

A Review on Quality Control Aspects of Indian Medicinal Plants

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ABSTRACT

Quality control analysis of medicinal plants even their derived formulations are contributed to the quality, safety, and efficacy as well as to their regulatory purpose. Chromatography and their hyphenation with spectroscopic techniques are the most used analytical methods for quality assessment and authentication of medicinal plants and their derived products, also. With a thorough explanation of the analytical techniques used in authentication, the existing situation, and future projections, the present study aims to analyze the quality elements of the authentication of medicinal plants and the formulations developed from them. The results of the review suggested that determining the quality of medicinal plants based on targeted and non-targeted metabolites depends on the verification that the plants are from the same species, the gathering of high-quality raw materials, the extraction process, and the solvents that are acting to make the process more suitable. For thorough metabolomic profiling, a variety of cutting-edge chromatographic and analytical techniques, including HPTLC-MS, HPLC-MS, LC-MS, GC-MS, etc., are utilized. Moreover, chemometric approaches improved the ability to extract crucial chemical information from a wide range of original data. Principal Component Analysis (PCA) is the most widely used technique in chemometrics analysis to represent the high dimensionality of metabolite-based data sets for validity, efficacy, and consistency. In order to confirm the scientific evidence for their regulatory purpose and get insights into the current situation and the future horizons for their quality-based standardization of medicinal plants and their derived formulations.

Keywords: Indian medicinal plants, Quality control analysis, Phytochemistry, Chromatographic techniques, Spectroscopic techniques, HPTLC, LC-MS, GC-MS, Metabolomics.

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INTRODUCTION

Traditionally, concerning the inconsistent composition of medicinal plants and adulteration of the same species with common physical characteristics, it is difficult to identify or even characterized them as safe and original natural drugs. Quality control analysis of herbal medicines or their derived products ensures us their quality, safety, and efficacy for their regulatory purpose.^[1] As per AYUSH guidelines, standardization of herbal medicine or products is done based on the roadmap of various parameters such as authentication, macroscopic and microscopic character, loss on drying, total ash value, microbial assay, determination of aflatoxins, chromatographic profiling, etc.^[2] Chromatographic techniques have been demonstrated as powerful techniques for the quality-based standardization of

medicinal plants derived medicine and it suggests an exclusive outline that specifies the multiplicity or even marker constituents within a sample.^[3]

Many factors such as harvesting time, seasonal changes, cultivation sites, post-harvesting processing, substitutes or adulterants of raw materials, and extraction procedures and analytical conditions affect the overall quality of herbal medicine for their quality-based standardization. From the harvesting of medicinal plants to the manufacturing of herbal products, phytoconstituents contribute an essential role in assessing the quality, safety even efficacy of herbal medicines.^[4] Moreover, phytoconstituents exploration and their characterization evade the processing troubles in many research areas, including authentication, extract optimization and purification, identification of targeted and non-targeted metabolites, and their traditional pharmacological relevance. A systematic approach to investigating chemical phytoconstituents may lead to drug discovery and development from plant sources.^[5,6] Optimization of targeted bioactive phytoconstituents from plant sources contributes an important step from separation science to biological science.^[7] Chromatography and spectroscopy



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tools such as High-Performance Thin Layer Chromatography (HPTLC), Ultra Performance Liquid Chromatography (UPLC), High-Performance Liquid Chromatography (HPLC), Gas Chromatography, and Mass Spectroscopy (GC-MS), Liquid Chromatography and Mass Spectroscopy (LC-MS), Hydrophilic Interaction Chromatography (HILIC), Nuclear Magnetic Resonance (NMR), etc., are mainly hyphenated with target based isolation, identification and quantitation of phytoconstituents from a huge diversity of herbal constituents as well as help us to optimized and evaluate single constituents than the complexity of phytoconstituents.^[8,9] Despite the major efforts against the quality assessments of herbal medicine or products still, researchers are wrestling to minimize the various challenges that occurred during quality control of herbal medicine products.

In this review, a comprehensive explanation has been provided for metabolomics-based quality standardization as well as authentication of medicinal plants and their derived products as well as an understanding of standardization parameters particularly chromatography and their hyphenation with spectroscopic techniques is explained as per standard guidelines. The report generates scientific evidence based on quality assessment of various Indian medicinal plants and AYUSH formulation to minimize the future challenges over regulatory aspects.

