

REVIEW ARTICLE

Analytical determinations of luteolin

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Abstract

Plants, through the photosynthesis process, produce the substances necessary for all the life cycles of nature, which are called "primary metabolites." Moreover, there are some plants that synthesize, in addition to these, other substances with more specific functions, which are known as "secondary metabolites." It is inside this group that flavonoids are located, whose main function is to protect organisms from damage caused by different oxidizing agents. Luteolin (3,4,5,7-tetrahydroxy-flavone) belongs to the sub-class of flavonoids known as flavones and is one of 10,000 flavonoids currently known, being one of the most bio-active flavonoids. Its various beneficial properties for health, together with the increasing reduction in the use of synthetic antioxidants, make the study of luteolin a very active field. Within this, the quantification of this molecule has become a subject of very special interest given that it is transversal to all fields. In this review article, we aim to give the reader a broad and deep vision of this topic, focusing on the events reported in the last 5 years and covering all possible techniques related to analytical determinations. We will discuss in terms of advantages and disadvantages between techniques, selectivity, sensitivity, costs, time consumption, and reagents as well as in the complexity of operations.

KEYWORDS

antioxidant, chromatography, electroanalytical chemistry, flavonoid, luteolin

Abbreviations: CILE, composite-modified carbon ionic liquid electrode; COFs, core-shell magnetic covalent organic frameworks composites; CV, cyclic voltammetry; DAD, diode array detector; DPV, differential pulse voltammetry; ESI, electrospray ionization; FLD, fluorescence detection; GCE, glassy carbon electrode; GCPE, glassy carbon paste electrode; HPLC, high-performance liquid chromatography; ITO, indium tin oxide; LC, liquid chromatography; LOD, limit of detection; LOQ, limit of quantitation; LSV, linear sweep voltammetry; LUT, luteolin; MS, mass spectroscopy; NPCP, nitrogen-doped porous carbon polyhedron; PCA, principal component analysis; PGE, pencil graphite electrodes; QQQ, triple quad; QTOF, quadrupole time-of-flight; RGO, reduced graphene oxide; RSD, residual standard deviation; SWAASV, square wave anodic adsorptive stripping voltammetry; SWV, square wave voltammetry; TM, titanium mesh; UFLC, ultra-fast liquid chromatography; UPLC, ultra performance liquid chromatography; UV, ultraviolet.

1 | INTRODUCTION

Flavonoids are benzo- γ -pyrone derivatives containing phenolic and pyranic rings in their molecular structures. Most of them have two benzene rings linked through a chain of three carbon atoms. Flavonoids are widely found in nature, mainly in fruits, seeds, and vegetables, as well as in diverse medicinal herb extract and pills.¹

The 3',4',5,7-tetrahydroxy-flavone, usually called Luteolin (LUT) fits in to the subclass of flavonoids known as flavones and it is considered one of the most bioactive flavonoids.²

As can be seen in Figure 1, LUT has both, resorcinol (Ring A) and a catechol (Ring B) in its chemical structure. This flavonoid is known for its beneficial effects on human health, such as cardiovascular protection, anti-allergic, anticancer activities, and anti-ulcer effects, and it prevents cataracts.³ LUT also inhibits platelet aggregation by vasodilating action,⁴ cataract prevention, anti-platelet, and antithrombotic action⁵⁻⁸; and LUT could suppress the oxidative damage of DNA.⁹ Recent studies also show and reinforce anti-inflammatory, antioxidant, anticancer, cytoprotective, and macrophage polarization effects.¹⁰

Since the beginning of the pandemic produced by SARS-CoV-2 in these few months, about 40 articles have been published reporting the benefits for human health in relation to the use of flavonoids, and in most of them there are studies of LUT or at least some mention, turning it, once again, into one of the flavonoids with the greatest potential, in this case, related to the treatment or the prevention of COVID-19. The mentioned works range from general reviews showing the advantages in the use of several flavonoids¹¹⁻¹³ to other works in which the focus is exclusively on LUT.¹⁴

The major development that has propelled flavonoid research involves improvements in the analytical techniques used for their characterization. In early research, scientists relied on techniques such as thin layer chromatography (TLC) and UV/vis spectrophotometry, which lack sufficient specificity and sensitivity. As analytical techniques applicable to flavonoids have developed, progressively more information about the numbers of

compounds and their structural properties have become available, thereby supporting more detailed research in the field.

Chromatographic techniques contribute significantly in the area of natural products, especially regarding identification, separation, and characterization of bioactive compounds from plant sources. Efficient screening of the compounds of different extracts can be performed with chromatographic assays, such as high-performance liquid chromatography (HPLC) to identify different components. Through this technique, the chromatographic "fingerprint" of a plant extract can be obtained, for example, which is very convenient for identification purposes.¹⁵

On the other hand, the possibility to connect multiple detection devices to methods such as HPLC has made this technique a valuable and essential tool for the flavonoids separation, including luteolin. Ultraviolet (UV) detection is currently the technique used in HPLC, which can be used with multi-wavelengths or photo diode array (PDA). It is a conventional tool in studies associated with detection, quantification and classification of compounds. For high-throughput analysis, the development of techniques such as ultra-high-performance liquid chromatography (UHPLC) and ultra-performance liquid chromatography (UPLC), coupled to mass spectrometer (MS) have emerged as an alternative to the traditional HPLC technique. These technologies are capable of separating and identifying compounds with significant gains in resolution, sensitivity, and marked reduction in the overall analysis time. On the other hand, the capillary electrophoresis (CE) coupled to MS detection can provide structural information of analytes present in real matrixes.

On the other hand, known for its high speed, its economy of resources and its extremely low detection limits, electrochemical methods become widely applied to diverse samples, included flavonoids and of course, luteolin between them.

Likewise, searching more consolidated techniques available in a greater number of laboratories, in spite of the expensive equipment, enables the rise of techniques such as fluorescence, which provide great specificity and low detection limits but usually determine only one analyte by experience.

Finally, electrophoretic techniques, broadly distributed in biology labs, are used as purification methods of natural products. Although its main use is qualitative, it can also be found in articles in which it is used in quantitative determinations of flavonoids, among other compounds.

A critical assessment of the potential of new analytical methods for the determination, qualitative and quantitative, of LUT is crucial in analytical chemistry regardless of the specificity of the method. Usually,

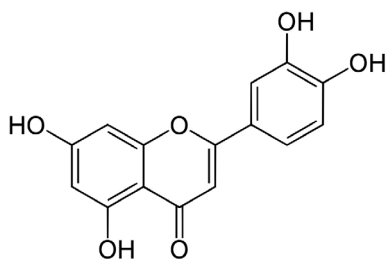


FIGURE 1 Chemical structure of luteolin

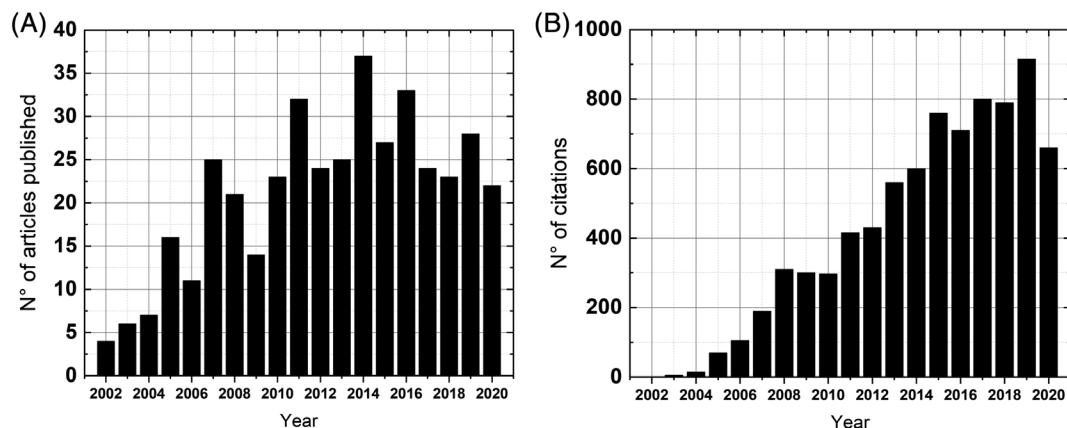


FIGURE 2 (A) Time evolution of articles published and (B) citations of the same. Keywords used: {"luteolin" + "chromatographic" + "determination"} (source: Web of Science)

validation criteria are used for this purpose, including parameters such as precision, accuracy, sensitivity, recovery, and so on. Thus, the potential assessment of a method consists in separate consideration and comparison of individual parameters with commonly accepted standards, as well as between different alternative methods.

This approach has the disadvantage that it is difficult to express the analytical potential of a methodology using one unified measure, which would cover all validation criteria and allow easy overall assessment. Due to the above, conducting a comprehensive assessment of an analytical method covering all the mentioned attributes is extremely difficult without special tools aimed for this purpose.¹⁶

Likewise, we propose a critical review of the publications related to luteolin quantification methods, published in recent years, which, in our opinion, are the most relevant in their area. We did this work, emphasizing the similarities and differences between methods, as well as trying to mark advantages and disadvantages of each of them.

