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LC–MS in the Development of Natural Product Based Antidiabetic Drugs: A Systematic Review

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ABSTRACT: Natural products have great potential as a source for developing antidiabetic drugs, but matrix complexity and phytochemical variations are the main challenges in identifying bioactive compounds. This systematic literature review aims to evaluate the role of liquid chromatography–mass spectrometry (LC–MS) in the development of natural product-based antidiabetic drugs, particularly in type 2 diabetes mellitus (T2DM). The literature search was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using the PubMed, Scopus, Web of Science, and ScienceDirect databases. The study results show that LC–MS plays an important role in comprehensive phytochemical profiling, high-confidence metabolite identification, and dereplication of complex natural matrices. Integration of LC–MS with metabolomics and pharmacology approaches provides a deeper mechanistic understanding of antidiabetic effects, including modulation of glucose and lipid metabolism. However, methodological heterogeneity between studies is still an obstacle, so protocol standardization and bioinformatics integration are needed to increase translational relevance towards clinical applications.

KEYWORDS: LC–MS; Metabolomics; Natural Products; Antidiabetic; Type 2 Diabetes Mellitus.

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion, causing persistent hyperglycemia and dysregulation of glucose and lipid metabolism. Although a variety of conventional antidiabetic therapies are available, the limited long-term effectiveness and inability of a single therapy to target the complexities of T2DM pathophysiology drives the need for the development of more comprehensive therapeutic approaches. [1]. In this context, dipeptidyl peptidase-4 (DPP-4) was selected as an important molecular target due to its central role in the regulation of incretin hormones. Inhibition of DPP-4 increases the activity of the hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), thereby increasing glucose-dependent insulin secretion, suppressing glucagon secretion, and has a relatively low risk of hypoglycemia. In addition, DPP-4 also plays a role in the modulation of inflammatory responses and metabolic homeostasis, thus its inhibition involves more than one biological mechanism relevant to the pathophysiology of T2DM [2][3][4].

Natural products have attracted attention as potential sources of antidiabetic drug candidates because they contain a variety of bioactive secondary metabolites with multitarget mechanisms of action. Several classes of compounds commonly reported to have antidiabetic activity include flavonoids (such as quercetin and kaempferol), phenolic acids (such as gallic acid, chlorogenic acid, and ellagic acid), terpenoids, and alkaloids. These compounds are known to target various molecular pathways, including inhibition of dipeptidyl peptidase-4 (DPP-4) and α-glucosidase, increased insulin sensitivity, and modulation of glucose and lipid metabolism. Nevertheless, the development of natural product-based antidiabetic agents still faces significant challenges, especially related to the complexity of the chemical matrix of plant extracts, variability in phytochemical composition, and difficulties in identifying the specific active compounds responsible for their biological activity [5],[6],[7].

One medicinal plant that is widely reported to have antidiabetic potential is guava leaves (Psidium guajava L.). Guava leaves are known to be rich in bioactive compounds, such as flavonoids, catechins, gallic acid, ellagic acid, and flavonoid glycosides, which contribute to hypoglycemic effects through various

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mechanisms, including increased insulin sensitivity, inhibition of carbohydrate digestive enzymes, antioxidant activity, and potential inhibition of dipeptidyl peptidase-4 (DPP-4). The diversity of phytochemical content makes guava leaves a representative model in studies on the development of natural product-based antidiabetic agents using a multitarget approach [8][9][10].

Liquid chromatography–mass spectrometry (LC–MS) has emerged as a key analytical platform to address these challenges. This technique enables comprehensive phytochemical profiling, compound dereplication, as well as metabolite identification with high sensitivity and resolution [11]. In the context of T2DM, integration of LC–MS with metabolomics approaches provides deeper mechanistic insights into the relationship between the chemical composition of natural products and endogenous metabolic changes, including modulation of glucose metabolism, lipids, and energy pathways relevant to disease pathophysiology [12].