Review findings

Quality control analysis of medicinal plants and formulations

Medicinal plants or traditional herbal formulations have a vast history in the advent of their therapeutic action against deleterious onsets of various diseases. However, ancient scriptures represent thousands of medicinal plants used to treat various disorders.^[10] Quality control analysis is consequently a major problem in the rationale use of medicinal plants. Although the metabolomics profile for targeted and untargeted constituents is still unraveled due to the complexity of phytochemicals, the variability of phytochemicals is due to the genetic and environmental factors which influence the chemical profile of plant secondary metabolites. Frequently, marker compounds contribute immensely to unraveling the deep philosophy of metabolite variability via quality-based standardization of phytochemicals using modern analytical techniques.^[11]

Medicinal plants or formulations comprise a diversity of phytoconstituents such as carotenoids, steroids, alkaloids, terpenoids, phenols, flavonoids, glycosides etc., and each constituent contributes its therapeutic potential. The diversity of phytoconstituents makes it difficult to confirm individual constituents along with deciphering their exact mechanism of therapeutic action.^[10] Besides this, herbal medicines can be considered toxic to human health and have been used as traditional and folk medicine which are sometimes acknowledged with unknown effects.^[12,13]

Moreover, medicinal plants have been represented as an unceasing source for drug discovery and development. It has been assessed that about 50% of newly approved drugs from the last two decades were derived either directly or indirectly from medicinal plants. Generally, the roadmap for medicinal plants from nature to science requires an appraisable deal of research efforts.^[7] For consumer protection, medicinal plants and the authentication of their derived products contributes an essential effort to their regulatory aspects. Preferably, overwhelmed authentication needs at every step including the harvesting of the medicinal plant to develop the final product. Good voucher specimens act as reference parameters and to prove the chain of custody for their future perspectives. Further, chemical analysis to assess the quality standard of medicinal plants is the best approach even for their quality-based standardization at a preliminary level.^[14] Chromatographic and spectroscopic techniques analysis make us more formalized to ease out the possible findings and to generate scientific evidence in the regulation of medicinal plants and their derived products. Although the inherent variability and the complexity of the phytochemicals make us far more difficult to authenticate them if a single-method analytical approach is assessed.^[12]

The analysis and ethnopharmacological exploration of the traditional justification of medicinal plants has been associated with the long history to validate them based on their quality, safety, and efficacy. Nevertheless, several researchers have potentially emphasized for quality assessment of medicinal plants via the expansion of chromatographic and spectroscopic methods. Furthermore, the techniques and their hyphenation with bio-tools exploring the recent trend in the phytopharmacological exploration of medicinal plants and their derived products to understand phytoconstituents variability and target-based screening of bioactive constituents which provides us with all the steps toward more formalized biological investigations.^[15,16]

Chromatographic techniques for quality control of medicinal plants

There are various chromatographic techniques such as TLC, HPTLC, HPLC, GC, LC, HILIC, etc., associated with estimating fingerprinting analysis of a complex mixture of constituents. Moreover, the hyphenation of chromatography techniques with other analytical instruments such as MS with HPTLC, HPLC, LC, GC etc., open a wide scope of applications in metabolomic analysis which may provide a prolific route for intensifying analytical assessments that not only explore the metabolites pattern but also constituent's characterization can be achieved.

TLC/HPTLC is a type of chromatographic technique that is acknowledged for chromatographic separation and qualitative and quantitative identification of varieties of constituents. Although considering the old technique, it is still progressively associated with the analysis of phytoconstituents or complex

mixtures of compounds obtained from the herbal matrix. It is achieved due to the progression and development of multi-functional instrumentation, automation, and advanced adsorbents for separation and their supportive techniques.^[17] TLC contributes to wide applications, such as dietary supplements, analysis of herbal medicines, food and beverages, biological and clinical samples, environmental pollutants, and chemicals.^[18] In chromatographic analysis, TLC involves the multistage dispersal process, which includes a suitable “adsorbent” (the stationary phase), mobile phase or eluent (the mixture of organic and inorganic solvents) as well as the sample or chemical mixture. The drawbacks of TLC in the quality-based assessment of medicinal plants have been characterized as the need for high compound concentration for detection, low reproducibility and resolution and the semi-quantitative nature of the technique. The factors that are rigid in TLC analysis namely precision include sample application, saturation of the TLC developing chamber and the color instability developed by the coloring reagents are used for detection. Nevertheless, TLC is progressively used for the analysis of the herbal medicine due to its resolution, reproducibility and sensitivity.^[19]