Finally, with the development of instruments that generate higher-order data and the in-depth study of chemometrics, chemical multiway calibration has begun to play an important role in qualitative and quantitative analysis, allowing analytes can be determined even in the presence of unexpected interferences. The possibility of detecting and modeling the presence of interferences in a sample has allowed for the development of analytical protocols, which greatly differ from classical univariate calibration methodologies.¹⁷

Thus, although to a lesser extent, the methodologies for the determination of luteolin are not beyond these proposals. For that reason, some works that tend to cover this novel field of analytics are mentioned for such aim.

Based on our experience in many determinations of toxic compounds,^{18,19} agri-food,^{20,21} and so on fundamentally through electroanalytical methods and particularly through the work carried out on various flavonoids,^{22,23} among them luteolin,^{24–26} it is that we made this review article about all the techniques developed for their determination, putting special emphasis on the most relevant ones in their fields in the last years.

2 | CHROMATOGRAPHIC DETERMINATIONS

Being one of the most widely distributed analytical technique to separate, identify, and usually quantify analytes, chromatographic techniques become the reference technique for the determination of thousands of analytes, and luteolin is not an exception.

Analyzing the production of the academic articles in the last few years through the use of the keywords {"luteolin" + "chromatographic" + "determination"}, we can find a big increase year by year with a big growth of its cites (Figure 2(A,B)).

Inside this topic, we will discuss some of the most relevant articles related to the field, separated by the kind of chromatographic; technically speaking, about the pressure of the chromatographic column.

2.1 | Thin-layer chromatography

Thin-layer chromatographic (TLC) is especially useful for the rapid screening of flavonoids in plant raw materials and extracts for food and pharma applications often focus on phenol carbonic acids and flavonoids prior to detailed analysis by instrumental techniques such as liquid

chromatography, especially because many samples can be analyzed simultaneously. The visual detection and comparison of ratio of fronts (RF) values of applied reference substances only render limited phytochemical information.

In most cases, silica is used as stationary phase, and plates are developed with either a combination of 2-(diphenylboryoxo) ethylamine and polyethylene glycol or with AlCl_3 . Detection is mainly performed using UV light at 350–365 or 250–260 nm or with densitometry at the same wavelengths. At present, TLC still plays an important role in flavonoid analysis.

On the other hand, other variants to TLC have also been implemented. Such as the use of thin-layer chromatographic scanning (TLCS) method for the qualitative and quantitative study of different components. TLCS not only is easy to use, economical, rapid, accurate, effective, but it also avoids the shortcomings of the traditional TLC, as well as the quantitative requirements.²⁷

Also, TLC can be found in an automated and standardized form, that is, high-performance thin layer chromatography (HPTLC). It is widely applied for phytochemical analysis of complex samples, such as extracts and fractions from isolation processes.²⁷

In addition, for many of these applications, the assignment or confirmation of molecular structures to TLC is important. As RF values alone are not often highly reproducible and do not allow the unequivocal assignment of a certain compound (currently established TLC-MALDI protocols involve scratching the chromatographic phase off the carrier and elution of the analyte prior to spectroscopic or mass spectrometric analysis), a matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is introduced to directly read out TLC traces reproducibly while maintaining the chromatographic resolving power.

On the other hand, different classification analysis using chemometric tools, such as principal component analysis (PCA), is widely implemented in combination with different analytical techniques.

In this sense, PCA is a useful statistical technique that has found application in fields such as patterns recognition, as the case of TLC.

Patel et al. proposed HPTLC method for quantitative estimation of two compounds, one of which was luteolin, in *Premna mucronata* Roxb., family Verbenaceae.²⁸ The separation was performed on silica gel 60 F254 HPTLC plates using toluene:ethyl acetate:formic acid (6:4:0.3) as mobile phase for elution of markers from extract. The determination was carried out in fluorescence mode using densitometric absorbance-reflection mode at 366 nm for luteolin. The calibration curve was found to be linear between 200 and 1000 ng/band, the limit of detection (LOD) was found to be 42.6 ng/band, while the

limit of quantitation was found to be 129.08 ng/band for luteolin, respectively. The methanolic extract of *Premna mucronata* was found to contain 10.2 mg/g luteolin. Thus, this method is capable of quantifying and resolving luteolin and can be applicable for routine analysis of extract and plant as a whole.

Satpathy et al. developed a novel HPTLC method for the quantification of two components, including luteolin, in *Hygrophila spinosa*.²⁹ The separation was carried out on HPTLC plates using the mobile phase toluene–ethyl acetate–formic acid (6.0:4.0:1.0, v/v), and detection was achieved at 349 nm. The method was accurate in triplicate results at different standard addition levels with average recoveries of 100.01% for luteolin. The limits of detection and quantification were for luteolin 2.36 and 7.55 ng, respectively. The luteolin contents in the alcoholic extract and ethyl acetate fraction were 0.172 and 0.464 mg/g, respectively. Thus, the developed method could be used for the quality control analysis and quantification of luteolin in herbal preparations containing *H. spinosa*.

Lan et al. determined the content of four compounds, including luteolin, in different growth stages in *Artemisia rupestris* L. by TLCS, which could be used as the theoretical basis for quality control and determination of harvest time.³⁰

Chloroform, methanol, formic acid, and water (6.35:0.63:0.17:0.07, v/v) were used as the developing solvent. The scanning wavelengths were 250 nm and 352 nm. The linearity ranges of luteolin were of 0.0172–0.0976 μg . Precision analyses showed a relative standard deviation less 5.0%. Their average recovery percentages were 99.9%.

Kroslakova et al. studied the feasibility of direct coupling of HPTLC with MALDI-TOF MS for determination qualitative of four components, among them luteolin, on phytochemical fingerprints. All compounds studied were distinctly detected in MALDI-TOF MS, particularly luteolin that could not have been distinguished by for a simple visualization of HPTLC.³¹

Thus, HPTLC-MALDI-TOF MS was successfully applied to the analysis of flavonoids in complex phytochemical mixtures. The combination of the two techniques had created a helpful tool for combating difficulties occurring during analysis associated with either HPTLC (co-elution) or MALDI MS (fragmentation) when used alone.

Hawryl et al. studied seven different *Scutellaria* species using TLC combined with chemometrics analysis.³² The qualitative characterization involved identifying fifteen compounds, among which was luteolin. The aim of this article was the fingerprint analysis of extracts from different species of the genus *Scutellaria* to estimate the identity of various plant materials by TLC and subsequent

PCA. Thus, the experiments gave information about the composition of the plant extracts and were helpful in the construction of fingerprints of the examined herbs and varieties to facilitate their identification and assist in *Scutellaria* chemotaxonomy.

Selected standards of flavonoids and phenolic acids were separated using silica gel TLC plates with the mobile phase consisting of ethyl acetate–toluene–formic acid (5:4.9:0.1, v/v) for dichloromethane and methanolic extracts. Dichloromethane extracts were also developed using cyanopropyl-bonded silica gel with the following mobile phases: propan-2-ol–*n*-heptane–formic acid (5:4.9:0.1, v/v) and methanol–water–formic acid (6:3.9:0.1, v/v), and after drying, they were sprayed using the anisaldehyde reagent. In the case of methanolic extracts, the same nonaqueous eluent was used and the aqueous eluent consisting of methanol–water–formic acid (4:5.9:0.1, v/v). The presence of selected standards in *Scutellaria* species was confirmed.

2.2 | Liquid chromatography

Liquid chromatography (LC) is one of the most popular separation techniques in which the mobile phase is a liquid used to dissolve the samples to analyze. The separation takes place inside of a solid column. To do that, the sample, dissolved in the mobile phase, passes through the column, which is packed with a stationary phase composed of different kinds of particles. The differences in the interaction between the molecules of the sample and the particles in the column produce different transit times of the mentioned molecules through the column. In this way, the analytes of the sample leave the column separated into fractions at different times. Nowadays, LC is a very used technique mainly in small scales work to purify and isolate components from mixtures.

The solvents used in this technique are common and its sole objective is to dissolve all the species present in the sample and to have a polarity contrast, in order to make a gradual elution of all compounds. Acid solvents like phosphoric acid, formic acid, and acetic acid, organics solvents like methanol, acetonitrile, and acetone as well as water and some buffers are the most common solvents used as mobile phase, mainly in gradients programs of elution.

Although the solvents used are not many and are similar among the different works, in the case of the columns, there are even fewer differences. Practically all the studies agree to use a C₁₈ column. C₁₈ means that the molecules in the column particles have 18 carbon atoms but could be different molecules that fit with that having

distinct atoms. Also, the columns could have different lengths.

The most commonly used detectors, coupled to LC, are those based on the technique of mass spectrometry, called mass/mass detectors (MS/MS), which are able to isolate and identify the components of the sample according to their mass/charge ratio by using electric and magnetic fields. Its ability to determine the molecular weight of the compound to be identified makes it one of the most powerful detectors.

Despite the fact that, for historical reasons, LC is the mother of all chromatography, and this distinction is usually made in some articles, the truth is that most articles that report studies with LC do so with HPLC columns. Knowing this and respecting this difference, made by the authors, we made this section and included it under the LC section.

