

The transformation of titrimetric methods in pharmaceutical, herbal and food analysis: a literature review (2013–2026s)

Faridah Faridah^{1*}, Diva Dwi Putri Permatasari¹, Andri Prasetyo¹, Intan Permata Sari¹

¹Faculty of pharmacy, Universitas Pancasila, Jakarta, Indonesia.

*Corresponding Author: faridah@univpancasila.ac.id

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ABSTRACT: The development of analytical methods in the fields of pharmaceuticals, plant/herbal ingredients, and food shows a significant transformation from classical titrimetry toward more selective and efficient instrumental and digital techniques. This study aimed to evaluate method transformation, comparative validity, and the application of green analytical chemistry (GAC) principles in pharmaceutical, herbal, and food analysis based on a literature review. A non-systematic narrative literature review was conducted on 28 Scopus-indexed journal articles covering titrimetry, UV-Vis spectrophotometry, chromatography (HPLC and RP-HPLC), Karl Fischer, atomic spectrometry, as well as μ PAD-based innovations, conductometry, and digital analysis. The synthesis showed that classical methods remain relevant because of their simplicity, low cost, and accessibility, but their selectivity may be limited in complex matrices. Instrumental methods generally provide improved precision, accuracy, and selectivity, particularly for multicomponent samples, whereas miniaturization and digitization enhance analytical efficiency and reduce resource requirements. However, explicit integration of GAC principles remained limited, with only 7 of the 28 reviewed studies demonstrating identifiable green analytical strategies. These findings indicate that analytical modernization does not necessarily result in greener methods. Overall, analytical method development is increasingly integrative, combining classical and instrumental approaches according to analytical requirements, matrix complexity, and sustainability considerations. This review therefore provides a structured evaluative framework for selecting and transforming analytical methods across pharmaceutical, herbal, and food matrices.

KEYWORDS: Analytical methods; food analysis; green analytical chemistry; herbal materials; pharmaceutical analysis.

▪ INTRODUCTION

The development of analytical methods in pharmaceuticals, plant/herbal ingredients, and food has evolved in response to increasing demands for accuracy, precision, selectivity, cost efficiency, and compliance with quality standards. Historically, classical methods based on titrimetry, including acid-base, redox, complexometric, and precipitation titrations, have provided an important foundation for quality control because of their procedural simplicity and well-established stoichiometric principles [1]–[5]. Studies on non-aqueous titrimetry for diuretic drug candidates demonstrate that classical methods can provide high linearity and precision when appropriately optimized [6]. Similarly, iodometric methods for amoxicillin and β -lactam antibiotics indicate that classical redox approaches remain applicable to pharmaceutical quality testing and can be combined with spectrophotometry to improve analytical flexibility [2],[7]. EDTA-based complexometric methods have also provided accurate results for minerals and electrolytes in pharmaceutical preparations and food products [3],[7],[8]. In herbal analysis, permanganometric titrimetry has been applied successfully to tannin determination [9],[10], while iodometric methods remain applicable to vitamin C determination in fruits and medicinal plants [11],[12]. Thus, titrimetry remains relevant, particularly in laboratories requiring simple, economical, and accessible analytical procedures.

However, increasing matrix complexity and the demand for higher selectivity have encouraged the adoption of instrumental approaches, including UV-Vis spectrophotometry, high-performance liquid chromatography (HPLC), coulometry, and atomic spectrometry [13]–[16]. Comparative analysis of acetylsalicylate demonstrates that spectrophotometry may provide higher precision than titrimetry under

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certain conditions, although limitations in absolute accuracy remain [13]. HPLC has demonstrated superior selectivity and reproducibility for pharmaceutical formulations, particularly when excipient interference is present [14]. In herbal analysis, RP-HPLC-UV and coulometric approaches enable the separation and quantification of individual organic acids, improving analytical validity compared with conventional acid-base titration [16]. Similarly, Karl Fischer analysis provides greater selectivity for moisture determination than loss on drying, particularly in plant materials containing volatile compounds [17],[18]. For sodium determination in food, comparisons of FAAS, FAES, ICP-AES, and thermometric endpoint titrimetry demonstrate that method selection should consider accuracy, cost, and analysis time [15]. The analysis of kombucha fermentation further shows that combining titration with HPLC can provide complementary information on total acidity and specific organic acids [19]. These findings indicate that instrumental methods do not necessarily replace classical approaches but can function complementarily to improve analytical reliability.

Recent developments have further incorporated miniaturization into analytical workflows, increasingly reflecting the principles of green analytical chemistry (GAC) [20]. Paper-based analytical devices have enabled redox titrimetric procedures for alcohol and antibiotic analysis to be adapted into portable systems with simplified procedures and reduced reagent requirements [7],[21]. Microfluidic paper-based analytical devices (μ PADs) have also been applied to argentometric chloride determination without indicators or additional instrumentation, providing a distance-based detection strategy with reduced analytical requirements [22],[23], while broader developments in μ PAD technology have demonstrated their potential as low-cost, portable, and easily fabricated analytical platforms [24]. Conductometric alternatives for chloride analysis provide a more environmentally friendly, faster, and cheaper approach while maintaining reliable analytical performance [25]. In addition, webcam-assisted EDTA complexometric titration for calcium determination in dairy products can improve endpoint objectivity and reduce dependence on visual judgment [26]. Integration of pH and conductivity measurements into titration systems has also demonstrated the potential to improve analytical performance in complex matrices [5]. These developments suggest that analytical modernization is increasingly directed not only toward precision and selectivity but also toward efficiency, accessibility, resource reduction, and sustainability [7],[21],[23],[26].