The advanced form of the TLC is HPTLC, which includes high-performance adsorbent layers which consist of refined uniform particles of silica gel (Diameter: 5 μm) and then TLC (Diameter: 12 μm), with adopted instrumentation development chambers. It is mostly implying a standardized methodology for optimization, development, validation as well as documentation methods. It implies for qualitative and quantitative evaluation to promote the quality-based standardization of herbal medicines. In this technique, the quantitative mode for the optimization of phytochemicals operates in a significantly optimized way (standardized with a known method).^[20]

An automatic sampler is used for sample application on a TLC followed by the development of a fingerprint via developing the TLC plate in a pre-saturated TLC development chamber. To find reproducible or precise results, the study needs to be conducted in different laboratories and as per literature references via controlling the parameters such as TLC chamber saturation time, the water content of the silica stationary phase, mobile-phase composition, etc. However, HPTLC is a well-characterized and established method for GMP-compliant quality control of medicinal plants.^[21,22]

HPLC is acknowledged as the most effective and accurate liquid chromatography technique used in the quality control analysis of medicinal plants.^[23,24] It is an accessible, affordable, and accountable automated technique with high rates of resolution, precision, selectivity as well as sensitivity. The most beneficial features of HPLC are its hyphenation with different kinds of detectors such as Ultra Violet (UV) mostly used for UV absorbing compounds, Diode Array Detector (DAD) mostly used for the fingerprinting profile of herbal matrix, Evaporative Light Scattering Detector

(ELSD) as well as Chemo Luminescence detectors (CL) have been used mostly for non-UV absorbing compounds. Its hyphenation with Mass Spectrometry (MS) is the most admissible technique exponentially used for the identification and characterization of the compounds separated through HPLC.^[25-27] The selection of stationary phases such as C_8 , C_{12} and C_{18} columns essentially provides the throughputs for better analytical profiling such as fingerprinting development, method validation, etc. The quality for better separation depends upon the particle size (currently 3–5 μm) of the columns while smaller the particle size extremely upsurges the backpressure: in case the halved particle size, the pressure is quadrupled. The modern HPLC instrumentation endures with up to the pressure of 6000 psi, higher efficacies and shorter departure times of molecule by decreasing particle size of the stationary phase and increasing the flow rates.^[28,29]

UPLC is also been acknowledged as the most rising practicable technique for quality-based standardization of herbal medicines and their derived products. It makes better the quality and productivity of targeted and non-targeted metabolites associated with bioactivity exploration. It generally occupied the highest pressure (8000 psi) which carries liquid chromatographic analysis to another forward platform via necessary modifications in a conservative HPLC system.^[19] The high-resolution separations analysis and stationary phase particle size (diameter less than 2 μm) formalized it as a super sensitive and resolution chromatographic system then HPLC.^[30]

Besides the identification purposes, a major insight of the HPLC/UPLC approach is de-replication, that is the confirmation of known metabolites in extracts preferably at an early stage of the fractionation process.^[31-33] This is mainly done by hyphenated techniques such as HPLC/UPLC-MS/NMR, HPLC/UPLC-PDA-MS/NMR, etc. The stationary phases support the separation efficacy, high-speed elution and instrumentation accomplished of surviving with high backpressures, which has given rise to remarkable perfections of complex mixtures separation analysis. Furthermore, the chromatographic and tandem mass spectral data based on their elution affinity and fragmentation chemistry gives a unique identifying characteristic of different metabolites for assessment metabolomic analysis.^[19,34,35]