By using LC–MS/MS, the group of Zhang could characterize 23 polyphenolic compounds from sesame oil, included luteolin with a LOD of 0.15 µg/kg.³³ Adding the technique of electrospray ionization (ESI), to produce ions from the analytes, coupled with the MS/MS detector, the group of Tomczyk could identify and quantified 31 compounds from *Ziziphora taurica* (subsp. *Taurica*), reaching a LOD value of 1.34 µg/L³⁴

In the work of Han and co-worked, a rapid LC–QQQ–MS method (triple Quad MS) was used for simultaneous determination of luteolin and others eight major compounds in *Eclipta prostrata* L. in different habitats.³⁵ The results yielded good analytical parameters and the speed with which these analyses can be performed stands out. Among the analytical parameters, is to highlight both the great stability of the method (residual standard deviation [RSD] intraday 1.56%; RSD interday 1.60) as well as its very low LOD, 1.77 ng/ml.

Although detection by MS/MS predominates in LC, there are other detection techniques such as diode array detector (DAD). Regarding that, in the work of Monago-Maraña et al., luteolin and other four more compounds from the extract of Paprika with and without “Protected Designation of Origin” were reported by using LC in series with DAD and fluorescence detection (LC–DAD–FLD). In the case of luteolin, it was found in the concentration range of 16–19 mg/kg and 11–21 mg/kg, respectively.³⁶ Notice that in this work, remarkable recuperation values could be achieved (between 98.4% and 99.2%) with excellent range values of intraday and interday stability, 0.79%–5.2% and 1.1%–7.7% RSD, respectively.

Table 1 summarizes the most relevant studies in relation to analytical determinations of luteolin (among others compound) by LC in the last years.

TABLE 1 List of the most relevant scientific articles related to the determination of LUT using LC

Method	Matrix	Number of compounds	Solvents	Flow rate (ml/min)	Concentration	Linear range	LOD	LOQ	Stability RSD (%)		References
									Precision RSD (%)	Recovery	
LC-QQQ-MS	Eclipta prostrata L.	8	Acetonitrile and water containing 0.1% HCOOH	0.3	4.64 mg/ml	0.028–20.17 µg/ml	1.77 ng/ml	11.22 ng/ml	Intraday 1.00 Interday 1.16	97.21	35
LC-DAD-FLD	paprika	5	Methanol:water (50:50, v/v)	2.0	190 mg/kg	0.05–15 mg/L	0.08 mg/L	0.03 mg/L	Intraday 0.15–5.2 Interday 1.1–5.4	NR	36
LC-MS/MS	Ginkgo biloba extract	11	0.1% Formic acid and methanol	1.0	0.088–0.350–1.400 µg/ml	0.035–3.5 µg/ml	0.0080 µg/ml	0.023 µg/ml	NR	92.4–95.4	37
LC-MS/MS	Sesame oil	23	0.01% acetic acid methanol and 0.01% acetic acid water	0.2	50–500 µg/kg	0.50–2000 µg/kg	0.15 µg/kg	0.50 µg/kg	Intraday 1.2–3.2 Interday 0.8–2.2	98.4–101.3	33
LC-ESI-MS/MS	Thymus schimperi Ronniger	23	0.1% Acetic acid in distilled water and acetonitrile	0.5	5–50 mg/L	NR	0.38 mg/L	1.27 mg/L	Prec. 8.82–14	79.15–108.16	38
LC-MS/MS	Jindenglong in rat plasma	5	Methanol, acetonitrile, and water and additives, formic acid, and acetic acid	0.5	4–400 ng/ml	2.0–500 ng/ml	NR	2.0 ng/ml	Intraday 1.89–3.10 Interday 3.07–5.49	105–106	39
LC-ESI-MS/MS	Ziziphora taurica subsp. taurica	31	0.1%, v/v formic acid solution and methanol	0.4	5347.32–5339.91–780.53 µg/g	NR	1.34 µg/L	4.46 µg/L	NR	NR	34
LC-ESI-MS/MS	Table olives	17	Water with 0.025% acetic acid and acetonitrile with 5% acetone	0.8	88.0 mg/kg	0.005–5.0 µM	0.0003 µM	0.0009 µM	Intraday 0.28–5.46 Interday 0.28–5.46	NR	40
LC-ESI-MS/MS	Cassia occidentalis Linn. stem	5	Methanol - 10 mM ammonium acetate buffer	0.6	3–75–150 ng/ml	1–200 ng/ml	NR	1 ng/ml	Intraday 0.37–5.67 Interday 4.42–5.67	84.62–94.98	41

Abbreviations: DAD, diode array detector; ESI, electrospray ionization; LC, liquid chromatography; MS, mass spectroscopy; FLD: fluorescence detection; QQQ: triple quad.

2.3 | High-performance liquid chromatography

HPLC is the technique commonly used for the separation of components in a mixture based on their differential distribution between mobile and stationary phases. It is a robust analytical technique mainly used for the qualitative analysis of non-volatile classes of compounds such as flavonoids.⁴² Since luteolin exists in complex natural matrices, the analytical methods implemented must be selective and sensitive.

In the sense, the application of HPLC can consist of both the qualitative and quantitative estimation of a particular composition of samples obtained from natural sources. The results of the qualitative analysis are evaluated based on the consistency in the retention time of reference standards and the compounds in the analyzed sample. Quantitative estimation is done based on the standard curve generated after reference standards are injected at different concentration levels.⁴²

The column is a major component of HPLC. The column contains the particles used as stationary phase. Stationary phases usually have a particle size ranging between 3 and 50 μm packing contained in a column with 2–5 mm bore size. Most of the separations are carried out on reversed-phase (RP) columns.⁴³ RP columns used in HPLC are more desirable and widely used for the analysis of multiple phytoconstituents routine HPLC methods use RP octadecyl silica columns for phenolic compounds. Silica-based C_{18} columns in RP-HPLC contain aliphatic C_{18} ligands, free silanols, water, and mobile phase modifier.⁴³

Thus, in the vast majority of the works reviewed for the determination of luteolin, the RP was implemented, employing octadecyl C_{18} -bonded silica columns, with the following conventional dimensions employed: column length 50–250 mm, internal diameter 3.9–4.6 mm, and particle diameter 1.8–10 μm .

Mobile phase selection depends on the type and nature of compounds to be separated by HPLC. Generally, water and organic solvents such as methanol and acetonitrile along with small concentrations of acetic acid, formic acid and tri-fluoroacetic acid (TFA) are used for the separation of luteolin from different matrices by RP-HPLC.

Gradient elution is generally performed with a binary solvent system comprising an organic modifier and a slightly acidified aqueous phase. Instead of linear elution gradients, complicated gradient profiles, comprising several steps and applying various slopes, are often used. Thus, in the HPLC analysis of luteolin, separations were obtained by acidifying the mobile phase. A weakly acidic mobile phase suppresses ionization, thereby, increasing

retention and decreasing the peak broadening that is caused by the formation of the deprotonated form.⁴³

For HPLC analysis, the selection of an appropriate column temperature and injection volume is another factor influencing detection. In this sense, the analyzes for luteolin were carried out between 25 and 30°C and injection volumes between 1 and 20 μl .

Another aspect to consider in the detection is the selection of a suitable detector. Detectors play a significant role in the precision, accuracy, and stability during the detection of a specific compound from complex samples.⁴⁴ The detectors used most often are based on UV absorbance or, less frequently, visible light absorbance. In analysis of luteolin, UV detectors can be used, due to the presence of aromatic rings in the molecule. Flavonoids display two UV-vis absorption maxima: an absorption band in the region of 240–285 nm ascribed to the A-ring, and a second band at 300–550 nm due to the B-ring. In particular, luteolin shows a maximum in the absorption band between 300 and 380 nm.⁴³

The use of a UV detector that performs the analysis only at one wavelength is limited in studies with mixing of components in the matrix, because the absorption maxima of different compounds maybe similar.⁴³ The solution to this problem is the use of a UV-diode array (UV-DAD), allowing for continuous adjustment of the wavelength across the UV-visible interval of the spectrum. Although, for luteolin, the detection limits (LODs) in HPLC-DAD were like those for UV detection.

Compared to the above detectors used in luteolin analysis, HPLC-MS offers higher sensitivity, selectivity and versatility. This type of detection is especially useful for reliable identification in complex matrices. The use of HPLC-MS obtains simultaneously information regarding not only the type, the amount, and the retention times of the particular compounds but also their molecular weight and fragmentation pathways.⁴⁵

The analysis with MS detector may be performed with different types of ionization in the ion source. In the case of luteolin, ESI was most commonly used.

Although luteolin may be determined in both positive $[\text{M} + \text{H}]^+$ and negative $[\text{M} - \text{H}]^-$ ion modes, the negative ionization mode was used in most cases. An important element of the MS detector is the analyzer. In the analysis of luteolin, the most commonly used analyzers were quadrupole and triple quadrupole. Due to the low resolving power of a single device, tandem mass spectrometers are much more frequently used. Such systems not only are more selective and sensitive but also allow for quantitative analysis, provide information about the structure of the compound, and characterize the fragmentation pathways of a single compound present in a complex matrix. Currently, in the analysis of flavonoids, a

combination of several detectors, mainly UV-MS, is most used.⁴²

HPLC still is the ideal analytical separation technique used commonly for quantitative and qualitative analysis of natural compounds.⁴⁶ Various studies have reported the optimized chromatographic conditions used for the separation of flavonoids from complex samples.⁴²

Ma et al. proposed a method based on HPLC coupled to a UV detector (set at 350 nm) for the simultaneous determination of seven compounds in bamboo leaves, included luteolin.⁴⁷

Calibration curves showed a linear regression between 1.54 and 24.72 $\mu\text{g/ml}$ for luteolin. LOD and LOQ were 0.19 $\mu\text{g/ml}$ and 0.58 $\mu\text{g/ml}$ for luteolin, respectively, the intraday precision (RSD, %) determined for three concentration levels was less than 1.07%, and the stability evaluated during 24 h (RSD, %) was 2.58%. The recoveries for luteolin were in the range of 107.39%–109.26% with an RSD of 0.83%.