Despite these developments, the literature remains fragmented across specific analytes, matrices, and analytical technologies. Previous studies have independently addressed antibiotics and antihypertensive drugs [14],[21], vitamin C and plant secondary metabolites [9],[12], and minerals and electrolytes in pharmaceutical and food matrices [3],[15]. Innovations such as simplified acid-base titration for determining the degree of deacetylation of chitosan have also not been integrated into a broader cross-matrix analytical framework [27]. In herbal analysis, geographical variation and processing conditions may alter phytochemical composition, emphasizing the need for robust and reproducible methods [9],[17]. Pharmaceutical excipients may interfere with analyte determination, making method selectivity an important consideration, particularly in multicomponent formulations [28]. Furthermore, although several studies incorporate elements of GAC, the integration of analytical performance, matrix complexity, method transformation, and sustainability remains insufficiently synthesized across pharmaceutical, herbal, and food applications [20],[24],[29].

Therefore, this study aimed to evaluate the transformation and validity of analytical methods in pharmaceutical, herbal, and food analysis through a comparative literature review informed by GAC principles. Specifically, the review addresses three questions: (1) how classical analytical methods have transformed toward instrumental and digital approaches; (2) what advantages, limitations, and levels of validity distinguish classical from instrumental methods across pharmaceutical, herbal, and food matrices; and (3) how matrix complexity is addressed while incorporating GAC principles into analytical method development. By synthesizing the available evidence, this study proposes an integrated framework in which classical, instrumental, miniaturized, and digital methods are viewed as complementary components of a rational analytical strategy. This framework emphasizes that analytical method selection is an adaptive process guided by analytical performance, matrix characteristics, resource requirements, and sustainability considerations.

MATERIALS AND METHODS

This study employed a structured narrative literature review design to analyze the transformation and validity of analytical methods applied in pharmaceutical, herbal, and food matrices. The narrative review approach was selected because it enables a conceptual synthesis and comparative evaluation of analytical methods without the strict procedural constraints required in systematic reviews, while still maintaining transparency in the selection and analysis of literature sources.

A total of 28 peer-reviewed research articles published in international scientific journals were used as data sources. These articles were selected because they reported the application, modification, or evaluation of analytical methods relevant to the scope of this review. The overall review procedure followed several stages, including literature identification, full-text reading, data extraction, method categorization, and comparative thematic synthesis, as illustrated in Figure 1.

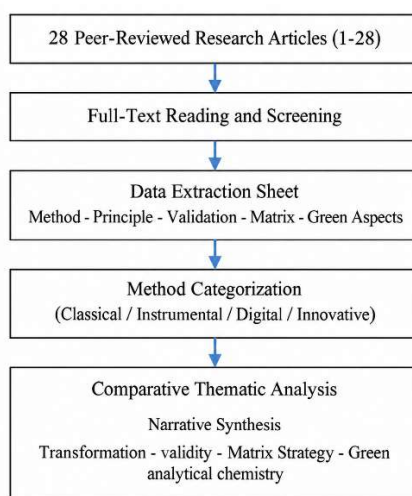


Figure 1. Structured narrative literature review process.

Information from each article was systematically recorded using a data extraction sheet developed for this study. The extracted variables included the type of analytical method, underlying analytical principle, reported validation parameters (such as linearity, precision, accuracy, detection limits, and robustness), analytical matrix (pharmaceutical, herbal, or food samples), and any reported aspects related to green analytical chemistry. Articles were included if they reported the development, validation, or application of analytical methods relevant to pharmaceutical, herbal, or food matrices.

The collected information was subsequently organized according to the type of analytical method and application matrix to facilitate comparative evaluation. The extracted data were then analyzed using a comparative thematic analysis approach to identify key patterns in the literature, including the transformation of classical analytical methods into instrumental or digital approaches, differences in validation characteristics between methods, strategies for addressing matrix complexity, and the integration of green analytical chemistry principles, illustrated in Figure 2.

Finally, the findings from the selected articles were synthesized narratively by comparing methodological characteristics and reported validation outcomes across studies. This approach allowed the identification of methodological trends and conceptual relationships between analytical techniques applied in different analytical matrices.

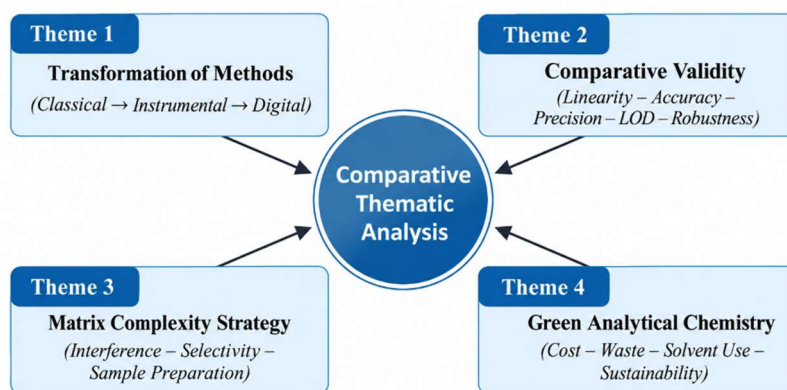


Figure 2. Comparative thematic analysis framework.

▪ RESULTS

Distribution of types of analysis methods used in 28 articles

Table 1. Research mapping of titrimetric methods in pharmaceutical, herbal and food analysis for the period 2015–2026.