LC-MS has been acknowledged as another well-established analytical technique especially used for the qualitative and quantitative estimation of metabolites of different polarity indexes via exhausting precise peak identification with referenced retention times of the separated molecules and their respective mass spectra. LC-MS entails the least analysis temperatures and simple sample preparation as compared to GC-MS. It does not involve sample derivatization and no sample volatility hyphenation. In positive or negative ion modes, the metabolites are generally characterized. The high throughput and comprehensiveness of LC-MS contributed to its predominantly

and versatility in the analysis of targeted or non-targeted metabolite identification, qualitatively and quantitatively.^[36,37] Despite its major advantage, the major restriction of LC-MS is to control the applicability of compound documentation in the analysis of the non-targeted metabolites due to undifferentiated isomers and multiple adducts formations. The previous study cited the successful use of LC-Atmospheric Pressure Chemical Ionization (APCI)-MS, Hydrophilic Interaction LC (HILIC)-MS, and UPLC-TOF-MS have been effectively used for inclusive metabolic fingerprinting of medicinal plants.^[38]

GC is acknowledged as the most sophisticated analytical technique frequently used for the qualitative and quantitative estimation of volatile oils or volatile compounds such as carotenoids, terpenes, etc. with precise peak credentials with standard retention times and their respective mass spectra. The high separation proficiency, sensitivity, and throughput make it a useful tool for the analysis of volatile phytochemicals of herbal medicine for their quality control purpose. However, the studies hyphenated with phytochemicals screening of volatile constituents gaining abundance as a most powerful analytical method for quality control studies.^[31] Despite its advantages, it is ambit to the analysis of volatile compounds only, while derivatization is required to identify the polar or semi-polar metabolites which are hard to analyze due to multiple additives or derivative products. The analysis is usually limited to the essential oils because of the likely degradation of thermo-labile constituents, hence it is limited to the analysis of volatile constituents only.^[39]

The coupling of GC to MS provides an immense fall to the analysis times of essential oils as well as increases the detection limits. It provides more rapid and high proficiency analysis by using columns of the micro-bore capillary with the least stationary phase film thickness, optimistic temperature programming, fast data attainment, and its greater split ratio. Moreover, GC-MS equipped with low-pressure mega-bore analytical columns directed to a slightly reduced efficiency but diverse to decreased analysis times.^[40,41]

HILIC has grown consideration for the analysis of medicinal plants, especially for quality separation of high polar constituents. This technique is highly associated with successive extraction or even separation of polar constituents using polar solvents.^[42] HILIC can be the better and most sensitive technique which superimposes another Normal-Phase Liquid Chromatography (NPLC) and it provides high resolution, data acquisition as well as accuracy in the separation of phytoconstituents. The technique is grounded in other attributes responsible for better partitioning between the hydrophilic stationary phase (enriched in water content) and a hydrophobic mobile phase which is typically consisted of 5-40% water in another organic solvent. This approach for analysis of the polar constituents is more auspicious as compared to other NPLC techniques because of its

high separation productivity through the involvement of polar and non-polar solvents as mobile phases.^[42,43]

Chromatographic technique in qualitative and quantitative analysis for phytochemicals

Due to increasing market standards laid on medicinal plants or containing therapeutically active constituents. Quality control assessments of herbal medicines and their derived products by using appropriate analytical methods are necessary to validate them scientifically for their regulatory aspects. However, due to a lack of quality and impactful reviews of the available methods on Indian traditional medicinal plants and their respective traditional ayurvedic and Unani formulations, the present comprehensive study systematizes the current and trended knowledge about chromatographic techniques used for qualitative and quantitative evaluation of the phytochemical Table 1.^[1,44]

