quadrupole tandem mass spectrometry)	1.80*	Sun et al., 2014
Labisa pumila	Methanolic extract	Dried leaves extracted with methanol 80% and added HCl; the extract was then dried and resuspended in methanol.	Intersil GL Science ODS-3 (4.6 × 150 mm, 5 μm)	Gradient A: water with trifluoroacetic acid (pH 2.5); B: acetonitrile Flow rate: 0.6 mL/min	UV-Vis (280 nm)	4.00*	Karimi et al., 2011
Michelia alba, *Caesalpinia pulcherrima*, *Nelumbo nucifera*	Ethanolic extract	Extraction with ethanol 95% by ultrasound and dilution in mobile phase	Luna C18 RP (4.6 × 250 mm, 5 μm)	Gradient A: water/acetic acid (25/1); B: methanol Flow rate: 1.0 mL/ min	UV-Vis (280 nm)	5.00	Samee and Vorarat, 2007

Nymphaea stellata	Soxhlet extraction	Hydroethanolic extract (70%)	HiQ Sil C-18 (250 × 4.6 mm, 5 μm)	Isocratic – phosphoric acid 0.01%/ acetonitrile Flow rate: 1.0 mL/ min	UV-Vis (265 nm)	6.50	Rakesh et al., 2010
Phyllanthus emblica	Fresh fruit juice	Juice dried by freeze-drying, then diluted with methanol:water	Zorbax SB RP-C18 (250 × 4.6 mm, 5 μm)	Gradient A: acetic acid 0.01%; B: methanol Flow rate: 0.9 mL/min	DAD (279 nm)	10.77	Sawant et al., 2011
Phyllanthus niruri	Dried extract	Roots, barks, and leaves extracted by aqueous decoction by reflux and dried	RP-18 LiChrospher (250 × 4 mm, 5 μm)	Gradient A: phosphoric acid 1%; B; acetonitrile with phosphoric acid 1% Flow rate: 0.6 mL/min	UV-Vis (275 nm)	5.00*	Couto et al., 2013
Psidium guajava	Maceration	Aqueous extraction and lyophilization	Gemini NX C-18 Phenomenex (250 × 4.6 mm, 5 μm)	Gradient A: phosphoric acid 0.5%; B: acetonitrile/phosphoric acid 0.5% Flow rate: 0.8 mL/min	DAD (280 and 352 nm)	9.00*	Verza et al., 2007
Punica granatum	Hydroalcoholic extract of bark	Diluted extract in methanol:water (60:40%)	Shimadzu ODS C-18 (4.6 × 250 mm, 5 μm)	Gradient A: water with formic acid 1%; B: acetonitrile Flow rate: 1.0 mL/min	UV-Vis (254 nm)	29.00*	Choi et al., 2011
Punica granatum	Juices, drinks, and aqueous extracts	Diluted in distilled water	Kinetex 2.6 μm C-18 (4.6 × 100 mm)	Gradient/isocratic – A: phosphoric acid 0.01%; B: acetonitrile with phosphoric acid 0.01% Flow rate: 1.8 mL/min	DAD (270 nm)	2.45	Qu et al., 2012
Rhizophora apiculata	Purified extracts containing hydrolizable and condensed tannins	Purified fractions by TLC	Intersil ODS Science Inc. (4.6 × 300 mm, 10 μm)	Isocratic – methanol and water (70:30) Flow rate: 1.0 mL/min	UV-Vis	2.96	Hong et al., 2011
Schinopsis brasiliensis	Spray dried extract	Dry extract made with Hydroethanolic extract	Phemomenex Gemini NX C18 (5 μm, 250 X 4.6 mm, 100 A)	Gradient – A: phosphoric acid 0.01%; B – Methanol. Flow rate: 1.0 ml/ min.	UV-Vis (271 nm)	8.5	Fernandes et al., 2015
Schinus terebinthifolius Raddi	Ethanol extract (EE), hydrolized extract (HE), and gel	EE: maceration; EH: extract with reflux and sulfuric acid; gel: solubilization of all compounds	RP 18 ACE 121 1503 (250 × 4.6 mm, 5 μm, 100 A)	Gradient A: acetonitrile:water; B: methanol: water with formic acid to pH 2.7 Flow rate: 1.0 mL/min**	DAD	3.19 and 1.69	Carvalho et al., 2009
Scutia buxifolia	Infusion	Aqueous extraction and lyophilization	Shimadzu (250 × 4.6 mm, 5 μm)	Gradient A: acetic acid 2%; B: methanol Flow rate: 0.7 mL/min	DAD (254 nm)	17.00*	Freitas et al., 2013
Stryphnodendron adstringens, *Stryphnodendron polyphyllum*, *Stryphnodendron obovatum*	Extract with acetone:water (7:3)	Turboextraction (20 min); the extract was concentrated, dried, and partitioned	Gemini NX C-18 Phenomenex (250 × 4.6 mm, 5 μm)	Gradient A: water/trifluoroacetic acid 0.05%; B: acetonitril/trifluoroacetic acid 0.05% Flow rate: 0.8 mL/min	UV-Vis (210 nm)	10.00	Lopes et al., 2009
Thymus vulgaris, *Salvia officinalis*, *Origanum majorana*	Maceration	Extract with methanol	Zorbax SB-C18 (250 × 4.6 mm, 5 μm)	Gradient A: formic acid 0.05%; B: methanol Flow rate: 0.8 mL/min	UV-Vis (280 nm)	5.85*	Roby et al., 2011
Triphala churna	Maceration	Extract with methanol	Phenomenex (250 × 4.6 mm, 5 μm)	Gradient A: acetonitrile; B: phosphoric acid 0.1% Flow rate: 0.8 mL/min	DAD (254 nm)	5.29*	Platel Madhavi et al., 2010

*The retention time is approximate.
**Approximately.

spectroscopy can be used, mainly in pharmacokinetic analyses (Sun et al., 2014) and UPLC (Table 1). The wavelength region between 270 and 280 nm is the most applied. Some studies use 210 nm, related to the primary absorption of gallic acid (Wang et al., 2000), or 254 nm, for general absorption of phenolic compounds (Arceusz and Wesolowski, 2013).