No.	Author	Research sample /scope	Main insight	Theory used	Research method	Research results	Limitations	Correlation with research
1	Ivanov A et al. (2021) [6]	4-GBA (diuretic candidate)	Validated non-aqueous titrimetric method	Non-aqueous acid-base; potentiometry	HClO ₄ titration in glacial acetic acid	r ² >0.99; recovery 98–103%; RSD ≤2%	Limited to one compound; chromatographic comparison	Simple analysis of weak acid/base drugs
2	Qarah NAS et al. (2020) [2]	Amoxicillin bulk and pharmaceutical preparations	Combination of titrimetry and iodometric spectrophotometry	Redox theory; Lambert law	Beer-Iodometric titration + UV-Vis	Sensitive; adequate LOD/LOQ; suitable for QC	Requires controlled reaction conditions	Pharmaceutical and food/herbal matrices containing reducing groups
3	Quin R et al. (2024) [8]	Iron supplements	Classical instrumental analysis vs	Fe ²⁺ /Fe ³⁺ redox; Lambert law	Beer-KMnO ₄ titration + UV-Vis	Comparable results; no significant t/F-test difference	Educational focus; limited industrial validation	Mineral analysis in supplements and fortified foods
4	Myers NM et al. (2019) [21]	Amoxicillin and ampicillin	Paper-based iodometric assay	Iodometric back-titration	Paper-based redox titration	Error detected 4–5%; substandard drugs	Lower precision than HPLC	Rapid screening and portable analysis
5	Balarabe MA et al. (2019) [3]	Ferrous fumarate tablets	Fe determination by permanganometry	Fe ²⁺ → Fe ³⁺ redox	Permanganometric titration	Variation between actual and label values	No complete statistical validation	Fe analysis in pharmaceutical preparations

No.	Author	Research sample / scope	Main insight	Theory used	Research method	Research results	Limitations	Correlation with research
6	Khagga BS et al. (2023) [49]	Pure rosuvastatin	EDTA complexometric drug analysis	EDTA complexation	EDTA-Mg titration	Content 103.05%	Limited precision/recovery testing	Analysis of metal-complexing compounds
7	Hreeba K et al. (2025) [13]	Commercial aspirin tablets	Titrimetric vs spectrophotometric accuracy	Acid-base; Beer-Lambert law	Back titration + UV-Vis	UV-Vis more precise; variation between brands	Accuracy of both methods limited	Simple pharmaceutical method validation
8	Taleuzzaman M et al. (2017) [4]	Raw materials and pharmaceutical products	Titrimetry as initial QC method	Acid-base, complexometry, redox,	Review of volumetric methods	Cheap and rapid for initial QC	Lower selectivity than HPLC	Screening of herbal and food materials
9	Boobphahom S et al. (2020) [24]	μPAD applications in drug, food, environmental and clinical analysis	Miniaturization enables portable, low-cost and high-throughput analysis	Microfluidics and paper-based analytical principles	Literature review of μPAD fabrication, detection and applications	μPADs enable low-volume analysis, portability, rapid readout and multiplex/high-throughput assays	Fabrication, fluid-control and sensitivity challenges	Supports transformation from conventional to miniaturized/digital analytical approaches
10	Fadhil AK et al. (2021) [14]	Antihypertensive drugs	Comparison of HPLC, CE, UV and titrimetry	Titrimetry chromatography and	Comparative review	HPLC provides greater selectivity and precision	Expensive instrumentation	Method selection for complex pharmaceutical/herbal matrices
11	Ochieng AO et al. (2025) [28]	Aspirin tablets	Effect of acid excipients	Matrix interference and stability	Titrimetry, UV-Vis and HPLC	HPLC more accurate; titrimetry overestimates	Simple methods less robust	Matrix effects in complex samples

No.	Author	Research sample /scope	Main insight	Theory used	Research method	Research results	Limitations	Correlation with research
12	Charnier C et al. (2016) [5]	Digestate samples	pH and conductivity improve titrimetric accuracy	Acid-base equilibrium; conductivity	Sensor-based titrimetry	R ² ≈0.94–0.95; lower error	Requires mathematical modelling/calibration	Development of modern titrimetric methods
13	Kimaru IW et al. (2018) [10]	Ca gluconate and Mg sulfate IV bags	EDTA titration for pharmaceutical electrolyte QC	EDTA-metal complexation	Complexometric titration	Ca and Mg accurately determined	Limited to divalent metals	Pharmaceutical QC
14	Wangiyana IGAS et al. (2021) [9]	<i>Gyrinops versteegii</i> leaves	Location and drying affect tannin levels	KMnO ₄ –indigo carmine redox	Permanganometric titrimetry	Tannin levels varied by location/processing	No instrumental comparison	Herbal standardization and phytochemical analysis
15	Miloshevsk M et al. (2023) [17]	Medical Cannabis varieties	Karl Fischer for selective water determination	Karl Fischer reaction	Semi-micro titration	Moisture 3.8–8.5%; rapid/selective	Requires homogenization and special tools	Water-content validation
16	Sergunova EV et al. (2019) [16]	Rosaceae fruits and herbal preparations	Combined methods improve organic-acid analysis	Acid-base, redox, chromatography	RP Coulometry, potentiometry, RP-HPLC-UV	HPLC more selective/precise	Expensive instrumentation	Herbal bioactive-component analysis
17	Ma C et al. (2026) [18]	Various plant parts	KF with formamide extraction	Karl Fischer and extraction	KF direct titration with extraction	Accurate, repeatable and robust	Extraction optimization required	Green analysis of herbal/food samples