Yin et al. proposed another very interesting HPLC method coupled to UV (set at 350 nm).⁴⁸ First, several experimental parameters that affected the extraction performance, such as the solvent, the microwave irradiation time, temperature, and solid-to-liquid ratio, the type of adsorbent, the amount of sample, the adsorption time, and volume of the eluent were optimized by Box–Behnken experiments design. Then, they developed a method for the simultaneous determination of seven flavonoids, including luteolin, in *Veronicastrum latifolium* (Hemsl.). Calibration curves were linear in the range of 3.906–250 $\mu\text{g/ml}$ for luteolin. The intraday and interday precision RSD were 1.41% and 3.93%, respectively. This method had a LOD of 0.027 $\mu\text{g/ml}$ and recoveries of 98.87%.

Zhang et al. described an interesting methodology based on gradient HPLC coupled to photo diode array detector (PDA) for determination of content of 16 phenolic compounds of seeds from nine tree peony (*Paeonia* section *Moutan* DC.) species native to China.⁴⁹ UV detection was recorded between 200 and 400 nm. Calibration curves were linear in the range of 1.15–57.3 mg/ml for luteolin. These authors reported a LOD and LOQ to luteolin of 0.11 and 0.35 mg/L, respectively. The method yielded very satisfactory results when it was applied to tree peony, with the intraday and interday precision RSD for luteolin were of 2.52% and 2.98%, respectively, and recoveries of 96.19%.

Du et al. proposed a method based on HPLC with diode array detector (DAD) to the simultaneous determination of 11 components in Yinzhihuang preparations and their constituent herbs.⁵⁰ Calibration curves were linear in the range of 0.01–1.0 μg for luteolin. The DAD spectra were recorded between 190 and 400 nm. The LOD and LOQ for luteolin were 0.0015 and 0.0051 μg ,

respectively. Recoveries of luteolin were between 98.1% and 110.1%. The intraday and interday precision RSD for luteolin were less to 1.04% and 1.2%, respectively.

Sarikahya et al. described several flavonoids and phenolic compounds in 19 different *Cephalaria* species by HPLC-MS/MS.⁵¹ This method was developed for quantitation of thirty-four components, including luteolin, using reverse phase in ESI mode. Calibration curves were linear in two range 0.3–25.2 ppb and 3.0–102.3 ppb, for luteolin. The recovery of the developed method was 99.8% to luteolin. LOD and LOQ values were of 0.7 and 3.5 ppb, respectively.

By using HPLC-MS/MS, Yan et al. could characterize 20 compounds, such as flavonoids, phenolic acids, and alkaloids, included luteolin, in abri herba and abri mollis herba.⁵² Calibration curves were linear in the range of 0.13–4680.00 ng/ml for luteolin, with LOD and LOQ of 0.01 and 0.03 ng/ml for luteolin, respectively.

In addition, the technique of ESI to produce ions from the analytes, coupled with the MS/MS detector, allowed Zhang to identify and quantify thirteen compounds from *Commelina communis*.⁵³ Calibration curves were linear in the range of 0.0083–0.53 $\mu\text{g/ml}$ for luteolin, reaching a LOD and LOQ of 0.0066 and 0.0264 $\mu\text{g/ml}$ for luteolin, respectively.

On the other hand, to a lesser extent, developments with HPLC-quadrupole-time of-flight (Q-TOF)-MS were implemented. Thus, Yang et al. determined 15 Flavonoids in *Scutellaria barbata*–*Hedyotis diffusa* Herb Pair by HPLC Q-TOF/MS.⁵⁴ These authors reported a LOD and LOQ to luteolin of 0.75 and 2.38 ng/ml, respectively. The method yielded very satisfactory results, with the intraday and interday precision RSD for luteolin were of 2.62% and 1.58%, respectively, and recoveries of 100.5%.

Shui et al. determined the content of luteolin in five crops of *Chrysanthemum morifolium* Ramat (Chr) by HPLC-UV method.⁵⁵ His proposal was to investigate luteolin content in different Chr cultivates by implementing multispectral images (MSI). A combination of MSI with a PCA and least squares-support vector machines (LS-SVM) was applied to classify Chr cultivars. PCA derived from the spectral and morphological features data of the samples explained 99.61% for summing up the first three principal components and the LS-SVM model achieved 98% discrimination accuracy in the prediction set. Additionally, partial least squares (PLS) and LS-SVM models were obtained to predict performance for luteolin content determination, with prediction correlation coefficient (Rp) of 0.949 and 0.965, and root mean square error of prediction (RMSEP) of 0.387 and 0.314 mg/g, respectively.

Table 2 lists the diverse applications in natural product analysis studied using HPLC method for qualitative and quantitative analysis of luteolin, in the last years.

TABLE 2 List of the most relevant scientific articles related to the determination of LUT using HPLC

Method	Matrix	Content	Number of compounds	Solvents	Flow rate (ml/min)	Concentration	Linear range	LOD	LOQ	Stability RSD (%)		References
										Precision RSD (%)	Recovery (%)	
HPLC-UV	Bamboo Leaves	0.4–87.7 µg/ml	7	0.1% formic acid in water and acetonitrile	1.0	1.545 6.180 24.72 µg/ml	1.54–24.72 µg/ml	0.19 µg/ml	0.58 µg/ml	Stab. 2.58 Intraday 0.28–1.07	107.40–109.26	47
HPLC-UV	Paronychia argentea Lam	0.4%	2	Water-methanol and acetic acid (700:300:10)	1.0	143.2–214.8–286.4 µg/ml	143.2–572.9 µg/ml	3.19 µg/ml	9.7 µg/ml	Prec. 5.1	NR	56
HPLC-UV	Rat plasma	3.04 µg/ml	3	Methanol and 0.2% phosphoric acid (50:50 v/v)	1.0	0.56 2.80 8.96 µg/ml	0.11–11.20 µg/ml	NR	0.11 µg/ml	Stab. 4.65–5.26	93.93–96.78	57
HPLC-UV	Veronicastrum latifolium yamazaki	4.1%	7	0.5% Phosphoric acid in aqueous solution and ACN	0.8	0.011–0.078 µg/ml	3.906–250 µg/ml	0.027 µg/ml	0.088 µg/ml	Intraday 1.41 Interday 3.93	98.87	48
HPLC-UV	Water	2–500 µg/L	3	MeOH:ACN:0.02 M H ₃ PO ₄ 35:35:30	1.0	2 10 500 µg/l	0.25–1000 µg/L	0.09 µg/L	0.2 µg/L	Intraday 2.16 Interday 2.52	81–105	58
HPLC-UV	Serum Green tea	50–100–200 ng/ml	2	Methanol 0.2%-aqueous phosphoric acid solution pH 3.2	1	50–100–200 ng/ml	0.005–3 µg/ml	4.5 ng/ml	1.5 ng/ml	Intraday 1.84 Interday 2.24	98.5 98.4	59
HPLC-DAD	Scutellaria L Taxa	0.041 0.047 (w/w%)	6	Water-acetonitrile-0.02% acetic acid	0.8	10–20–60 µg/ml	1–75 µg/ml	0.058 µg/ml	0.232 µg/ml	Intraday 0.04–0.30 Interday 0.11–0.67	99.74–107.26	60
HPLC-DAD	Abnormal Savda munziq	0.1980 mg/g	6	0.3% v/v formic acid in water 0.3% v/v formic acid in methanol	1.0	165.67–285.76 mg/g	0.23–1.38 µg/mL	0.022 µg/ml	0.074 µg/mL	Stab. 0.11 Prec. 0.37	99.39	61
HPLC-DAD	Yinzhihuang and their herbs	0.928 5.101 mg/g 0.1936 0.3911 mg/ml	11	ACN and 0.1% formic acid water	1.0	0.020–0.500–0.900 µg	0.010–1.0 µg	0.0015 µg	0.0051 µg	Intraday 0.48–1.04 Interday 0.42–1.2	98.1–100.1	50
HPLC-DAD	Dimocarpus longan	0.115–0.194 mg/g	5	Methanol 0.2% phosphoric acid	0.3	NR	0.00920–0.0460 µg/ml	NR	NR	Estab. 1.68 Prec. 1.98	93.28–103.74	62
HPLC-DAD	Olive oil	0.1–3.24 mg/kg	9	0.1% formic acid in water Methanol/i-PrOH 90:10 v/v With 0.1% formic acid	1.0	10 mg/kg	0.16–100 mg/L	0.023 mg/kg	0.077 mg/kg	Prec. 4.6	71–85	63

(Continues)

TABLE 2 (Continued)