Therefore, after the optimization of the parameters of analysis (extraction, mobile phase, stationary phase, and detection) it is possible to obtain different retention times. It is possible to obtain times of retention from 1.69 min up to 29 min for HPLC and up to 2 min for UPLC (Table 1). The great difference between the retention times can be related to the gradient system used in the analysis, such as the work performed by Choi et al. (2011).

Capillary electrophoresis (CE)

Although still little used for natural products, capillary electrophoresis and its related techniques (capillary zone electrophoresis [CZE], micellar electrokinetic chromatography [MEKC], capillary electrokinetic chromatography [CEC]) could be an excellent green alternative for identification of these compounds, mainly gallic acid (Gotti, 2011). The technique consists in the separation of different ionizable compounds by difference of the migration front of an electric field. The first time this technique was applied dates from 1930 by the Swedish chemist Arne Tiselius (Spudeit et al., 2012).

Cartoni et al. (1996) used capillary electrophoresis in separation of gallic acid and other phenolic compounds in Italian wines and other alcoholic beverages. To this aim, they used a fused silica capillary 43 cm long, in the hydrodynamic method at 25°C with a UV-Vis detector. After several tests, the best pH for analysis was determined to be 8.3, with a potential of 15 kV using sodium bicarbonate buffer at 50 mM. Wu and Sheu (1996) applied CZE and MEKC to the separation of components of *Paeoniae radix*, a formulation used in traditional Chinese medicine composed of dried roots of *Paeonia veitchii* Lynch or *Paeonia lactiflora* Pall, using a buffer solution of $Na_2B_4O_7$.

Using micellar electrokinetic chromatography (MEKC), Prasongsidh and Skurry (1998) developed a method to analyze the gallic acid and other phenolic compounds (reverastrol and quercetin, catechin) in wines. They used a fused silica capillary of 64.5 cm and obtained good separation between the compounds in up to 11 min. Veher and Koel (2003) produced a similar work, with in plant extracts, however (*Myrica gale* L., *Hippophae rhamnoides* L., *Rosa majalis* L., and *Reynutria japonica* Houtt.). They used capillary electrophoresis coupled to a UV-Vis detector in 240 nm, an uncoated capillary of 75 cm, and as a buffer sodium tetraborate, pH 9.4, and concentration of 25 mM. Another study (Yue et al., 2006) determined the gallic acid and salidroside in *Rhodiola dumulosa* and medicinal preparations. Once again, the pH of the buffer solution was fairly alkaline (between 8 and 11), aimed at improving the ionization of the compounds. A column of fused silica was used at 25°C with voltage of 15 kV, obtaining good results in the separation of compounds.

Other techniques

Solubility is an important physico-chemical parameter to evaluate. Daneshfar et al. (2008) assessed the solubility of gallic acid at different temperatures (between 25° and 60°C) and in ethyl acetate, water, ethanol, and methanol; the methanol presented better solubility. For both, the authors used UV-Vis spectrophotometry (269, 269.5, 273, and 273.5 nm) for quantification.

Chemiluminescence analyses were applied by Li et al. (2012) for quantification of gallic acid. They used luminol-$AgNO_3$-Ag for complexation and reading in a spectrophotometric flow system in the region of UV-Vis. This was possible due to oxidation caused by the gallic acid reagent, allowing its detection.

Thermal analysis, in particular, differential scanning calorimetry (DSC) and thermogravimetry (TG), can also be applied to the identification of compounds and potential degradations and herbal drugs (Fernandes et al., 2013). When determining the DSC curve of gallic acid at a heating rate of 10°C/min in N_2 atmosphere, Shyam et al. (2012) found a start temperature melting point ($T_{on\ set}$) at 136.5°C, which may suggest that the sample was not pure or the occurrence of polymorphism, due to the gallic acid melt at 210°C. Guo et al. (2012) performed thermogravimetric analysis at different heating rates (5, 10, and 15°C/min) and obtained three stages of degradation. The first one (± 65°C) could be related to the loss of oxygen of the hydroxyl at position *orto*, the second (± 135°C), to the production of CO_2, and the third, to complete degradation beginning at 305°C.

Conclusion

The biological activity of gallic acid, either as an isolated molecule or as a constituent of plant matrices, is of great importance. Thus, different analytical methods are needed for identification and quantification of this active ingredient in various biological matrices.

Although some methods, such as liquid chromatography, are well consolidated, innovative vision is important for application of green methods such as capillary electrophoresis and infrared spectroscopy and little-exploited methods, such as thermal analysis. The approaches described in this work can be useful in the evaluation of gallic acid from raw materials such as herbal drugs, up to the final product, such as teas and capsules.

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