No.	Author	Research sample /scope	Main insight	Theory used	Research method	Research results	Limitations	Correlation with research
18	Tantray AK et al. (2017) [12]	16 plant types	Spectrophotometry more sensitive than titration	DNPH and redox reactions	Spectrophotometry + redox titration	DNPH produced higher vitamin-C values	Titration less sensitive	Vitamin analysis in food/herbs
19	Ploegaerts G et al. (2016) [15]	Tomato and low-sodium sauces	Comparison of sodium analysis protocols	Atomic spectroscopy and thermometric titrimetry	FAAS, FAES, ICP-AES and TET	Recovery near 100%; TET and dry-ashing/FAAS efficient	ICP-AES costly; some methods time-consuming	Comparative validation of food analysis methods
20	Miranda B et al. (2016) [19]	Kombucha fermentation	Titration and HPLC monitoring	Acid-base; Gran plot; chromatography	Potentiometric titration + HPLC	Total acid increased linearly; validated by t-test	Titration selective non-for individual acids	Fermented herbal/food products
21	Tareen H et al. (2015) [11]	Citrus fruits and papaya	Vitamin-C determination	Ascorbic acid-iodine redox	Iodometric titration	Highest vitamin C in oranges	Influenced by maturity/extraction	Phytochemical analysis of plant materials
22	Dutta J et al. (2022) [27]	Chitosan	Simple titration for degree of deacetylation	Acid-base; validation	NMR HCl-NaOH titration + NMR	DD 77-91%; NMR-supported	Requires controlled normality/sample preparation	Pharmaceutical excipient and biomaterial analysis
23	Nogueira SA et al. (2019) [7]	Whiskey samples	μ PAD for portable alcohol analysis	Redox/permanganometry	Paper-based redox titration	$R^2 = 0.992$; LOD 2.1%	Reagent stability ~40 min	Portable analytical methods

No.	Author	Research sample / scope	Main insight	Theory used	Research method	Research results	Limitations	Correlation with research
24	Cai L et al. (2020) [22]	Tap water and chloride standards	Indicator-free argentometric μ PAD	Precipitation argentometry	and μ PAD distance-based detection	LOD 1.7 mg/L Cl^- ; comparable to conventional titration	Limited analyte scope; UV optimization	Low-cost portable ion analysis
25	Rahbar M et al. (2019) [23]	Biological fluids and water	Trapezoidal μ PAD improves sensitivity	Argentometry and AgCl precipitation	Paper microfluidics	LOD 0.05 mM; improved sensitivity	Requires channel/reagent optimization	Portable pharmaceutical/food analysis
26	Popescu S et al. (2024) [43]	Fruits, vegetables and fortified foods	Review of vitamin-C titrimetric methods	Redox, iodimetry, DCPIP	Literature review	Economical and suitable for routine analysis	Interfering reducing compounds; lower sensitivity than HPLC	Antioxidant analysis in food/herbs
27	Aguirre-Londoño J et al. (2019) [25]	Nariñense cheese	Conductometry as alternative for chloride	Conductivity; argentometric precipitation	Potentiometry vs conductometry	Significant correlation; faster and greener	Matrix-specific validation needed	Alternative inorganic-ion analysis
28	Shyichuk A et al. (2025) [26]	Milk and dairy products	Webcam as EDTA titration endpoint detector	Ca-EDTA complexometry; analysis	image Semi-automatic webcam titration	$R^2 = 0.9999$; RSD 0.3–2.9%	Limited to color-based indicators	Low-cost digital detection

The analytical methods identified across the 28 reviewed studies (Table 1) were classified into five main categories: classical titrimetry, UV-Vis spectrophotometry, chromatography and advanced instrumental techniques, Karl Fischer titration for moisture analysis, and innovative approaches based on miniaturization and digitization. Classical acid-base, redox, complexometric, and precipitation titrations remain applicable to routine quantitative analysis because of their simplicity and accessibility. The reviewed studies also show increasing consideration of reagent consumption, waste generation, energy requirements, and environmental impact alongside analytical performance.

The reviewed studies demonstrate multiple pathways of analytical modernization. UV-Vis spectrophotometry was used independently or in combination with titrimetric methods, while HPLC, RP-HPLC-UV, atomic spectrometry, and Karl Fischer titration provided instrumental approaches for pharmaceutical, herbal, and food analysis. Classical titrimetric procedures were further integrated with paper-based and microfluidic platforms, conductometric detection, and webcam-assisted endpoint determination. The incorporation of pH and conductivity measurements enhanced conventional titration systems, while acid-base titration supported by ^{13}C -NMR demonstrated the use of an independent instrumental technique for method validation. Overall, these studies indicate that analytical development increasingly combines classical procedures with instrumental, miniaturized, and digital approaches. Quantitatively, 16 studies employed titrimetric methods as primary or complementary approaches, whereas 13 employed modern instrumental methods, reflecting overlap between methodological categories and indicating that classical and modern techniques function as complementary rather than mutually exclusive approaches.

Among the 28 reviewed studies, UV-Vis spectrophotometry was applied either independently or in combination with titrimetric methods [18]. Chromatographic techniques, including HPLC, RP-HPLC-UV, and HILIC, and atomic spectrometric techniques, including FAAS, FAES, and ICP-AES, were reported in several studies. Karl Fischer titration was used for moisture-content determination (Studies 18–19). Further developments included paper-based analytical devices (PADs and μ PADs), conductometric detection, and webcam-assisted endpoint determination. Analytical methods were further enhanced by integrating pH and conductivity measurements into an SNAC titration system and by using ^{13}C -NMR spectroscopy to support the validation of acid-base titration. Overall, 16 studies employed titrimetric approaches as primary or complementary methods, whereas 13 employed modern instrumental approaches as primary or complementary methods.