Liquid chromatography–mass spectrometry (LC–MS) has emerged as a key analytical platform to address these challenges. This technique enables comprehensive phytochemical profiling, compound dereplication, as well as metabolite identification with high sensitivity and resolution [13]. In the context of T2DM, integration of LC–MS with metabolomics approaches provides deeper mechanistic insights into the relationship between the chemical composition of natural products and endogenous metabolic changes, including modulation of glucose metabolism, lipids, and energy pathways relevant to disease pathophysiology [14].

Although the application of LC–MS in natural product-based antidiabetic research continues to increase, the available scientific evidence is still scattered and shows high methodological heterogeneity [15]. To date, there is no systematic literature review available that comprehensively evaluates the role of LC–MS as an integrated analytical platform in the development of natural product-based antidiabetic drugs in T2DM [14]. Therefore, this systematic review aims to evaluate in a structured manner the application of LC–MS in phytochemical profiling, identification of bioactive metabolites, integration with metabolomics and pharmacological approaches, as well as methodological limitations affecting translational relevance towards clinical applications.

2. METHODS

2.1. Tools and Materials

The tools used in this research include electronic scientific databases, namely PubMed, Scopus, Web of Science, and ScienceDirect which are used for systematic literature searches. Additionally, software using a Lenovo IdeaPad Slim 5i laptop (Intel® Core™ i5- 14th Generation RAM 8GB/16GB, Mendeley reference management was used to manage citations, identify duplicate articles, and support the study selection process. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used as a reference in the design and reporting of this systematic review.

The research material is in the form of full-text scientific articles consisting of original research articles and systematic reviews discussing the application of liquid chromatography–mass spectrometry (LC–MS) in the development of natural product-based antidiabetic drugs. The articles reviewed were obtained from relevant international journals in the fields of pharmaceuticals, analytical chemistry, metabolomics, and natural product research, and were selected based on predetermined inclusion and exclusion criteria.

2.2 Study Design

This research was conducted as a systematic literature review to evaluate the application of liquid chromatography–mass spectrometry (LC-MS) in the development of natural product-based antidiabetic drugs, particularly those aimed at type 2 diabetes mellitus (T2DM). This review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency, reproducibility, and methodological rigor in the process of identification, selection, and synthesis of available scientific evidence.

2.3. Literature Search Strategy

The experimental procedure must be explained in sufficient detail so that someone else can repeat the experiment. A comprehensive literature search was conducted using several electronic databases, including PubMed, Scopus, Web of Science, and ScienceDirect. The search strategy combined controlled vocabulary and

free text terms related to LC-MS, natural products, and antidiabetic activity. The following keyword operators are applied:

("liquid chromatography–mass spectrometry" OR "LC–MS" OR "LC–MS/MS") AND ("natural products" OR "medicinal plants" OR "phytochemicals") AND ("antidiabetic" OR "diabetes").

2.4. Eligibility Criteria

Studies were selected based on predetermined inclusion and exclusion criteria.

Inclusion criteria include:

1) Original research article or systematic review;
2) Studies investigating natural products, plant extracts, or isolated phytochemicals with antidiabetic-related activity;
3) Studies that use LC-MS or LC-MS/MS as the analytical method for compound identification, profiling, metabolomics, or pharmacokinetic analysis;
4) Studies that provide sufficient methodological details regarding LC-MS analysis

Exclusion criteria were:
1) Abstracts of conference proceedings, editorial articles, letters to the editor, or opinion pieces;
2) Studies that did not use liquid chromatography–mass spectrometry (LC-MS)-based analytical approaches;
3) Publications that specifically discuss synthetic antidiabetic agents without involving natural products;
4) Articles not written in English as well as publications that do not provide full text access.

2.5. Study Selection Process

All search result records were imported into the reference management software, and duplicate entries were removed. The article selection process was then carried out in two stages. In the first stage, an assessment of the title and abstract was conducted independently to determine suitability based on the predetermined inclusion criteria. In the second stage, the full-text manuscripts of articles that passed the initial selection were reviewed further to determine final eligibility. Differences of opinion during the selection process were resolved through discussion until consensus was reached. The overall flow of study selection is presented in the form of a PRISMA flow diagram.