Method	Matrix	Content	Number of compounds	Solvents	Flow rate (ml/min)	Concentration	Linear range	LOD	LOQ	Stability RSD (%)		References
										Precision RSD (%)	Recovery (%)	
HPLC-DAD	Aromatic organic acid preservatives	54.9 µg/L	7	Methanol/water 0.25% phosphoric acid (v/v 60:40)	1.0	100 µg/L	5–1000 µg/L	0.5 µg/L	5 µg/L	NR	90.4	64
HPLC-DAD	Onion Chili And leek	—	4	0.1 M phosphoric acid in water and methanol	1.0	50 100 125 160 200 mg/L	50–200 µg/g	0.3 mg/L	1.1 mg/L	Intraday 18 Interday 23	76–108	65
HPLC-DAD	Grape juice	0.81–106 µg/L	4	Methanol 0.1% v/v water (55/45) v/v	1.0	1 100 µg/L	0.5–200 µg/L	0.095 µg/L	0.31 µg/L	Intraday 1.7–9.6 Interday 2.5–2.7	70.3–120	66
HPLC-DAD	Tea	20	3	NR	NR	10	14–1500	3	1.4	Intraday 2.8–4.8	88.4–101.4	67
	Urine	100				100	1.5–1500	0.3	1.5	2.8–5.2	84.9–92.5	
	wine	200 ng/ml				200 ng/ml	2.5–1500 ng/ml	0.5 ng/ml	2.5 ng/ml	1.4–3.2 Interday 2.4–3.3 2.6–5.9 1.7–2.6	86.7–92	
HPLC-DAD	Seed Tree peony	8.74–14.33 mg/100 g DW	16	Water/acetic acid 99.1 v/v acetonitrile	0.5	NR	1.15–57.30 mg/L	0.11 mg/L	0.35 mg/L	Intraday 2.52 Interday 2.98	96.19	49
HPLC-ESI-MS	Xiaobuxing-Tang	0.004 mg	13	ACN—water with 5 mM ammonium formate	0.2	20–200–2000 ng/ml	20–2000 ng/ml	5 ng/ml	15 ng/ml	Stab. 86.6–104.5	86.2–89.6	68
HPLC-ESI-MS	Commom cnidium fruit	0.89 µg/g	16	ACN and water 0.1% acetic acid	1.0	2.89–5.63 µg	8.20–410.0 ng/ml	2.89 ng/ml	8.01 ng/ml	Stabil. 3.9 Intraday 3.3 Interday 3.1	97.84	69
HPLC-MS/MS	Abri Herba Abri mollis Herba stems	13.03 µg/g 9.28 µg/g	20	Methanol + acetonitrile and 0.5% acetic acid in water	0.8 and 1	0.70 µg	0.13–4680.00 ng/ml	0.01 ng/ml	0.03 ng/ml	Intraday 5.87 Interday 6.4	94.3 108.2	52
HPLC-ESI-MS-MS	Commelina communis Linn.	0.1948–0.5639 - 0.6065 - 0.1599 µg/g	13	Water containing 0.1% formic acid and acetonitrile 0.1% formic acid: 2 mM ammonium formate - methanol	0.3 0.8	0.2242 0.2796 0.3349 µg	0.008360–0.5350 µg/ml	0.006661 ng/ml	0.0264 ng/ml	Intraday 1.04 Inter day 0.92	98.64–100.8	53

TABLE 2 (Continued)

Method	Matrix	Content	Number of compounds	Solvents	Flow rate (ml/min)	Concentration	Linear range	LOD	LOQ	Stability RSD (%)		References
										Precision RSD (%)	Recovery (%)	
HPLC-MS/MS	Cephalaria	0.01–4.45 mg/g	34	0.1% formic acid solution in water and in methanol	0.3	NR	NR	0.7 ppb	3.5 ppb	NR	99.8	51
HPLC-MS/MS	Semen Cuscutae	2–25–50 ng/ml	13	0.1% formic acid in water and acetonitrile	0.3	2–25–250 ng/ml	1–250 ng/ml	NR	1 ng/ml	Intraday 5.1 Interday 2.8	87.4–106.2	70
HPLC-EL-MS	Perilla frutescens var. japonica seeds	0.07–0.47 mg/g	3	0.5% acetic acid and MeOH	0.5	NR	0.01–100 mg/ml	0 mg/ml	0.003 mg/ml	NR	NR	71
HPLC-QTOF-MS	Punica granatum L. Husk		50	0.1% formic acid/water and H ₂ O and methanol	1.2	NR	NR	NR	NR	NR	NR	72
HPLC-QTOF-MS	Scutellaria barbata-Hedyotis diffusa Herb Pair	122.3 ng/g	15	Water containing 0.1% formic acid and acetonitrile containing 0.1% formic acid	0.45	3058.7 6117.3 9176.0 µg	187.5–7500 ng/ml	0.75 ng/ml	2.38 ng/ml	Intraday 2.62 Interday 1.58	97.7–100.5	54

Abbreviations: DAD, diode array detector; ESI, electrospray ionization; HPLC, high-performance liquid chromatography; MS, mass spectroscopy; UV, ultraviolet; QTOF, quadrupole time-of-flight.

2.4 | Ultra-high performance liquid chromatography

Ultra-high performance liquid chromatography (UHPLC, usually called ultra-high pressure liquid chromatography) is a subcategory of HPLC technique able to operate up to 600 bar (8700 psi), which use particles of sub-2 μm size and a very low dispersion. These characteristics allow to both save solvent and increase performance reducing run times.⁷³

UHPLC is one of the last developed chromatographic techniques, although the first continuous reports in time are from the early 2000s, there is a marked rise in the number of publications around 2010. Among several analytes studied by UHPLC, luteolin appears like others, in the last few years. For that reason, there are only a few works using UHPLC to carry out analytical determinations of luteolin. A list of the most relevant work, to our criteria, is shown in Table 3.

Among them, the work of Hu stands out because of its analytical parameters. Working with grape juice, they reach a value of 0.5 ng/ml in the determination of luteolin (analyzing three compounds at the same time).⁷⁷ Although having excellent values of stability and recovery, it lacks a wide lineal range, which is extremely important at the time to work with samples of unknown analyte concentration.

Note that is easy to see in Table 3 how the simultaneous compound analysis is improved by the use of MS/MS reaching to analyze 26 different compounds drawn on the benefit of a triple quadrupole.

2.5 | Ultra performance liquid chromatography

UPLC, is defined by its creator, the company Waters®, as the chromatographic technique that uses sub-2 μm particle in low dispersion columns and in combination with high pressure (1034 bar; 15,000 psi).

In a very brief comparison between UPLC and HPLC, we can say that UPLC decreases process cycle time, reducing cost and the use of solvents and even the sample injection volume, increasing the sample throughput. Compared to HPLC, UPLC column (with an inner diameter of 0.75–1.8 mm vs. HPLC 3–10 mm) suffer higher backpressure which reduces its useful life. In the same line, the very small particles used in the UPLC columns, in most of the cases are not renewable.

Related to UHPLC, the higher loading capacity is close to three times higher using fully porous particle columns in UPLC than using superficially porous particle columns on a UHPLC system. (UPLC versus UHPLC:

Comparison of Loading and Peak Capacity for Small Molecule Drugs - Kenneth J. Fountain)

Like the case of UHPLC, UPLC is one of the last developed techniques, by Waters in 2004. Although today, there are thousands of reported where this technique is used, it is still not as popular as the HPLC technique and that is why the number of works found, in particular for luteolin determinations, is less. Table 4 describes the most relevant studies, in our judgment, with relation to analytical determinations that include luteolin, among other analytes of interest, in a wide variety of matrix, mainly extracts, but not limited to them.

As can be seen from the bibliography cited in Table 4, the determinations performed using UPLC in most of the cases are focused in improving the analytical parameters at the expense of working with a lower number of analytes. This does not necessarily have to be the case, but it is what we find in most cases. Likewise, it can be observed how the used flows are lower, but by using smaller volumes of samples and being more efficient in the technique, this does not increase the analysis time, but the opposite.

Within this field of work, the one carried out by Li and co-workers,⁸⁶ in which determines simultaneously 18 chemical constituents in an antitussive used in the traditional Chinese medicine. This work stands out not only for the number of simultaneous determinations, of course, LUT including, but it also reaches excellent values in terms of LOD (1.562 ng/ml) and linear range (25–1600 ng/ml). Possibly this linear range of three orders of magnitude, which in terms of linearity is very good, become an issue to work with such low concentrations, especially if the concentration of the sample to be determined is completely unknown.

3 | ELECTROCHEMICAL DETERMINATIONS

A quick search with the keywords {"luteolin" + "electrochemical" + "determination"} show us a constant article production with a marked growing of citations (Figure 3 (A,B)).

Several articles report an analytical technique coupled with an electrochemical device used as a sensor to quantify the desired analyte in the sample. In this section, we will not be occupied to them, instead, will be focused on pure electroanalytical determinations, devices usually called "electrochemical sensors."

