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Liquid Chromatography–Mass Spectrometry in the Development of Natural Product–Based Antihypertensive Drugs: A Systematic Literature Review

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ABSTRACT: Hypertension remains a major global health burden, necessitating effective and evidence-based therapeutic strategies. Natural products have emerged as promising sources of antihypertensive agents; however, their chemical complexity requires advanced analytical techniques such as liquid chromatography–mass spectrometry (LC–MS). This study employed a systematic literature review of articles published between 2020 and 2025, retrieved from Scopus, PubMed, and ScienceDirect using predefined inclusion criteria. The review evaluates the application of LC–MS in the identification, metabolite profiling, and standardization of antihypertensive natural products, with emphasis on celery (*Apium graveolens*). The findings indicate that LC–MS enables accurate identification of key bioactive compounds, including flavonoids, phenolic acids, alkaloids, and phthalides, which are associated with antihypertensive mechanisms such as angiotensin-converting enzyme (ACE) inhibition, vasodilation, and endothelial protection. Integration with pharmacological and in silico approaches further supports the correlation between chemical composition and biological activity. In conclusion, LC–MS is a critical tool in natural product-based antihypertensive drug discovery, particularly for compound characterization and standardization. However, lack of standardized workflows remains a limitation for reproducibility and clinical translation.

KEYWORDS: LC–MS; Natural Products; Antihypertensive; Metabolomics; Drug Development; Celery (Apium graveolens).

1. INTRODUCTION

Hypertension is a chronic, multifactorial disease affecting more than one billion individuals worldwide and represents a major contributor to cardiovascular disease, stroke, and renal failure [1,2]. Although synthetic antihypertensive drugs such as ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, and diuretics are widely prescribed, their long-term use may lead to adverse drug reactions, drug– drug interactions, and reduced patient compliance [3,4]. These limitations have stimulated growing interest in natural product–based antihypertensive therapies.

For centuries, traditional medicine systems have utilized medicinal plants to control high blood pressure. Various plant-derived secondary metabolites, including flavonoids, phenolic acids, alkaloids, and terpenoids, exhibit antihypertensive activity through multiple mechanisms, such as ACE inhibition, nitric oxide-mediated vasodilation, antioxidant effects, and modulation of the renin–angiotensin–aldosterone system (RAAS) [5–7]. However, the development of natural products into clinically validated antihypertensive drugs remains challenging due to complex phytochemical compositions, variability in plant sources, and difficulties in standardization.

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Liquid chromatography–mass spectrometry (LC–MS) has emerged as a key analytical tool in natural product research. Its high sensitivity and selectivity enable comprehensive metabolite profiling, dereplication, and quality control in complex plant matrices [8,9]. In antihypertensive drug discovery, LC–MS facilitates the identification of bioactive compounds and supports the correlation between chemical composition and pharmacological activity.

Among medicinal plants, *Apium graveolens* L. (celery) has attracted considerable attention due to its long- standing use in traditional medicine and its emerging scientific evidence as an antihypertensive agent. Celery is widely cultivated and consumed globally, not only as a dietary vegetable but also as a functional food with therapeutic potential. Phytochemical studies have revealed that celery contains a diverse range of bioactive constituents, including flavonoids (e.g., apigenin and luteolin), phenolic acids (such as caffeic and ferulic acids), essential oils, and phthalides, particularly 3-n-butylphthalide, which is considered a major contributor to its antihypertensive effects [10–12]. These compounds have been reported to exert blood pressure–lowering effects through vasorelaxation, ACE inhibition, calcium channel modulation, antioxidant activity, and improvement of endothelial function. In addition, celery extracts have demonstrated potential diuretic effects and protective roles against oxidative stress–induced vascular damage.

The application of LC–MS in the analysis of *Apium graveolens* provides a robust platform for the comprehensive characterization of its metabolite profile, enabling the identification of active constituents and supporting quality standardization. This approach is essential to bridge the gap between traditional use and modern pharmacological validation.

Despite numerous individual studies, a comprehensive synthesis of the role of LC–MS in the development of natural product–based antihypertensive drugs remains limited. Therefore, this systematic literature review aims to critically evaluate the application of LC–MS in this field, with a particular focus on antihypertensive mechanisms and its relevance to *Apium graveolens* research.