2.6. Data Extraction

Data were systematically extracted from the included studies using a standardized extraction form. The following information was collected:

1) Author and year of publication
2) Identified sources of natural ingredients and bioactive compounds
3) Type of LC–MS instrumentation and analytical conditions
4) Research design and experimental model (in vitro, in vivo, or in silico)
5) Reported antidiabetic-related results and proposed mechanisms of action;

Extracted data were tabulated to facilitate qualitative synthesis and comparison between studies.

2.7. Data Synthesis and Analysis

Descriptive qualitative analysis was used to present a summary of the application of LC–MS techniques in natural product-based antidiabetic research. Data synthesis focused on mapping trends in LC–MS methods used, types of natural sources analyzed, groups of compounds related to antidiabetic activity, and reported pharmacological mechanisms. Given the significant variation in study designs, experimental models, and outcome parameters used, a quantitative meta-analysis was not performed in this review.

3. RESULTS

3.1. Study Selection and Characteristics

After going through a selection process following PRISMA guidelines, the studies included in this review were original research articles. The selected literature was obtained from relevant journals in the fields of pharmacology, analytical chemistry, metabolomics, and natural product research, including journals focused

on chromatography, analytical chemistry, pharmacological research, and evidence-based complementary and alternative medicine. Most of the analyzed studies utilized high-resolution LC–MS platforms to perform comprehensive metabolite profiling and dereplication of natural compounds in complex matrices, thereby supporting their relevance in antidiabetic research based on metabolomics approaches.

All tables and figures must have a caption and/or legend and be numbered (e.g., Table 1, Figure 2). Captions should be written in sentence case. Table headings should be placed above the tables, while figure legends should be placed below the figures. Tables and figures should be inserted into the relevant sections after their first mention in the text. Efforts should be made to place tables or figures at the top or bottom of each page where possible. Figures may also be submitted as separate files in PNG or JPEG format if necessary. High-quality images should be provided whenever possible [16][14][17].

After completing the systematic screening stages and feasibility evaluation, a total of six studies were selected for inclusion in the qualitative synthesis, as they demonstrated a direct relevance to the application of LC–MS-based metabolomics analysis in identifying antidiabetic candidates derived from natural products. Original research articles generally present experimental data regarding the use of LC–MS in phytochemical profiling and metabolite identification, while review articles contribute by providing methodological frameworks as well as mechanistic insights supporting antidiabetic drug development. A summary of the characteristics of the included studies, including study type, LC–MS platform used, and analysis objectives, is presented systematically in **Table 1**.

Of the ten studies analyzed, non-QTOF LC–MS/MS platforms were most frequently used (50%), followed by QTOF-based LC–MS systems (30%). Flavonoids were identified as the dominant phytochemical group (70%), with the main mechanisms including hypoglycemic effects, glucose regulation, DPP-4 inhibition, and increased insulin sensitivity.

3.2. LC–MS Platforms and Identified Phytochemical Classes

In all included studies, LC–MS and LC–MS/MS techniques were consistently employed to characterize complex natural matrices derived from medicinal plants with antidiabetic activity. The use of high-resolution platforms, such as Quadrupole Time-of-Flight (QTOF) and Orbitrap instruments, enables accurate molecular mass determination as well as detailed MS/MS fragmentation analysis. This capability supports reliable compound annotation and metabolite dereplication, thereby increasing confidence in the identification of bioactive compounds with potential roles in the regulation of glucose metabolism and antidiabetic mechanisms [17],[16],[18],[14].

Egbuna et al. reported that several bioactive compounds, including quercetin, kaempferol, rosmarinic acid, cyanidin, rutin, catechin, luteolin, and ellagic acid-belonging to the polyphenolic group (flavonoids and phenolic acids)-are frequently associated with antidiabetic activity [19]. Similarly, Tran et al. described various bioactive constituents in antidiabetic plants, such as flavonoids, terpenoids, alkaloids, glycosides, and phenolic compounds, which contribute to their therapeutic effects [20]. Furthermore, Chahrour et al. confirmed that plant-derived compounds, including flavonoids, terpenes/terpenoids, tannins, and glycosides, play significant pharmacological roles in improving glucose regulation in diabetes mellitus [21].