Although most articles in this field choose differential pulse voltammetry (VPD) as electrochemical technique for its intrinsic characteristics beneficial for quantification (i.e., time consumption, sensibility, portability), there

TABLE 3 List of the most relevant scientific articles related to the determination of LUT using UHPLC

Method	Matrix	Content	Number of compounds	Solvents	Flow rate (ml/min)	Concentration	Linear range	LOD	LOQ	Stability (%)		References
										Precision (%)	Recovery (%)	
UHPLC-MS/MS	Eriogon breviscapus extract	NR	12	0.1% formic acid in water and acetonitrile	0.3	10–20–100–160 ng/ml	10–200 ng/ml	6.0 ng/ml	10 ng/ml	Intraday 0.18–2.54 Interday 0.66–2.00	93.88–103.28	74
UHPLC-MS/MS	Jatropha gossypifolia -infusion - extract - fruit	14.9 µg/g 81.1 µg/g 5.7 µg/g	19	0.1% acetic acid in water and acetonitrile	0.8	9.7–14.9–80.9–13.4–81.1–5.7 µg/g	NR	NR	NR	NR	NR	75
UHPLC-QQQ-MS-MS	Tomato extract Lettuce extract	17–56 mg/kg 13–22 mg/kg	26	Methanol ammonium acetate 30 mM with formic acid	0.2	2.5 mg/kg 5 mg/kg	NR	10 µg/kg	25 µg/kg	Interday 9.0	64 61	76
UHPLC-DAD	Grape juice	Detected not quantified	3	60% (0.1% v/v phosphoric acid water) and 40% methanol	0.3	10 50 100 ng/ml	1–200 ng/ml	0.5 ng/ml	1 ng/ml	Intraday 2.1–3.2 Interday 3.7–4.5	97.8–103.5	77

Abbreviations: DAD, diode array detector; MS, mass spectroscopy; UHPLC, ultra high performance liquid chromatography; QQQ, triple quad.

TABLE 4 List of the most relevant scientific articles related to the determination of LUT using UPLC

Method	Matrix	Content	Number of compounds	Solvents	Flow rate (ml/min)	Concentration	Linear range	LOD	LOQ	Stability (%)		References
										Precision (%)	Recovery (%)	
UPLC	Compositae species extract	0.66–0.89 g/100 g	4	0.1% formic acid in water and acetonitrile	—	2.5–10–100 µg/ml	1–100 µg/ml	0.26 µg/ml	0.79 µg/ml	Intraday 0.60–2.15 Inter 0.68–2.34	95.49–106.23	78
UPLC	Disporopsis pernyi extract	2.51 µg/ml	4	0.1% formic acid in water and acetonitrile	0.2 ml/min	1.44	62.81–439.60 µg/ml	0.264 µg/ml	0.879 µg/ml	Prec 1.68 1.06 1.65	96.2–102.6	79
UPLC	Dimocarpus longan extract	0.109–0.192 mg/g	5	Methanol 0.2% phosphoric acid	0.3 ml/min	NR	0.00920–0.0460 µg/ml	NR	NR	Prec. 0.23 Stab. 1.06	93.28–103.74	62
UPLC-MS/MS	Yigan Jiangzhi Formula in Rat plasma	NR	14	0.1% formic acid in water and 0.1% formic acid in acetonitrile	0.4	2.5–50–400 ng/ml	1.0–500 ng/ml	NR	1.0 ng/ml	Intraday 2.01–3.40 Interday 2.99–10.76	74.68–77.32	80
UPLC-MS/MS	Antitussive	1.362–14.819 µg/g	18	0.1% HAc and MeOH 0.1% HAc	0.2 ml/min	0.90 9.000 36.000 µg	25–1600 ng/ml	1.562 ng/ml	3.125 ng/ml	Intraday 4.5 Interday 4.0	94–100.5	76
UPLC-MS/MS	Maydis stigma extract in rat plasma -normal group -diabetic group	414.4 ± 56.58 µg/L 746.2 ± 104.4 µg/L	6	Methanol and 0.1% formic acid water	0.3	5–125–800 ng/ml	1.0–1000 ng/ml	NR	1 ng/ml	Intraday 5.3–8.7 Interday 2.2–8.0	91.5–96.9	81
UFLC-ESI-MS/MS	Ginkgo biloba extract in rat Plasma -extract - pure compounds	58.21 ± 33.48 ng/ml 10.70 ± 8.06 ng/ml	7	0.1% formic acid-water and methanol	0.2	1.25–35–200 ng/ml	0.50–250 ng/ml	NR	0.5 ng/ml	Intraday 8.4–10.8 Interday 2.9–12.3	89.1–95.9	82
UPLC-ESI-MS/MS	Fios Lonicerae Japonicae - Fructus Forsythiae herb -Shuang-Huang-Lian oral liquid -Fufang Qin-Lan oral liquid -Qing-Re-Jie-Du oral liquid -Yin-Qiao-Jie-Du tablet	0.8800–10.86 µg/ml 05676–1.582 µg/ml 1.154–4.353 µg/ml 12.56–20.52 µg/tablet	26	acetonitrile/methanol (4:1, v/v) - 0.4% formic acid	0.4	NR	0.5490–70.31 ng/ml	0.04110 ng/ml	0.1370 ng/ml	Prec. 1.58 Intraday 4.47 Interday 3.13	96.2–100.50	83

TABLE 4 (Continued)

Method Matrix	Content	Number of compounds	Solvents	Flow rate (ml/min)	Concentration	Linear range	LOD	LOQ	Stability (%)		References
									Precision (%)	Recovery (%)	
UPLC/ ESI- MS	Aster tataricus extract	5	Acetonitrile and water both with 0.1% formic acid	0.3	0.39 ng/ml	0.1855–11.88 ng/ml	1.950 µg/ml	9.270 µg/ml	Prec. 2.49	99.87	84
UPLC/ ESI- MS	jussara (<i>Euterpe edulis</i>) Trace amounts extracts	27	Water and acetonitrile both acidified with 0.01% formic acid	0.5		65–1500 µg/L	2.66 µg/L	8.85 µg/L	NR	NR	85

Abbreviations: ESI, electrospray ionization; MS, mass spectroscopy; UPLC, ultra-performance liquid chromatography; UFLC, ultra-fast liquid chromatography.

are some that make use of other ones like linear sweep voltammetry (LSV), square wave voltammetry (SWV), and square wave anodic adsorptive stripping voltammetry (SWAASV), which achieve very good results.

In the next lines, we have summarized the articles according to our opinion, which produced the most relevant information in the field of electroanalytical sensor for luteolin determination in the last years.

There is a huge spectrum of samples in which luteolin has been quantified by electrochemical methods, among them: foods (tomato, carrot, peanut hulls, paprika, etc.), drinks (watermelon juice, Grape juice, Chrysanthemum tea, etc.), medicines (*Lamiophlomis rotata* Kudo and *Duyiwei* capsules, etc.) and human body related (urine, serum, thyme).

Most of the sample preparations are very simple, but could include dried, filtration and/or extractions steps. Is worth to mention that the usual chemical compound to extract luteolin is ethanol, which together with the characteristics of the electrochemical methods, turns it into a green and sustainable analytical method.

To sum up, an ideal electrochemical sensor has the features of high selectivity (determination of an analyte in presence of interfering substances), high stability (it can be used for a long period of time), high sensitivity (it allows the obtention of low LOD) and, finally, a wide linear range.

Regarding to the LOD, the work reported by Fu and Liu et al. reaching 1.7 pM,⁸⁷ together with the articles published by Dong and Guo et al., what reaches concentration of 3.3 pM,⁸⁸ and the work of Qu and Lu et al. obtaining a LOD value of 3 pM,⁸⁹ are the most promising in the field. It is noteworthy, in the case of these last two studies, in addition to extremely low detection limits, they achieve the measurement in a very short time, 60 s and 30 s, respectively. An additional improvement of the methods developed by Qu and Lu et al. is the electrode stability. The electrode, a three-dimensional nickel oxide and Ni-metal-organic frameworks nanoarrays modified titanium mesh (NiO@Ni-MOF/TM) could be suitable for its use for 4 weeks with 97.6% of its original response.

Continuing with this topic, it is good to note that most of the reports about the stability of the electrode are in the range between hours to a few weeks, usually no more than two. Is in this context it is where the gold-palladium-reduced graphene oxide nanofilm modified glassy carbon electrode (Au-Pd-rGO/GCE) reported by Tong and co-workers stand out, achieving a 3 months stability.⁹⁰

The time that the analysis takes is not a minor issue. There are works that need to extend the experimental time until 25 min to reach the extremely LOD reported. In general, we could say that the electrochemical measurement takes around 3 min and clearly there is a compromise between LOD and measurement time.