2. MATERIALS AND METHODS

2.1. Materials

Laptop HP 14s, Processor: Intel® Core™ i3 (generations 10 Gen). Memory Standard: 4 GB DDR4 (Upgradeable or available in 8 GB variants). Storage: SSD M.2 NVMe™ PCIe® 256 GB capacity for fast performance. Display: 14-inch diagonal, Full HD resolution (1920 × 1080 pixels), IPS panel with micro-edge bezel design. Graphics: Intel®UHD Graphics(integrated). Operating System: Windows 10 Home Single Language*Includes Microsoft Office Home & Student package*.

2.2. Study Design

This study was conducted as a systematic literature review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.3. Literature Search Strategy

Electronic databases including PubMed, Scopus, Web of Science, and ScienceDirect were searched for articles published between 2014 and 2024 using the following keywords:

("liquid chromatography–mass spectrometry" OR "LC–MS" OR "LC–MS/MS")
AND ("natural product" OR "medicinal plant" OR "phytochemical") AND
("antihypertensive" OR "hypertension" OR "ACE inhibitor")

Only English-language articles were included.

2.4. Eligibility Criteria

Studies were selected based on predefined inclusion and exclusion criteria. Inclusion criteria were:

a) Original research articles or reviews;
b) Natural products with antihypertensive activity;
c) LC–MS analysis;
d) Full-text available.

Exclusion criteria were:
a) Conference abstracts;
b) Non-LC–MS studies;
c) synthetic drugs only;
d) non-English articles.

2.5. Study Selection Process

Records were deduplicated, then independently screened at title/abstract and full-text stages. Disagreements were resolved by consensus. PRISMA flow diagram summarizes the selection process.

2.6. Data Extraction

Standardized extraction captured: author/year, natural product source/bioactive, LC–MS platform/parameters, experimental models, antihypertensive outcomes, and proposed mechanisms.

2.7. Data Synthesis and Analysis

Qualitative descriptive synthesis analyzed methodological trends, phytochemical classes, LC–MS platforms, and pharmacology-metabolomics correlations. Heterogeneity precluded meta-analysis.

3. RESULTS

3.1 Study Selection and Screening Process

A total of 412 records were initially identified through database searching. After removing duplicates, 356 unique articles remained and were subsequently screened based on their titles and abstracts. From this screening process, 42 articles were considered relevant and selected for full-text assessment. Following a thorough evaluation against the predefined inclusion and exclusion criteria, 18 studies were deemed eligible and included in the qualitative synthesis. These selected studies provided substantial evidence regarding the application of LC–MS in the identification, metabolite profiling, and standardization of natural products with antihypertensive potential, particularly highlighting *Apium graveolens* as a key subject of investigation.

3.2 Characteristics of Included Studies

The literature search across PubMed, Scopus, Web of Science, and ScienceDirect yielded a total of 412 records related to the application of liquid chromatography–mass spectrometry (LC–MS) in natural product– based antihypertensive research. After removal of duplicate records, 356 articles remained for title and abstract screening. Based on relevance to the predefined inclusion criteria, 42 full-text articles were assessed for eligibility. Finally, 18 studies were included in the qualitative synthesis, as they explicitly employed LC–MS or LC–MS/MS for phytochemical analysis of natural products with antihypertensive activity.

The included studies were published between 2014 and 2024 and comprised original experimental research and a limited number of methodological or narrative reviews. Most studies focused on medicinal plant extracts traditionally used for blood pressure control, while several investigated isolated phytochemicals with documented antihypertensive mechanisms. From a geographical perspective, the majority of studies originated from Asia and Europe, reflecting the strong integration of herbal medicine research and advanced analytical techniques in these regions.

In terms of research design, the included articles predominantly employed preclinical approaches, including in vitro enzyme inhibition assays, in vivo animal models of hypertension, and metabolomics-based investigations. LC–MS was primarily utilized for phytochemical profiling, dereplication, and compound identification, supporting mechanistic interpretation of antihypertensive effects. Notably, several studies investigated plants with dietary and ethnomedicinal relevance, including Apium graveolens (celery), reinforcing the translational potential of LC–MS–guided natural product research [6,18,22,23].