3.3. Integration of LC–MS Analysis with Experimental Models

In several antidiabetic studies, LC–MS analysis has been integrated with metabolomics-based in vivo models to evaluate changes in endogenous metabolism following treatment with plant extracts or isolated natural compounds. LC–MS is widely used to monitor metabolite alterations in plasma, tissues, or organs of diabetic animal models, thereby providing in-depth biochemical insights into the therapeutic effects observed in type 2 diabetes mellitus (T2DM).

For example, plasma metabolomic profiles from mouse models of T2DM have demonstrated significant alterations in lipid metabolites, amino acids, and glucose metabolism when compared with control groups. These changes reflect the metabolic disturbances characteristic of T2DM and are typically analyzed using untargeted LC–MS approaches. This methodology enables the identification of metabolic biomarkers associated with insulin resistance, lipid dysregulation, and oxidative stress, providing mechanistic insights beyond conventional blood glucose measurements alone [13],[22].

Table 1. Characteristics of studies involving the application of LC–MS in natural product-based antidiabetic research

Author (Year)	Plant (Part)	LC–MS mthod	Ky Compounds Idntifid	Antidiabtic Activitis/Targets
Ojiwoli (2005); Deguchi et al. (2010); Tran et al. (2020)	*Psidium guajava* L. (leaves)	LC–MS / LC–MS/MS	Quercetin, Catechin, Gallic acid, Ellagic acid	Hypoglycemic effect, potential DPP-4 inhibition
Baliga et al. (2014)	*Syzygium cumini* (seeds)	UHPLC-QTOF-MS	Ellagic acid, Myricetin	Decreased blood glucose, antioxidant activity
Farooq et al. (2020)	*Butea monosperma* (leaves)	UHPLC-QTOF-MS/MS	Apigenin, Luteolin derivatives	α-glucosidase and α-amylase inhibition
Unuofin et al. (2021)	Quercus robur (leaves)	UHPLC-QTOF-MS	Complex polyphenols	α-glucosidase inhibition
Tiwari et al. (2021)	*Gymnema sylvestre* (leaves)	LC–MS/MS	Gymnemic acids	Increased insulin sensitivity
Zhou et al. (2022)	*Morus alba* (leaves & fruit)	LC–MS metabolomics	Flavonoids, Chlorogenic acid	Hypoglycemic effect (T2DM model)
Ismail et al. (2022)	*Matricaria aurea* (herb)	LC–MS/MS	Flavonoids, Phenolics	DPP-4 inhibition, multitarget activity
Abdel-Ghani et al. (2023)	*Cinnamomum burmannii* (bark)	UPLC-ESI-MS/MS	Procyanidin, Cinnamaldehyde	Improved insulin sensitivity
Elkhawas et al. (2024)	*Lobelia* spp. (aerial part)	LC-ESI-MS/MS	Alkaloids & phnolics	Modulation of T2DM-related metabolic targets
Nallapaty et al. (2024)	*Momordica charantia* (fruit)	HR-LC-MS	Charantin, Flavonoids	Hypoglycemic effect, glucose regulation

Note: This table summarizes studies conducted during the period 2014–2024 that utilized reversed-phase LC–ESI and high-resolution mass analyzers for compound annotation.

Table 2. Integration of LC–MS analysis with pharmacological models and proposed antidiabetic mechanisms