Objects and analysis matrices in reviewed articles

The 28 reviewed studies covered three main categories of analytical objects: pharmaceutical ingredients, herbal and plant materials, and food products, as illustrated in Figure 3. Pharmaceutical studies included diuretic drug candidates, amoxicillin and other β -lactam antibiotics, iron supplements, rosuvastatin, antihistamines, antihypertensive drugs, aspirin, and electrolytes in intravenous fluids. Herbal and plant studies addressed tannins in *Gyrinops* leaves, moisture in *Cannabis* flowers and plant materials, organic acids in herbal *simplicia*, vitamin C, and fruits. Food-related studies included sodium in food, kombucha fermentation, vitamin C, chloride in cheese and water samples, calcium in milk, and alcohol in beverages. μ PAD-based studies also examined chloride in water and biological fluids. Overall, 12 studies focused on pharmaceutical matrices, 8 on herbal and plant materials, and 9 on food products, with some studies involving more than one matrix category. All reviewed studies involved real samples or matrices rather than relying exclusively on pure standards.

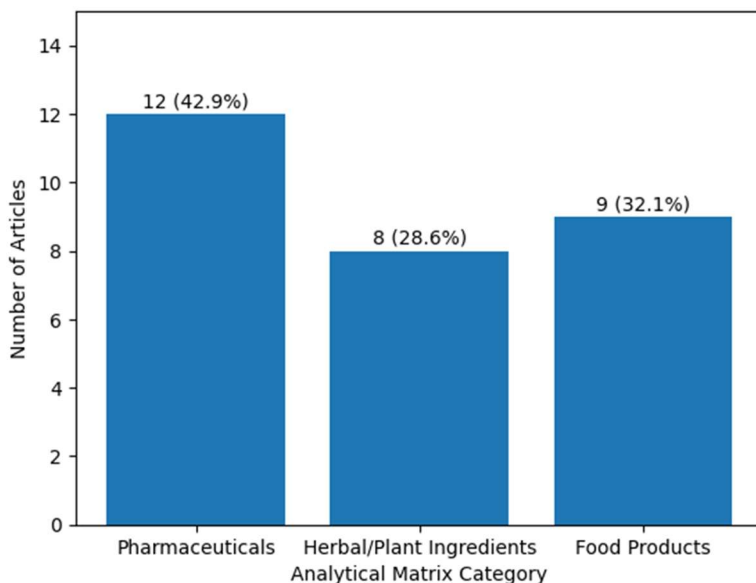


Figure 3. Distribution of analytical objects and real matrices in the reviewed studies (n = 28).

Reported validation parameters

The reported validation parameters included linearity, precision, accuracy (recovery), limits of detection and quantification (LOD and LOQ), repeatability, robustness, and statistical tests such as t-test, F-test, and ANOVA, as summarized in Figure 4. Study 6 reported linearity with a coefficient of determination close to 1 and RSD <2% [49]. Studies 7 and 16 used t-test, F-test, and/or ANOVA at a 95% confidence level to compare analytical methods [13],[16], with Study 7 reporting no statistically significant difference between the compared methods [13]. Precision was compared between titrimetric and spectrophotometric approaches, while analytical methods were also evaluated in terms of precision, selectivity, and cost efficiency. Studies 9 and 17 reported repeatability and robustness for Karl Fischer methods [24] and [18], and Study 16 reported recoveries close to 100% for different sodium determination techniques [16]. For detection capability, the reported results included a detection limit of 1.7 mg/L for chloride and an LOD of 0.05 mM. Analytical performance was also demonstrated by an R^2 of 0.9999 and RSD values of 0.3–2.9%. However, some studies did not report complete validation parameters and instead provided label-level or comparative data.

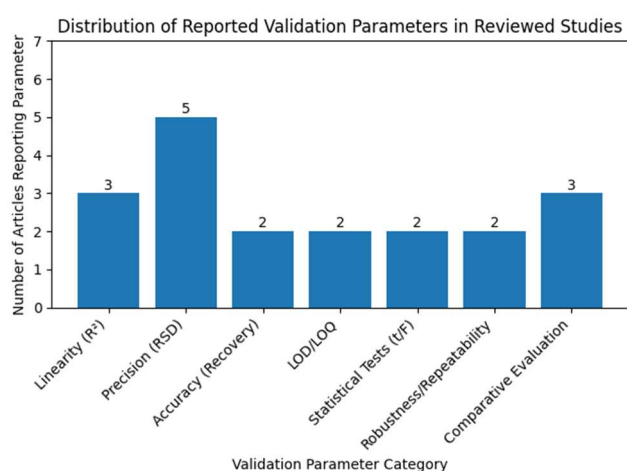


Figure 4. Distribution of reported validation parameters in the reviewed studies.

Forms of transformation of analysis methods

The transformation of analytical methods reported in the literature can be classified into four main forms, as illustrated in Figure 5.