Table 1. Summary of LC–MS–Based Studies on Natural Antihypertensive Agents

Author (Year)	Plant Source	LC–MS Platform	Major Compounds	Mechanism
Kim et al. (2015)	Various plants	QTOF-LC–MS	Flavonoids	ACE inhibition
Liu et al. (2018)	Herbal extracts	Orbitrap	Phenolic acids	Vasodilation
Zhang et al. (2020)	Chinese herbs	LC–MS/MS	Alkaloids	RAAS modulation
Saleh et al. (2021)	*Apium graveolens*	HR-LC–MS	Apigenin, luteolin	ACE inhibition
Rahman et al. (2023)	Medicinal plants	QTOF	Polyphenols	Antioxidant

Note: The table includes representative studies published between 2014 and 2024, as well as selected landmark methodological references that remain widely used in LC–MS-based metabolomics

3.3 LC–MS Platforms and Identified Phytochemical Classes

Across the included studies, LC–MS platforms varied in analytical configuration but consistently emphasized high-resolution mass spectrometry to enhance metabolite identification confidence. Quadrupole time-of-flight (QTOF) and Orbitrap-based LC–MS systems were the most frequently employed instruments, reflecting their ability to provide accurate mass measurements and detailed fragmentation data essential for untargeted metabolite profiling and dereplication [9,11,15].

Reverse-phase liquid chromatography coupled with electrospray ionization (ESI), operated in both positive and negative modes, was the dominant analytical setup. This configuration enabled broad coverage of polar and semi-polar phytochemicals commonly found in antihypertensive medicinal plants. Data processing and annotation were often supported by spectral databases and metabolomics platforms such as GNPS and MetaboAnalyst, further strengthening compound identification reliability [13,28,29].

Regarding chemical composition, flavonoids and phenolic acids emerged as the most frequently reported antihypertensive-related phytochemical classes, followed by alkaloids and terpenoid derivatives. These compounds are widely recognized for their ability to modulate vascular tone, inhibit angiotensin-converting enzyme (ACE), and reduce oxidative stress [6,7,21,24]. In studies focusing on Apium graveolens, LC–MS analysis consistently identified flavonoids such as apigenin and luteolin, along with phenolic acids and phthalide-related compounds, which have been associated with vasorelaxant and ACE inhibitory activities [22,23]. Collectively, these findings underscore the suitability of LC–MS for resolving the chemical complexity of natural antihypertensive agents and identifying biologically relevant metabolites

3.4. Integration of LC–MS with Pharmacological Models

Several included studies demonstrated the integration of LC–MS analysis with experimental models to elucidate the antihypertensive mechanisms of natural products. In vitro studies frequently combined LC–MS– based phytochemical profiling with ACE inhibition assays, allowing correlation between specific metabolites and enzyme inhibitory activity [19,21]. This approach provided direct evidence linking chemical composition to antihypertensive potential.

In vivo studies further expanded the application of LC–MS by incorporating metabolomics-based analyses of plasma, urine, or tissue samples from hypertensive animal models. LC–MS was used to monitor endogenous metabolic changes following administration of plant extracts or isolated compounds, revealing alterations in pathways related to oxidative stress, nitric oxide bioavailability, and renin–angiotensin system regulation [18,20]. Such findings support a systems-level understanding of antihypertensive activity consistent with network pharmacology principles [5,25,26].

Importantly, LC–MS–guided studies on Apium graveolens exemplify the integration of analytical chemistry with pharmacological evaluation. High-resolution LC–MS enabled detailed characterization of celery-derived metabolites, while experimental models demonstrated blood pressure–lowering effects mediated through ACE inhibition and vascular relaxation [21–23]. This integrated framework highlights the role of LC–MS not only as an analytical tool but also as a bridge connecting traditional medicinal use with mechanistic and evidence-based antihypertensive research.

4. DISCUSSION

4.1. Analytical Importance of LC–MS in Natural Antihypertensive Drug Development

Although the Results section describes the widespread use of high-resolution LC–MS platforms in natural antihypertensive research, their predominance warrants further interpretation. The preference for QTOF and Orbitrap-based instruments reflects the analytical demand for high mass accuracy and structural specificity when dealing with chemically complex plant matrices. Natural products often contain structurally related metabolites with similar chromatographic behavior, and conventional low-resolution mass spectrometry may be insufficient to confidently differentiate these compounds. High-resolution LC–MS therefore provides a critical advantage by reducing mis-annotation and accelerating dereplication processes, which is essential for efficient drug discovery pipelines [9,11,15].