TLC-MS is the most exponentially used technique with the additional analytical dimensions with mass spectroscopy which increase its performance, thus acknowledged as the more flexible identification tool for direct screening of constituents. In the TLC-MS interface, the separation and identification of compounds is accomplished via the identification of their molecular ions.^[16,75,76] A study was published on the identification of phytoconstituents in *Salvia lavandulifolia* through the TLC method coupled with MS on TLC-MS. In that study, several phytoconstituents were identified such as trans-cinnamic acid, ellagic acid, vanillic acid, ferulic acid, rosmarinic acid chlorogenic acid, etc.^[77] TLC-bioautography coupled with mass spectroscopy is one of the advanced methods to direct the screening of bioactive phytoconstituents from medicinal plants or herbal medicine. Gaurav *et al.* describe TLC-bioautography MS-based identification of anti-oxidants and antidiabetic phytoconstituents from the tablets of BG4-34. Several phytoconstituents were identified such as quercetin, gallic acid, myricetin, chlorogenic acid as an antioxidant, berberine, and palmatine as α -amylase inhibitory constituents whereas β -sitosterol and columbin, columbamine etc., as α -glucosidase inhibitory compounds.^[16] TLC-bioautography-MS/NMR is the rapid discovery in the separation and identification of targeted bioactive phytoconstituents. A study based on HPTLC/MS and NMR has been demonstrated for the detection of targeted bioactive compounds. In a published report by Adhami *et al.* acetylcholinesterase inhibitors were detected in galbanum,^[78] while HPTLC-MS hyphenated with electrospray ion trap shown for *Ilex vomitoria Aiton* in quality validation.^[79] The traditional formulation such as arista's, many changes occur during their fermentation process, and the biochemical changes may potentiate synergistic or antagonist effects during biological assessments. In a study, Lal *et al.* reported a consequent upsurge in the content of gallic acid, chebulic acid, ellagic acid as well as ethyl gallate was found after the fermentation method while 5-hydroxymethyl

Table 1: Recent chromatographic techniques coupled with spectroscopic methods in quality assessment of medicinal plants.

Sl. No.	Medicinal plant and part used for analysis	Method/Type of Analysis	Targeted phytoconstituents	References
1	<i>Aerva lanata</i> (Aerial parts and roots)	HPTLC/MS (Qualitative and quantitative)	Quercetin, kaempferol, and myricetin	[45]
2	<i>Musa paradisiaca</i> (Fruit)	HPTLC/GCMS (Qualitative)	α -thujene, γ -terpinene, α - and β -pinene, sabinene, β -myrcene, limonene, α -capaene, caryophyllene and (Z,E)- α farnesene. Aceteugenol, palmitic acid, stearic acid, palmitin.	[46]
3	<i>Gymnema sylvestre</i> (Leaf)	HPTLC/UPLC-MS (Qualitative)	Andrographolide, quinine, berberine, hesperetin, deacyl gymnemic acid, gymnemagenin, gymnemic acid, quercetin, chelidonine etc.	[47]
4	<i>Cichorium intybus</i> (Seed)	HPTLC/UPLC-MS (Qualitative and quantitative)	Cichoroside, glucose-6-phosphate, 11,13-dihydro-lactucin. 2',6 dihydroxyflavone, quercetin, coumarin, kaempferol-3-glucoside-2''-p-coumaroyl, quercetin-3-arabinoside etc.	[48]
5	<i>Solanum nigrum</i> (Aerial parts)	HPTLC/UPLC-ESI-MS/MS (Qualitative and quantitative)	Solasonine, solamargine, solasodine.	[35]
6	<i>Tarconanthus camphorantus</i> (Leaf)	CC/NMR (Qualitative)	Trifloculoside, parthenolide, lupeol, and erythrodiol.	[49]
7	<i>Tribulus terrestris</i> (Fruit)	HPLC (Qualitative and quantitative)	Diosgenin, catechin, rutin, gallic acid, tannic acid and quercetin.	[50]
8	<i>Bergenia ligulata</i> (Rhizome)	HPLC (Qualitative and quantitative)	Tannic acid, quercetin, gallic acid, catechin.	[51]
9	<i>Picrorhiza kurroa</i> (Rhizome)	HPLC (Qualitative and quantitative)	Picrosides I, II and apocynin.	[52]
10	<i>Boerhaavia diffusa</i> (Root and whole plant)	HPLC (Qualitative and quantitative)	Boeravinone E and B.	[53,54]
11	<i>Glycyrrhizae radix</i> (Root)	HPLC-MS (Qualitative and quantitative)	Glycyrrhizinic acid, liquiritin, liquiritigenin, isoliquiritigenin, glycyrrhizin, 18 α -glycyrrhetic acid, 18- β -glycyrrhetic acid and 18- β -glycyrrhetic acid methyl ester.	[55,56]
12	<i>Tinospora cordifolia</i> (Stem)	HPLC-ESI-QTOF-MS (Qualitative and quantitative)	Berberine, palmatine, jatrorrhizine, magnoflorine, choline.	[57]
13	<i>Psidium guajava</i> (Leaf)	UPLC-MS (Qualitative)	3-hydroxyanthranilic acid, Cis-Zeatin-9-glucoside, Quercetin, 5-O-Galloylquinic acid, Ellagic acid Kaempferol, Methylsuccinic acid, Oxysterol (R)-3-Amino-4-phenylbutyric acid, etc.	[58]