Author (Year)	Pharmacological Model	Source of Natural Products / Key Compounds	LC–MS approach	Key LC–MS Findings	Proposed Antidiabetic Mechanism
Baliga et al. (2014)	In vivo (STZ-induced diabetic rats)	*Syzygium cumini* (ellagic acid, myricetin)	UHPLC-QTOF-MS	Dominant polyphenol profile	Decreased blood glucose, antioxidant activity
Irawan et al. (2018)	In vitro (enzymatic assay)	*Archidendron bubalinum* (phlorizin, astilbin)	LC–MS	Identification of enzyme-inhibitory flavonoids	α-glucosidase inhibition
Farooq et al. (2020)	In vitro (α-glucosidase/α-amylase)	*Butea monosperma* (apigenin, luteolin)	UHPLC-QTOF-MS/MS	Active flavonoid annotation	α-glucosidase and α-amylase inhibition
Nadeem et al. (2020)	In vitro antidiabetic screening	*Cuscuta reflexa* (flavonoids, phenolics)	UHPLC-QTOF-MS/MS	Profiling of complex phenolic compounds	Multitarget antidiabetic activity

Author (Year)	Pharmacological Model	Source of Natural Products / Key Compounds	LC–MS approach	Key LC–MS Findings	Proposed Antidiabetic Mechanism
Tran et al. (2020)	In silico & in vitro	*Psidium guajava* (quercetin, catechin)	LC–MS/MS	Identification of bioactive flavonoids	Potential DPP-4 inhibition, hypoglycemic effects
Unuofin et al. (2021)	In vitro (enzyme inhibition)	*Quercus robur* (polyphenols)	UHPLC-QTOF-MS	Polyphenol dereplication	α-glucosidase inhibition
Tiwari et al. (2021)	In vivo (T2DM animal model)	*Gymnema sylvestre* (gymnemic acids)	LC–MS/MS	Triterpenoid saponin profiling	Increased insulin sensitivity
Zhou et al. (2022)	In vivo (HFD/STZ-induced T2DM)	*Morus alba* (flavonoids, chlorogenic acid)	LC–MS metabolomics	Normalization of glucose metabolites	Hypoglycemic effect, metabolic regulation
Ismail et al. (2022)	In vitro & in silico	*Matricaria aurea* (flavonoids, phenolics)	LC–MS/MS	Identification of multitarget ligands	DPP-4 inhibition and related pathways
Abdel-Ghani et al. (2023)	In vivo (insulin resistance model)	*Cinnamomum burmannii* (procyanidin, cinnamaldehyde)	UPLC-ESI-MS/MS	Polyphenol and aromatic aldehyde profiling	Improved insulin sensitivity
Elkhawas et al. (2024)	In silico & metabolomic pathway analysis	*Lobelia* spp. (alkaloids, phenolics)	LC-ESI-MS/MS	Bioactive metabolite mapping	Modulation of T2DM-related metabolic targets
Nallapaty et al. (2024)	In vivo (diabetic rats)	*Momordica charantia* (charantin, flavonoids)	HR-LC-MS	Identification of glycosides and flavonoids	Hypoglycemic effect, glucose regulation

Notes:
This table presents representative studies conducted between 2014 and 2024 and highlights key LC–MS methodological approaches. Most studies remain at the preclinical stage; therefore, workflow standardization and translational validation are still required.

4. DISCUSSION

4.1 Analytical Significance of LC–MS in Natural Antidiabetic Research

Metabolomics-based LC–MS approaches have been widely applied in antidiabetic research to overcome the chemical complexity of plant extracts and enable comprehensive identification of bioactive compounds. Through both untargeted and targeted LC–MS techniques, researchers can map alterations in endogenous metabolites associated with disruptions in glucose, lipid, and amino acid metabolism in diabetes. For instance, the application of LC–MS in the study of antidiabetic medicinal plants facilitates the identification of flavonoids, alkaloids, phenolics, and saponins that contribute to hypoglycemic effects. Additionally, this approach enables the detection of metabolic biomarkers associated with improved insulin sensitivity and energy homeostasis. LC–MS also plays a critical role in compound dereplication, thereby accelerating the discovery of novel antidiabetic candidates from natural products while minimizing redundancy in research efforts [12]. Therefore, LC–MS serves not only as an analytical tool but also as a central platform in the development of molecular evidence-based natural product-derived antidiabetic drugs [14].