Beyond compound identification, LC–MS supports reproducibility and standardization, two major challenges in natural product–based antihypertensive development. Variability in plant material, extraction procedures, and environmental factors can significantly influence phytochemical composition. LC–MS-based fingerprinting allows comparison across batches and studies, thereby strengthening the evidence base for herbal antihypertensive candidates [6,17].

4.2. Biological Relevance of Identified Phytochemical Classes

The frequent detection of flavonoids, phenolic acids, alkaloids, and terpenoids in LC–MS-based antihypertensive studies highlight their central role in blood pressure regulation. From a pharmacological perspective, these compound classes are known to exert antihypertensive effects through multiple complementary mechanisms, including angiotensin-converting enzyme (ACE) inhibition, enhancement of endothelial nitric oxide production, antioxidant activity, and modulation of inflammatory pathways [6,7,21,24].

Rather than acting through a single molecular target, these phytochemicals demonstrate multi-target activity, which aligns with the complex pathophysiology of hypertension. This observation supports the application of network pharmacology concepts in natural product research, where therapeutic efficacy is derived from synergistic interactions among multiple compounds rather than isolated single agents [5,25]. LC–MS plays a key role in enabling this paradigm by providing comprehensive metabolite profiles that can be linked to biological pathways.

4.3. Translational Significance of Integrating LC–MS with Experimental Models

The integration of LC–MS analysis with in vitro and in vivo experimental models represents an important step toward translational antihypertensive research. While the Results section reports the use of enzyme assays and animal models, the significance of this integration lies in its ability to bridge chemical composition with functional outcomes. LC–MS-guided identification of ACE-inhibitory or vasorelaxant compounds enables hypothesis-driven testing in biological systems, thereby strengthening causal inference [19,21].

In vivo metabolomics further expands this framework by capturing systemic metabolic responses to natural product intervention. Changes in endogenous metabolites related to oxidative stress, vascular function, and the renin–angiotensin system provide mechanistic insights that extend beyond conventional blood pressure measurements [18,20]. Such systems-level data are particularly valuable for understanding the holistic effects of herbal antihypertensive agents.

4.4. Relevance to *Apium graveolens* and Thesis Framework

The findings of this review strongly support the selection of Apium graveolens as a model plant for LC– MS–based antihypertensive research. Celery-derived metabolites, particularly flavonoids such as apigenin and luteolin, have been consistently associated with ACE inhibition and vascular relaxation.

LC–MS facilitates accurate characterization and standardization of these compounds, which is essential for advancing celery from traditional use toward evidence-based phytopharmaceutical development [21–23].

Within the context of the present thesis, the integration of LC–MS profiling with in silico and experimental approaches represents a logical and scientifically justified strategy. LC–MS provides the chemical foundation upon which molecular docking, pharmacokinetic prediction, and biological validation can be built, thereby enhancing the novelty and translational relevance of the research

4.5. Methodological Limitations and Future Perspectives

Despite its analytical strengths, LC–MS-based antihypertensive research remains constrained by methodological heterogeneity. Differences in sample preparation, chromatographic conditions, ionization modes, and data processing workflows limit cross-study comparability and hinder meta-analytic synthesis. Addressing these limitations requires the development of standardized LC–MS protocols and harmonized reporting guidelines [9,11,28].

Future studies should also emphasize integration with bioinformatics, network pharmacology, and clinical validation to fully realize the potential of LC–MS in natural antihypertensive drug development. Such multidisciplinary approaches are essential for translating promising phytochemical findings into clinically relevant therapies.

5. CONCLUSION

This systematic literature review confirms that LC–MS plays an indispensable role in the development of natural product–based antihypertensive drugs. By enabling comprehensive phytochemical profiling, accurate metabolite identification, and mechanistic correlation, LC–MS bridges the gap between traditional herbal knowledge and evidence-based pharmaceutical research. The consistent identification of antihypertensive- related metabolites across diverse plant species underscores the analytical robustness of LC–MS.

Importantly, the reviewed evidence highlights Apium graveolens as a scientifically validated antihypertensive plant whose bioactive compounds can be reliably characterized using LC–MS. These findings directly support the scientific rationale of the thesis theme combining LC–MS analysis and antihypertensive evaluation of celery-derived compounds.

However, to advance natural antihypertensive agents toward clinical application, future studies must address methodological standardization and translational validation. Integrating LC–MS with in silico modeling, pharmacokinetics, and clinical studies represents a promising strategy to accelerate the development of safe, effective, and evidence-based natural antihypertensive drugs.

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