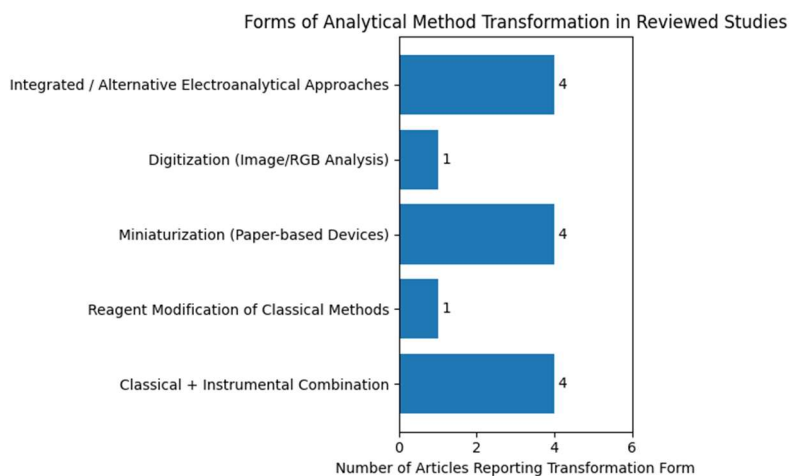


Figure 5. Forms of analytical method transformation reported in the reviewed studies.

The reviewed studies demonstrated several forms of methodological transformation. First, classical titrimetric methods were combined with instrumental techniques, including spectrophotometry and HPLC. Second, classical procedures were modified through changes in reagents, such as the use of Pyridinium Fluoro Chromate (PFC) in antihistamine titration. Third, titrimetric procedures were miniaturized using paper-based devices. Fourth, titration endpoint detection was digitized using webcams and RGB image analysis. Other transformations included the integration of pH and conductivity measurements within a single titration system, the use of conductometry as an alternative detection approach to conventional precipitation titration, and the application of coulometry for the quantification of organic acids. Modification of Karl Fischer analysis through formamide extraction was also reported. Overall, 11 of the reviewed studies demonstrated transformations of classical analytical procedures toward improved selectivity, efficiency, portability, or objectivity.

Matrix complexity and interference

A total of nine reviewed studies reported matrix interference or environmental factors that could affect analytical results, as illustrated in Figure 6. These factors included interference from organic acid excipients in aspirin analysis, geographical and processing-related variation in tannin content, differences in selectivity between titrimetric and RP-HPLC methods for herbal simplicia, and the influence of volatile compounds on loss-on-drying results. Other reported issues included interference from reducing compounds in vitamin C titration, the inability of titration to distinguish individual organic acids, the need for further validation of conductometric methods across different food matrices, and the dependence of webcam-based results on lighting conditions. Overall, the findings indicate that matrix composition, sample characteristics, and measurement conditions can influence analytical results across the reviewed methods.

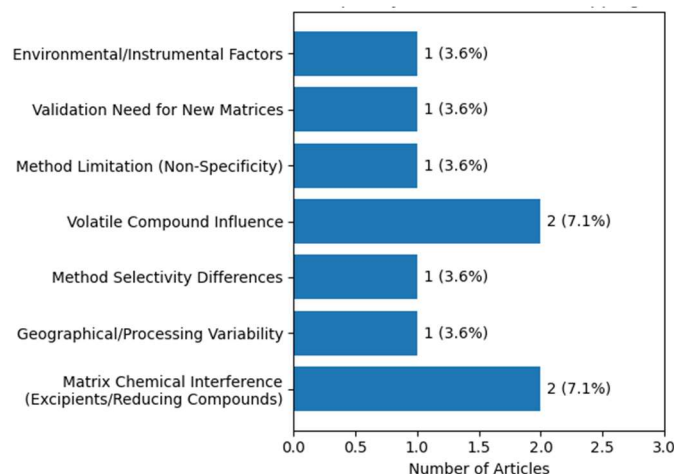


Figure 6. Matrix complexity and interference categorization mapping in the reviewed studies (n = 28).

Aspects of green analytical chemistry

Among the 28 reviewed studies, seven (25.0%) explicitly demonstrated elements consistent with green analytical chemistry (GAC), primarily through reagent reduction, miniaturization, and improved operational efficiency, as illustrated in Figure 7. The reported green strategies included replacing azeotropic toluene distillation with formamide extraction, reducing reagent volumes and chemical waste through paper-based analytical devices, reducing silver nitrate consumption through conductometric approaches, and minimizing the use of additional indicators through digital image analysis. Sensor integration also improved analytical efficiency without increasing reagent consumption. Overall, these findings show that GAC-related strategies were applied across both classical and instrumental analytical approaches.

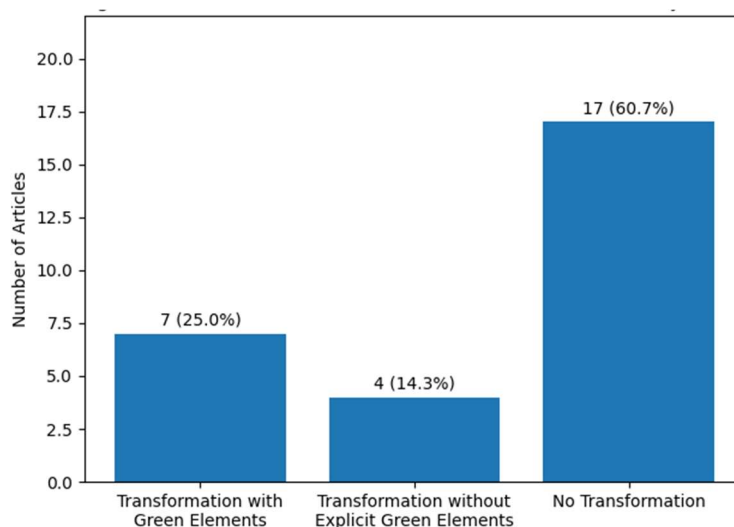


Figure 7. Integration of method transformation and green sustainability (n=28)

Among the 11 studies that demonstrated methodological transformation, seven explicitly incorporated elements consistent with green analytical chemistry, whereas the remaining studies primarily focused on improving selectivity, analysis time, or instrumental integration without reporting measurable reductions in reagent consumption or waste generation. Some studies did not explicitly use the term green analytical chemistry but reported practices consistent with selected green principles, such as reduced reagent volumes, shortened analysis time, miniaturization, or simplified analytical procedures. Overall, the findings indicate that methodological transformation and GAC-related practices did not always occur simultaneously, with some innovations improving analytical performance without explicitly incorporating environmental considerations.