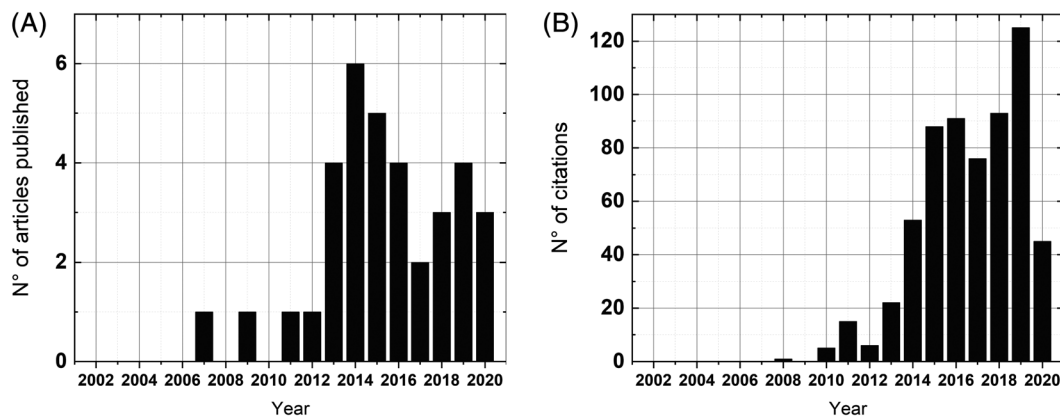


FIGURE 3 (A) Time evolution of articles published and (B) citations of the same. Keywords used: {"luteolin" + "electrochemical" + "determination"} (source: Web of Science)

Finally, an item that involves cost, portability, and stability is the simplicity of the electrode and/or the method used. At this point, it is important to highlight the work carried out by the group of Galeano-Díaz in which by moving the focus to data analysis instead of the electrode modification, they get good results (even in selectivity) through the use of a bare GCE together with a data analysis based on partial least squares analysis (PLS).⁹¹

Probably in the case of luteolin determination in real samples, it is more important that the sensor has a wider linear range than that it has an extremely low LOD. In a sample with an unknown value of luteolin concentration, it is important that the measured value falls within the calibration curve to avoid errors. Although it is interesting to have the ability to quantify analytes in the order of picomolar concentrations, in the case of luteolin it is not essential, since the concentrations usually to be determined are much higher. It is at this point where we want to highlight the work of Zheng's group and, one more time, the work of Tong's group in which values of a lineal range of (1×10^{-8} to 1×10^{-5}) M and (1×10^{-8} to 8×10^{-5}) M are, respectively, reported.

In addition to the previously mentioned parameters, there are others that are important and characterize an electrochemical sensor, such as the potential and pH at which they work, the percentage of recovery when the developed method is tested against a standardized method and its sensitivity, among others.

Finally, as mentioned in the introduction, chemometrics is an area that has become very important. In turn, within chemometrics multivariate calibration is one of the most prominent. In multivariate calibration, methods based on the data processing of the vectorial type are used, that is, spectra or other data like voltammograms, called first order, for the simultaneous determination of two or more analytes or an analyte in the presence of interferents.

In this sense, Tesio et al.⁹² developed a calibration model to simultaneous electroanalytical determination of luteolin in the presence of rutin in a pharmaceutical formulation using artificial neural networks. The methodology is based on square wave voltammetry at glassy carbon electrodes modified with multiwalled carbon nanotubes dispersed in polyethylenimine. According to values declared by the manufacturer, differences of 7.4% and 8.0% were calculated for luteolin and rutin, respectively. Results obtained with electroanalytical methodologies were in very good agreement with those obtained by HPLC.

Table 5 gathers the most important data extract from the articles reporting electrochemical determinations of luteolin published in the last years.

4 | OTHERS ANALYTICAL TECHNIQUES RELATED TO THE LUTEOLIN QUANTIFICATION

It is clear that the field of —luteolin quantification— is dominated by chromatographic techniques, followed, in a second place in popularity, by the electrochemical methods. Nevertheless, there are some other relevant techniques that do not fit into either of these two categories and we think they deserve being mentioned. The fact that these techniques are less widespread does not imply that their results are not competent enough compared to the popular ones. In this section, we will make a small brief of the articles we find most interesting.

Fluorescence spectrometry is a very powerful analytical technique. The work of Huang and co-workers shows its application to the quantification of luteolin.¹¹² In the proposed method, they use luteolin to quench the fluorescence of ofloxacin, which works in the lineal range from 2.00×10^{-7} to 8.00×10^{-5} M. They can achieve a

TABLE 5 List of the most relevant scientific articles related to the determination of LUT using electrochemical methods

Electrode	Technique	Matrix	Determinate concentration	pH	t acc (s)	E acc (V)	Linear range (M)	LOD (M)	Recovery (%)	Stability	References
PDDA-RGO/GCE	DPV	Thyme	$(1.19-9.02) \times 10^{-6}$ M	5.0	120	0.4	1×10^{-8} to 1×10^{-5}	1×10^{-9}	98.2–101.3	3 weeks	93
In ₂ O ₃ NPs/GCPE	SWV	Thyme, urine, serum	$(3.96-4.37) \times 10^{-8}$ M	5.0	180	-0.2	9.98×10^{-9} to 8.84×10^{-9}	1.99×10^{-10}	101.46–101.83	50 days	94
Nbim-CNT/GCE	DPV	Grape juice	$(6-24) \times 10^{-8}$ M	6.0	600	OCP	5×10^{-9} to 3.2×10^{-6}	6.0×10^{-10}	98–104	40 days	95
SS-β-CD-Pd@RGO	DPV	Human serum	$(5-75) \times 10^{-7}$ M	3.0	200	-0.2	1×10^{-8} to 1×10^{-5}	5.2×10^{-9}	98.8–106.0	30 days	96
MWCNTs-BMIMPF ₆ /GCE	DPV	Chrysanthemum	(1.86 ± 0.04) mg/g	4.5	200	NR	5×10^{-9} to 1×10^{-6}	5.0×10^{-10}	98.2–101.5	2 weeks	97
SH-β-CD-GNs/AuNPs/GCE	DPV	Human serum	$(4-100) \times 10^{-9}$ M	5.0	60	NR	1×10^{-11} to 1×10^{-5}	3.3×10^{-12}	97.1–103.2	2 weeks	87
HAP-CNT/GCE	DPV	NR	3×10^{-6} M	2.0	150	0.4	4×10^{-7} to 1.2×10^{-5}	8×10^{-8}	NR	50 times test	98
Au-Pd-rGO/GCE	DPV	Chrysanthemum, peanut shells	$(5-15) \times 10^{-6}$ M	7.0	NR	NR	1×10^{-8} to 8×10^{-5}	9.8×10^{-10}	97.4–103.4	12 weeks	89
PCV-MWCNTs/GCE	DPV	Chrysanthemum	1.73 ± 0.06 mg/L 2.54 ± 0.05 mg/L	7.0	NR	NR	2×10^{-8} to 7×10^{-5}	5.0×10^{-9}	94.8–105.4	4 weeks	99
PEDOT-MnO ₂ /GCE	DPV	Lamiophlomis rotata Kudo (capsule)	$(5-15) \times 10^{-9}$ M	3.0	NR	NR	5×10^{-9} to 7×10^{-6}	1.8×10^{-9}	98.3–103.5	4 weeks	100
GCE	DPV	Paprika	$(96-219)$ mg/kg	2.0	NR	NR	$(0.25-12)$ μg/ml	0.42 μg/mL	NR	NR	90
MIP-MoS ₂ GN-CNTs/GCE	LSW	Chrysanthemum tea, carrot	$(5-100) \times 10^{-8}$ M	7.0	600	OCP	4×10^{-8} to 2×10^{-6}	9.0×10^{-9}	90.0–102	10 days	101
MOF-525/MPC/GCE	DPV	Serum, urine, tomato and watermelon juice	$(2-100) \times 10^{-8}$ M	7.0	350	0.1	$(5-100) \times 10^{-9}$ to $(1-50) \times 10^{-7}$	3.5×10^{-10}	95.3–104.1	15days	102
BNNS-AuNPs/GCE	SWV	Peanut hulls	$(4.271-4.117) \times 10^{-6}$ M	6.0	1500	NR	$(5-1200) \times 10^{-12}$ to $(2-1200) \times 10^{-8}$	1.7×10^{-12}	99.92–103.38	NR	85
		Perilla	$(2.693-2.544) \times 10^{-6}$ M						98.30–99.80		
CuCo@NPCP	DPV	Human serum	$(1-20) \times 10^{-8}$ M	7.0	350	0.1	$(2-25000) \times 10^{-6}$	8×10^{-11}	99.6–102.2	4 weeks	103
MOF-801/MC/GCE	DPV	Green tea, urine	$(1-2) \times 10^{-5}$ M	7.0	400	0.1	$(2-20) \times 10^{-8}$ to $(2-100) \times 10^{-7}$	2.90×10^{-9}	95.20–104.05	7 days	104
Pt-BPC/CILE	DPV	Duyiwei capsule	5.0×10^{-6} M	3.0	350	0.4	$(0.008-100) \times 10^{-6}$	2.6×10^{-9}	98.33–103.75	1 week	105
GQDs-GNPs/GCE	DPV	Peanut hulls		5.0	120		$(1-1000) \times 10^{-8}$	1×10^{-9}	98.8–101.4	2 weeks	106

(Continues)

TABLE 5 (Continued)

Electrode	Technique	Matrix	Determinate concentration	pH	t _{acc} (s)	E _{acc} (V)	Linear range (M)	LOD (M)	Recovery (%)	Stability	References
			1.32×10^{-6} to 1.42×10^{-6} M								
PGE	SWAASV	Human serum Urine	$(5.79-38) \times 10^{-8}$ M $(7.63-59.9) \times 10^{-8}$ M	3.0	300	0	$(4.90-19.7) \times 10^{-8}$	1.34×10^{-9}		NR	107
β -CD-MIP/ITO	DPV	Duyiwei capsule	$(12.0-27.3) \times 10^{-6}$ M	6.0	180	NR	$(5-3000) \times 10^{-8}$	2.4×10^{-8}	96.2-102.7	2 weeks	108
MWCNTs/PEDT-Au/ GCE	SWV	Human serum	$(1-1000) \times 10^{-8}$ M	3.0	90	0.1	$0.001-0.1 \times 10^{-6}$ $0.1-15 \times 10^{-6}$	2.2×10^{-10}	99.63-103.1	4 weeks	109
NiO@Ni-MOF/TM	DPV	Duyiwei capsule	$(1-100) \times 10^{-11}$ M $(1-50) \times 10^{-9}$ M	4.0	30	NR	$(1-10) \times 10^{-6}$	3×10^{-12}	97.00-105.00	4 weeks	88
NIPA-AA-MWCNTs/ GCE	DPV	Peanut shell Tomato	$(1.5-5.9) \times 10^{-7}$ M $(8-10) \times 10^{-7}$ M	5.0	NR	NR	$(1-15) \times 10^{-10}$	1.45×10^{-11}	93.3-106.6 95.0-99.0	NR	110
Fe ₃ O ₄ @TAPB-DMTP- COFs	DPV	Carrot Chrysanthemum tea	0-2-5 μ M/L 0-2-5 μ M/L	7.0	90	0.4	$(1-200) \times 10^{-8}$ $(2-70) \times 10^{-6}$	7.2×10^{-9}	98.5×102.0	3 h	111