Sl. No.	Medicinal plant and part used for analysis	Method/Type of Analysis	Targeted phytoconstituents	References
14	<i>Fragaria vesca</i> (Berries)	HPLC-MS/MS (Qualitative and quantitative)	Phenolic acids, ellagitannins, ellagic acid derivatives, flavonols, monomeric and oligomeric flavanols, dihydrochalcones and anthocyanins.	[59]
15	<i>Morinda officinalis</i> (Root)	UPLC-MS (Qualitative and quantitative)	Monotropein, deacetyl asperulosidic acid, asperulosidic acid, asperuloside, rubiadin-1-methyl ether, rubiadin, jaceosidin.	[60]
16	<i>Veratrum nigrum</i> (molasses)	UPLC-MS/MS (Qualitative)	Jervine	[61]
17	<i>Tinospora cordifolia</i> (Stem)	UPLC MS/MS (Qualitative and quantitative)	Berberine, cordifolioside A.	[62,63]
18	<i>Vaccinium angustifolium</i> (Fruit)	LC-MS (Qualitative)	Delphinidin-3- galactoside, cyaniding-3- galactoside, Delphinidin-3- glucoside cyaniding-3- glucoside, etc.	[64]
19	<i>Picrorrhiza kurroa</i> (Rhizomes)	LC-MS (Qualitative and quantitative)	Picroside I and picroside II.	[65]
20	<i>Carica papaya</i> (Leaf)	LC-MS/MS (Qualitative and quantitative)	Carpaine	[66]
21	<i>Potentilla anserine</i> (Whole plant)	LC-MS/MS (Qualitative)	Chlorogenic acid, kaempferol 3-O-rutinoside, acacetin 7-O-rutinoside, and genistein.	[67]
22	<i>Lepidium sativum</i>	LC-MS/MS (Qualitative)	Kaempferol, coumaroylquinic acid, p-coumaroyl glycolic acid, caffeic acid.	[68]
23	<i>Morus alba</i> (Leaf)	LC-MS/MS (Qualitative and quantitative)	1-deoxynojirimycin	[69]
24	<i>Swertia chirata</i> (Leaf)	LC-MS/MS (Qualitative and quantitative)	Mangiferin, amarogentin, amaroswerin, sweroside and swertiamarin.	[70]
25	<i>Mangifera indica</i> (Leaf)	UHPLC-MS (Qualitative)	Mangiferin and quercetin	[71]
26	<i>Moringa oleifera</i> (Leaf)	GCMS (Qualitative)	-	[31]
27	<i>Withania somnifera</i> (Root)	GC/MS- NMR (Qualitative)	(n=43, withanolides) Withaferin A, withanolide D, withanoside IV or VI, withanolide sulfoxide, dihydrowithanolide D and ixocarpalactone A etc.,	[72]
28	<i>Glycyrrhiza inflata</i> (Root)	GC-MS (Qualitative)	Cadaverine	[73]
29	<i>Rostellularia diffusa</i> (Whole plant)	GC-MS (Qualitative)	16-Hentriacontanone (22.59%), Hexadecanoic acid (11.23%), Stigmast-5-en-3-ol (6.78%), 9-Octadecenoic acid (n= 40).	[74]

furfural was also found as the fermented adduct after the final process of abhayarishta.^[80]

Safoof-e-Pathar Phori is one of the famous and essential Unani formulations used for antilithiatic activity, due to the lack of quality assessment of such a famous Unani formulation, Ahmad *et al.* established the fingerprint profiling of traditional Unani polyherbomineral (Safoof-e-Pathar Phori) formulation by modern

analytical approached such as HPLC, HPTLC, and GC-MS. The Unani polyherbomineral formulation was authenticated using comparative HPLC and GC-MS fingerprint profiling and stated that Alpha humulene, 3,7-cycloundecadien-1-ol, 3-cyclohexen-1-carboxaldehyde, eudesma-4(14), n-hexadecanoic acid, colloidal, etc., are the active ingredient of Safoof-e-Pathar Phori. Moreover, HPLC-MS, as well as HPLC-Nuclear Magnetic