DISCUSSION

Transformation of classical methods towards instrumental and digital approaches

The synthesis findings show that the transformation of analytical methods in the fields of pharmaceuticals, herbal ingredients, and food does not take place in a substitutional manner, but integrative and evolutionary (Figure 2). The literature demonstrates that classical titrimetry methods remain a key foundation in many studies, mainly due to their clear stoichiometric principles, low cost, and ease of operation [1–5]. The development of non-aqueous titrimetry for diuretic drug candidates suggests that optimization of solvents and titrants can result in high linearity and precision that meet validation criteria [6]. In the analysis of antibiotics and antihistamines, modification of redox reagents such as iodate-iodide and PFC demonstrates that classical methods can be extended in scope without dependence on complex instruments [2],[6],[21]. Even in iron analysis, redox titration shows statistical equivalence with UV-Vis spectrophotometry based on t-test and F-test [3],[8]. These findings suggest that classical methods are still scientifically competitive in certain contexts.

Nevertheless, matrix complexity encourages the use of instrumental techniques such as HPLC, RP-HPLC, and ICP-AES to improve selectivity and precision [14]–[16],[21],[28]. In aspirin analysis, comparative analytical approaches demonstrate differences in precision and accuracy between instrumental and titrimetric methods [13],[28]. In the analysis of kombucha fermentation, the combination of titration and HPLC allows the quantification of total acidity and identification of specific acids [19]. For herbal ingredients, RP-HPLC-UV can provide improved selectivity for the determination of individual organic acids [16]. Karl Fischer analysis offers greater selectivity for moisture determination than loss on drying, particularly in plant materials containing volatile compounds [17]. These findings suggest that instrumental methods are often used as complementary or confirmatory approaches rather than as complete substitutes for classical methods.

Further developments are seen in the miniaturization and digitization of classical methods. Paper-based devices (PADs and μ PADs) allow redox and precipitation analysis with minimal reagent consumption [7],[22],[24],[37],[38],[41]. Distance-based argentometric detection provides competitive detection limits without additional instrumentation [22]. The integration of webcams into complexometric titration reduces endpoint subjectivity and improves precision [16]. Conductometry, as an alternative to precipitation titration, also shows a strong correlation with standard methods [6],[25]. The integration of pH and conductivity sensors in SNAC systems demonstrates that physicochemical parameters can be combined to improve accuracy [5]. Overall, these findings confirm that analytical method transformation is adaptive and innovative while maintaining the fundamental principles of classical analytical chemistry.

The significance of this finding lies in clarifying that the development of analytical methods does not mean abandoning classical methods, but rather adapting them to meet modern demands. The present study contributes to the field of analytical methods by compiling a methodological evolution map that demonstrates continuity between traditional techniques and modern technologies. This perspective is particularly relevant to analytical laboratories seeking practical and sustainable approaches, where simple and cost-effective methods can remain valuable for reliable quality control across pharmaceutical, herbal, and food matrices [34],[40],[42]. The conceptual contribution of this research is to strengthen an integrative paradigm for the development of pharmaceutical, herbal, and food analytical methods.

Advantages, limitations, and validity of methods

The synthesis demonstrates that classical methods excel in simplicity, cost efficiency, and ease of implementation [1],[28],[31],[40]. Non-aqueous titrimetry and complexometric methods show acceptable precision and recovery [4],[6],[10]. In the analysis of vitamin C and iron, titrimetric methods provide valid and reproducible results [11],[43]. However, the main limitation of classical methods is their lower selectivity in complex matrices, especially when excipients or interfering components are present [40],[42]–[45]. In aspirin analysis, organic acid excipients caused overestimation of the analyte level by titrimetry [13],[28]. In tannin analysis, geographical and processing variations affect quantification results [9]. These findings demonstrate that the validity of classical methods is highly dependent on matrix characteristics and homogeneity.

In contrast, instrumental methods such as HPLC and RP-HPLC show high selectivity due to the separation stage before detection [14],[16],[19],[21],[28]. Atomic spectrometry techniques for sodium analysis provide high accuracy, with recovery close to 100% [1],[15]. Karl Fischer analysis provides selective

determination of water, particularly in plant materials containing volatile compounds [17],[18]. UV-Vis spectrophotometry can provide higher sensitivity or precision than in some analyses [15],[28]. However, instrumental methods have limitations, including higher costs, instrument maintenance requirements, and operational complexity [26],[30],[36],[42],[45]. Furthermore, spectrophotometric methods remain susceptible to spectral interference, particularly in complex matrices [13],[43].