Compared with conventional analytical techniques such as HPLC or basic spectroscopic methods, LC–MS offers significantly higher sensitivity and superior structural elucidation capabilities. This allows for the detection of low-abundance metabolites that may possess important antidiabetic activity. Such capability is particularly essential in complex natural product research, where minor metabolites may contribute substantially to biological effects but are difficult to identify without advanced analytical tools. Advanced mass spectrometry techniques, including LC–MS/MS and LC-QTOF-MS, have demonstrated strong

capabilities in identifying biomarkers and metabolite profiles associated with diabetes and other metabolic disorders with high resolution. Furthermore, LC–MS-based metabolomics studies on herbal extracts have successfully linked specific compounds to antihyperglycemic activity, such as inhibition of the α-glucosidase enzyme, highlighting the clinical relevance of this technique in natural product-based antidiabetic drug discovery [23].

4.2 Linking Chemical Profiles to Pharmacological Outcomes

The integration of metabolomics-based LC–MS data with pharmacological studies has provided important insights into the biological relevance of phytochemicals identified in natural product-based antidiabetic research. A number of studies have demonstrated strong correlations between metabolites detected via LC–MS and the modulation of key metabolic pathways involved in diabetes mellitus, including glucose and lipid metabolism, as well as insulin signaling pathways such as PI3K/Akt (phosphoinositide 3-kinase/protein kinase B) and AMPK (AMP-activated protein kinase).

This approach enables direct correlation between complex chemical profiles of plant extracts and changes in metabolic biomarkers observed in both in vivo and in vitro models. By linking LC–MS-derived chemical profiling data with pharmacological outcomes and network pharmacology analysis, researchers can achieve a systems-level and multitarget understanding of the mechanisms of action of natural antidiabetic compounds. These metabolomics- and network-based approaches are aligned with the modern paradigm of antidiabetic drug discovery, which emphasizes multi-pathway interactions and synergistic effects of phytochemicals rather than the traditional "one compound–one target" concept [7][24][25].

Although preclinical data do not always allow for establishing definitive cause–effect relationships, the consistency of findings across independent studies demonstrating associations between LC–MS-based metabolite profiling and improved metabolic parameters reinforces the role of LC–MS as a reliable approach for bridging the chemical composition of natural products with observed pharmacological antidiabetic effects.

4.3 Methodological Limitations and Future Directions

Despite its many advantages, the reviewed literature reveals considerable methodological diversity in LC–MS workflows, including differences in sample preparation techniques, chromatographic conditions, types of mass spectrometers, and data processing methods. This variability limits comparability between studies and highlights the importance of developing standardized protocols and utilizing advanced bioinformatics tools to enhance the translational value of research findings [26][27].

The standardization of LC–MS protocols, along with the integration of advanced approaches such as bioinformatics, systems biology, and network pharmacology, represents a crucial step toward improving mechanistic interpretation and translational relevance in natural product-based antidiabetic research. Several metabolomics studies indicate that methodological variability and limitations in computational analysis remain major obstacles in linking metabolite profiles with molecular mechanisms and clinical outcomes in diabetes.

Therefore, the implementation of standardized LC–MS workflows, combined with tissue-specific analysis and multi-omics integration, is expected to strengthen the biological validity of findings and accelerate the translation of potential antidiabetic candidates into clinical applications. This approach is consistent with recent developments in diabetes metabolomics research, which emphasize systemic and multitarget understanding as the foundation for more effective and evidence-based drug discovery [28][29].

5. CONCLUSION

This systematic review confirms that LC–MS is a crucial analytical platform in the discovery and development of natural product-based antidiabetic drugs, owing to its ability to perform comprehensive phytochemical profiling, high-confidence metabolite identification, and dereplication of complex natural matrices.

The integration of LC–MS with pharmacological and metabolomics approaches provides a strong biochemical foundation for understanding the mechanisms of action of antidiabetic candidates with multitarget properties. Nevertheless, the predominance of preclinical evidence and the high degree of methodological variability among studies highlight the need for standardization of analytical protocols and strengthening of bioinformatics approaches.

In the future, the application of integrative and translational strategies is expected to accelerate the utilization of LC–MS-based findings toward the development of natural product-based antidiabetic drugs with clear clinical relevance.

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