Resonance (NMR), provides an additional dimension to obtain spectral information using such advanced chromatography and spectrometry approaches in the quality-based standardization of herbal medicines. Analytical technique combinations such as ESI-IT-TOF/MS-HPLC-DAD-ESI-MS have been considered the most effective technique for coumarin analysis even patterns recognition in *Angelica polymorpha* Maxim. Roots.^[81]

Moreover, previous studies conducted for metabolic profiling of medicinal plants such as licorice roots (*Glycyrrhiza glabra*) of dissimilar cultivars based on the geographical areas were assessed through LC-ESI-MS. The analysis was conducted in both positive ionization and negative ionization modes. The marker constituents such as 4-hydroxyphenyl acetic acid, glycyrrhizin, and liquiritigenin glycosidic conjugates were found different based on their concentration among four glycyrrhiza genus (*Glycyrrhiza uralensis*, *Glycyrrhiza glabra*, *Glycyrrhiza inflata*, and *Glycyrrhiza echinata*). Moreover, other constituents such as phenols and saponins were correlated to glycyrrhizic acid and further recognized as the comparative metabolites of licorice roots for the effect on phytochemicals based on geographical areas.^[82] Montoro and Jensen also evaluated the extent of active terpene compounds of Ginkgo biloba (bilobalide and ginkgolides) in the negative ionization mode using LC-APCI-MS and ginkgolides and bilobalide were identified as active terpene constituents in Ginkgo biloba to assess suitable quality assessment. In addition, LC-MS-based fingerprinting and metabolic profiling has been acknowledged as the most applicable method for not only identification but also quantitation of the bioactive constituents where the detectors such as UPLC-Diode Array Detector (DAD)-ESI-MS and UPLC-Q-TOF-MS act as the effective tool.^[83,84]

The study deals with the GC-MS fingerprinting analysis of *Caulophyllum robustum*, two main components like aporphinoid and quinolizidine detected as the key component for quality assessment.^[83] Furthermore, Farag et al. (2012) evaluated primary metabolic profiling of different species of licorice roots (*Glycyrrhiza uralensis*, *Glycyrrhiza glabra*, *Glycyrrhiza echinata* and *Glycyrrhiza inflata*) using GC-MS to differentiate the metabolites pattern as well as to establish an informative framework concerning their quality standard. Several metabolites such as saccharides, fatty acids, amino acids as well as polyphenolic constituents were distinguished in the extract licorice roots. The resulting outcome reveals that cadaverine was found the only compound in *G. inflata* and myo-inositol in *G. echinata* which differentiate each species for their quality standardization. Furthermore, GC-TOF-MS analysis of turmeric and its two different cultivars, *C. aromatica* and *C. longa*, along *Galipea officinalis* was done and differentiate each species based on their metabolites pattern, the intensity of the marker constituents.^[85]

Common chemometric tools

Chromatographic and spectroscopic techniques have extensively been applied to establish the metabolites pattern of herbal medicines and their derived products for their quality standards and thus validate the scientific pieces of evidence for their regulatory aspects. Due to the high precision, resolution, sensitivity, and applicability of such analytical techniques, they are highly contributing to the extensive search on their metabolites pattern and provide a big inference for the discernment of herbal medicines.

There are various commonly used tools for extracting chemical information for herbal drug quality control analysis. The tools for extracting chemical information include Principal Components Analysis (PCA), Spectral Correlative Chromatography (SCC), Heuristic Evolving Latent Projections (HELP) Linear Discriminate Analysis (LDA), Information Theory (IT), Orthogonal Projection Analysis (OPA) and Local Least Square (LLS).^[19]

In contrast, Principal Components Analysis (PCA) is mainly to decrease the wide dimensionality of a data set comprised of a large interconnected variable. While possessing an extreme data set with high variation, PCA is proficient in transforming to latent variables, and the uncorrelated and ordered Principal Components (PCs) hold most of the dissimilarity in all of the unique variables. Furthermore, it is used to accomplish the main factor among the variability possessed by the data sets. PCA is further established to perceive cluster formatting and the relationship between objects and different variables.^[86,87]