From a critical standpoint, method validity should be assessed contextually according to the analyte and matrix rather than as an absolute measure [42],[44]. A critical synthesis of the reviewed literature indicates that a tiered approach—using titrimetry for routine or preliminary analysis and instrumental methods for confirmation or complex matrices—is a rational strategy supported by the literature [40],[42],[44],[46]. The significance of these findings is that method selection should consider analytical performance, efficiency, matrix characteristics, and resource requirements [40],[42],[44]. The contribution of this research is to clarify a comparative evaluation framework for classical and instrumental methods based on empirical evidence from the reviewed studies.

Matrix complexity and green analytical chemistry

The findings suggest that matrix complexity is a major factor affecting analytical accuracy [19],[31],[47]. Excipient interference in pharmaceutical formulations [28], variations in plant composition due to geographical and processing factors [42], and the presence of volatile compounds in herbal ingredients are concrete examples reported in the literature. In kombucha fermentation, titration cannot distinguish individual organic acids and therefore requires HPLC confirmation [19]. In vitamin C analysis, other reducing compounds can interfere with the redox reaction [12],[43]. These findings demonstrate that controlling matrix complexity is essential for method validity.

The literature also shows the application of green analytical chemistry principles through miniaturization and reduction of hazardous reagents. μ PADs and PADs reduce reagent volumes and chemical waste [20]–[22]. Conductometry reduces the use of silver nitrate consumption [43]. The use of formamide in Karl Fischer is a more environmentally friendly alternative to toluene distillation [19]. Digitizing titration endpoints with webcams reduces dependence on visual recognition and operator judgment [26]. The integration of pH and conductivity sensors in SNAC systems improves the robustness of titrimetric analysis while maintaining the practical advantages of titration for small-scale monitoring [5]. Such methodological improvements are consistent with the broader GAC emphasis on analytical efficiency and resource use [44]. These findings suggest that sustainability principles are increasingly being integrated into analytical method development.

The significance of these findings is to strengthen the relevance of green analytical chemistry in pharmaceutical and food analysis [44]–[46],[48]. The study contributes by integrating empirical evidence that methodological innovations can improve efficiency while maintaining analytical performance [14],[49]. This perspective is particularly relevant to modern laboratories seeking to reduce environmental impact without compromising analytical quality [36],[47].

Research implications

The theoretical implication of this research is to strengthen an integrative paradigm for analytical method development by combining classical principles with modern technologies. The practical implication is a tiered approach in which method selection is guided by matrix complexity, analytical performance, and validation requirements. Paper-based and miniaturized analytical platforms further demonstrate the potential to improve accessibility, reduce analytical scale, and support more resource-efficient workflows [37],[50]. Similarly, developments in green liquid chromatography illustrate how analytical performance can be maintained while reducing solvent consumption and environmental impact [51]. The continued application of simple and economical titrimetric procedures also demonstrates that classical methods remain relevant when appropriately adapted to analytical needs [49]. These findings provide a basis for analytical chemistry curricula that balance classical and instrumental methods and support the design of pharmaceutical and food testing laboratories that consider both analytical quality and sustainability. Overall, this integrative interpretation moves beyond a merely descriptive comparison and advances a structured evaluative framework for method selection across different analytical matrices.

Research limitations

The present study uses a non-SLR literature review design and therefore does not apply a systematic selection protocol or meta-analysis. The analysis is based on 28 predetermined articles, so relevant studies outside the selected literature were not assessed. Furthermore, the synthesis was conducted using a comparative narrative approach without meta-statistical analysis. Variations in validation parameters across studies also limit direct numerical comparisons. Nonetheless, the analysis is based on the empirical evidence presented in Table 1, which summarizes the 28 reviewed articles.

Taken together, these limitations highlight an important conceptual gap: although recent analytical research increasingly incorporates green and sustainable approaches, the evaluation of analytical methods requires consideration of analytical performance, applicability, and environmental impact in an integrated manner [52]. This study addresses this gap by providing an integrative framework for evaluating the transformation and validity of pharmaceutical, herbal, and food analytical methods while incorporating green analytical chemistry considerations.

CONCLUSION

A critical synthesis of 28 reviewed articles indicates that analytical method development in pharmaceutical, herbal, and food analysis is evolutionary and integrative rather than a complete replacement of classical methods by modern instrumental techniques. Acid-base titrimetry, redox, complexometry, and precipitometry remain relevant because of their simplicity, cost efficiency, and ease of implementation, particularly in routine testing and resource-limited laboratories. In contrast, instrumental methods such as UV-Vis spectrophotometry, HPLC, RP-HPLC, ICP-AES, and Karl Fischer offer greater selectivity and precision for complex matrices containing interferents. Method transformation is also reflected in miniaturization and digitization through μ PADs, conductometry, pH-conductivity integration, and webcam-based endpoint detection, supporting reagent reduction and analytical efficiency in line with green analytical chemistry principles. Overall, method validity depends on the analyte and matrix context, supporting a tiered, evidence-based strategy that combines classical and instrumental approaches. The main contribution of this review is a structured comparative framework integrating methodological transformation, empirical validity, matrix complexity, and sustainability to guide analytical method selection across pharmaceutical, herbal, and food matrices.

Future research should focus on standardizing robustness and reproducibility, particularly for miniaturized and digital methods, and on experimentally validating tiered analytical strategies across diverse matrices. Further development should incorporate green analytical chemistry through reduced use of hazardous solvents and reagents. Simple digital technologies can also be integrated with classical methods to improve endpoint objectivity and precision without substantially increasing operational costs. Research should further examine how natural matrix complexity affects analytical accuracy under different conditions. These directions can strengthen the integration of analytical validity, operational efficiency, and environmental sustainability in pharmaceutical, herbal, and food analysis.

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