Abbreviations: CV, cyclic voltammetry; COFs: core-shell magnetic covalent organic frameworks composites; CILE, composite-modified carbon ionic liquid; DPV, differential pulse voltammetry; GCE, glassy carbon electrode; GCPE, glassy carbon paste electrode; ITO, indium tin oxide; LSV, linear sweep voltammetry; NPCP, nitrogen-doped porous carbon polyhedron; PGE, pencil graphite electrodes; RGO, Reduced graphene oxide. SWAASV, square wave anodic stripping voltammetry; SWV, square wave voltammetry; TM, Titanium mesh.

LOD value of 1.27×10^{-9} g/ml. The work is carried out with samples extracted from honeysuckle with petroleum ether and then redissolved in buffer solution of Borax-HCl at pH 6.00.

In the same line, the article published by the group of Lu reported the synthesis of glutathione (GSH)-capped Mn-doped CdTe quantum dots, which are used as fluorescence probes and applied to the luteolin determination.¹¹³ Here, the flavonoid, acts one more time as a quencher of the fluorescence of quantum dots, and the fluorescence quenching is closely proportional to the amount of the flavonoid. Related to this article, it is important to highlight the wide linear range achieved ($6\text{--}138 \times 10^{-6}$ M). The work is carried out by working with phosphate buffer solution at pH 9, reaching a LOD value of 6.1×10^{-8} M. To evidence the developed method, the authors use the synthetic matrix of the commercial Duiwei capsules, and they have been able to find a luteolin concentration values between 18.05 and 28.38×10^{-6} M.

Although very good analytical parameters are achieved in both works, it is necessary to mention that they only quantify luteolin as a unique analyte in a real sample (i.e., honeysuckle or Duiwei capsules), which compared to most of the mentioned techniques, can be taken as a disadvantage (only the presence of numerous interferences was studied).

On the other hand, Li et al.¹¹⁴ developed a novel fluorescent nanosensor that could be successfully applied to efficient detection of *cis*-diol-containing three flavonoids, including luteolin, in onion skin and human urine samples. With that purpose, novel boronate affinity imprinted quantum dots (BA-CdTe@MIPs QDs) were used to develop a selective and sensitive fluorescent nanosensor based on controllable oriented surface imprinting approach. The BA-CdTe@MIPs QDs exhibited linear decrease in fluorescence intensity with the increase of concentration of flavonoid in the 0.05–25 μ M concentration range. LOD was evaluated to be 0.02 μ M. The recoveries for the spiked onion skin and urine samples were evaluated to be 83.50%–104.00% and 86.67%–105.00%, respectively.

Another little-known technique in the determination of luteolin is electrophoresis. Briefly, this technique consists on the differential migration of molecules relative to a fluid under the influence of a spatially uniform electric field.

Regarding that, Chem and Xing reported the application of micellar electrokinetic capillary chromatography for the separation and determination luteolin and others five compounds in peanut shells ethanolic extract working with borate buffer at pH 9.24.¹¹⁵ They obtained really good analytical values like an extremely low LOD of 4×10^{-7} g/ml ($\approx 1.4 \times 10^{-9}$ M), a wide linear range,

$0.002\text{--}2 \times 10^{-3}$ g/ml ($\approx 7 \times 10^{-9}$ to 7×10^{-6} M) and a high reproducibility, with 0.097% RSD. Finally, working with the extract of the real sample, in this case peanut shells, they found a luteolin concentration of 6.314×10^{-3} g/ml ($\approx 2.2 \times 10^{-5}$ M).

For their part, the group of Lunte and co-workers, reported a capillary electrophoretic method for determination of eight polyphenolic compounds in three different red wine samples, included among them, luteolin. In agreement with the authors, we would like to underline the speed of the proposed method, that in comparison with the current methods is truly fast. The eight determinations, including the sample pretreatment, were performed in about 15 min.¹¹⁶

Although the analytical parameters are not surprising, it is clear that it can be an excellent method to use routinely with these types of samples. This can be affirmed since in the work it can be observed that the variation of luteolin concentration in the three types of wines is very small and that, as we said previously, it is a very fast method.

A work that achieves very interesting analytical parameters is the one carried out by Maher and co-workers, determining luteolin (and apigenin) by capillary electrophoresis, with diode array detection, in thyme and parsley methanol extracts.¹¹⁷ Its LOD was 1.05 μ g/ml ($\approx 3.7 \times 10^{-6}$ M) with a linear range from 3 to 800 μ g/ml ($\approx 1.0 \times 10^{-5}$ to 2.8×10^{-3} M). But in comparison with the work of Lunte, this method applied to luteolin takes more time (only the elution time 27 min).

Electrophoresis, in general, is a good option to the popular chromatography because of its simplicity, high resolution, low utilization of samples and chemicals and usually short analysis time.

5 | CONCLUSIONS

Over the last years, many different methods to quantify luteolin have been proposed. Chromatographic and electrochemical methods stand out for being the most used but are not the only ones. A shorter list of publications referring to the use fluorescence- and electrophoresis-based methods can be found. In this way, in this review current techniques for the determination of luteolin in real samples are shown, putting emphasis on the chromatographic and electroanalytical methods.

Many techniques provide a real possibility for the sample preparation prior to the analysis with sufficient specificity. However, there is not a standard available technique for the sample preparation and/or for the whole procedure. The liquid extraction is, in many cases, the first step in the preparation process of the sample.

It is important to mention that, all through the article, we have highlighted and compared analytical developments that imply separation before determination (electrochemical sensors) with other methodologies, in which such separations are part of themselves, that is, they take place in the same equipment (chromatographies). The application of thin layer chromatography to identify different components from extracts is a classical method but still very used today. Through this technique, the chromatographic "fingerprint" of an extract can be obtained, which is very important for identification purposes, mainly limited to qualitative determinations.

To quantify luteolin in different matrices, it is highlighted that the possibility to connect multiple detection devices to HPLC has made this technique a valuable and essential tool for the separation of other flavonoids. Ultraviolet detection is currently technique used in liquid chromatography and, even, it is used with multi-wavelengths or photo diode array. Thus, it is a conventional tool in studies associated with detection, quantification, and classification of flavonoids, included the luteolin. On the other hand, the development of liquid chromatography coupled to mass spectroscopy has extended the field of application of mass spectroscopy, allowing the analysis and identification of compounds from new natural products.

For high-throughput analysis, the development of new techniques such as ultra-efficiency liquid chromatography and UHPLC has emerged as an alternative to the traditional HPLC technique in the last years.

The relevance of UPLC technology mainly focuses on the improvement of the analytical parameters at expense of working with a lower number of analytes, while UHPLC, coupled to MS/MS detection, has the ability to analyze several analytes.

The results previously discussed clearly demonstrate that electroanalytical techniques are powerful tools to study compounds of interest to human and animal health, among them luteolin. The main advantage of electrochemical techniques over others such as chromatography, spectrophotometry, and so on is that they require less expensive equipment, less solvent use, they are quicker and show, in some cases, a greater sensitivity. Furthermore, voltammetric techniques also offer the possibility to developing electrochemical detectors for coupling to flow systems when becomes necessary to implement a pre-separation step in complex samples in the presence of several analytes.

Critical assessment of the potential of new analytical methods for the determination, qualitative and quantitative, of luteolin is crucial in analytical chemistry regardless of the specificity of the method. Usually, validation criteria are used for this purpose, including parameters

such as precision, accuracy, sensitivity, recovery, and so on. This approach has the disadvantage that it is difficult to express the analytical potential of a methodology using one unified measure, which would cover all validation criteria and allow easy overall assessment. Due to this, conducting a comprehensive assessment of an analytical method covering all the mentioned attributes is extremely hard without special tools dedicated to this purpose.

Taking into account that luteolin is found in nature and in most laboratory determinations in relatively high concentrations, it is worth mentioning that LOD is no longer the most important analytical parameter. Thus, parameters such as the linear range became much more interesting, making the proposed method practical in everyday use.

In summary, we venture to say further developments may be expected with regards miniaturization, that is, the coupling of micro- and/or nano technologies, analytical instruments that they should facilitate the analysis of minute samples, and help to create better operating conditions for detection of luteolin in real samples still unknown. Besides hoping that with the instruments that generate higher-order data and the in-depth study of chemometrics, chemical multiway calibration will definitely start to play an important role in qualitative and quantitative analysis, allowing analytes to be determined even in the presence of unexpected interferences.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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