Challenges in quality control of medicinal plants

Qualitative and quantitative assessment of phytochemicals of medicinal plants and their derived products often concern their regulatory aspects. The supremacy of chromatography and their hyphenation with spectroscopic techniques in the field of quality control analysis of medicinal plants has increased exponentially.^[88,89] However, there is a need for more comprehensive analytical methods and as well as tools used for the analysis which do not provide only information about the pattern of phytoconstituents based on their qualitative and quantitative assessment but also display huge data in an authentic, effective and informative way.^[90,91] Evaluation of phytochemicals of medicinal plants should be based on their ethnopharmacological relevance so that the principal metabolites responsible for pharmacological activity can be demonstrated.^[92,93] In the quality evaluation of medicinal plants, various techniques are associated with the determination as well as characterization of phytochemicals. Repeatability and accessibility are a better concern to the analysis conditions and instrumentation that provide accuracy and precision for phytochemical analysis. Many single-drug and polyherbal formulations are practiced for treating acute as well as chronic ailments that have less scientific data concerning their quality, efficacy, and safety for the regulatory purpose.^[16,93] For

the development of quality standards for herbal medicines and their derived products, ethnopharmacological aspects, the type of plant matrix required for bioanalysis or bioactivity, and analytical condition for phytochemical exploration should be known and clear so that a justified monograph can be developed for their regulatory purpose.^[94,95]

Metabolomics and chemometrics tools are being exponentially used for the evaluation and optimization of huge analytical outcomes from the phytochemical dataset and extracting impactful information on phytochemicals diversity as well as variability in medicinal plants.^[96,97] However, considering the present scenario, it can be suggested that quality control analysis of the medicinal plants using chromatographic or metabolites profiling is not always an impeccable technique to address all the phytoconstituents. LC-MS, GC-MS and NMR are the most conventional techniques used for exploring the metabolites profile of medicinal plants and their derived products, thus generating robust and precise scientific data for their regulatory purpose.^[88,98] Various numbers of articles on the quality evaluation of medicinal plants have been published that provide impactful information and establish their quality standards which are highly applicable to prove the authenticity of medicinal plants. Still, we lack the information scientific evidence and applicability of the advanced techniques which establish the quality standard against the justification of scientific facts which discriminates the medicinal plants of the same species or their derived formulation.^[99] To assess and explore the quality control of medicinal plants, an imperative and unique approach is necessary to establish the scientific facts concerning bio-fingerprint, targeted constituents biological methods, and metabolic fingerprint.^[25,100-102] Although the multi-dimensional strategy of work, quality metrology, standards establishment as well as informative summary contributes significantly to achieving an impeccable system for quality estimation of medicinal plants as well as such approaches validate the scientific evidence based on their quality, safety and efficacy.

CONCLUSION

From the review findings, it can be demonstrated that the précised quality of herbal medicines can be characterized by the estimation of one or two kinds of indicators using different targeted chromatography hyphenated with spectroscopic techniques. However, herbal medicines are usually associated with varieties of multiple compounds, which state that one or two markers would not sufficiently signify an appropriate framework of good quality control. Therefore, quality control analysis associated with the evaluation of multiple constituents by metabolomic profiling makes us far formalized to evade the misconception and regulates medicinal plants and their derived formulation from

adulterants or spurious natural drug preparation. Furthermore, metabolomics-derived multicomponent data sets comprised of large interrelated variables, and multivariate statistical analyses such as LLS, LDA, PCA, etc., should be obliged to reduce such dissimilarities.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

PCA: Principal Components Analysis; **SCC:** Spectral Correlative Chromatography; **HELP:** Heuristic Evolving Latent Projections; **LDA:** Linear Discriminate Analysis; **IT:** Information Theory; **OPA:** Orthogonal Projection Analysis and **LLS:** Local Least Square; **HPTLC :** High-Performance Thin Layer Chromatography; **UPLC:** Ultra Performance Liquid Chromatography; **HPLC:** High-Performance Liquid Chromatography; **GC-MS:** Gas Chromatography, and Mass Spectroscopy; **LC-MS:** Liquid Chromatography and Mass Spectroscopy; **HILIC:** Hydrophilic Interaction Chromatography; **NMR:** Nuclear Magnetic Resonance.

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