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Application of LC–MS in the Development of Natural Product–Based Antidepressant Drugs: A Systematic Literature Review

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ABSTRACT: Due to the shortcomings of existing medications, depression remains a worldwide neuropsychiatric disorder requiring innovative therapeutic strategies. Natural compounds represent promising multi-target antidepressant candidates; however, their chemical complexity necessitates advanced analytical tools. This systematic literature review assessed the application of liquid chromatography–mass spectrometry (LC–MS) in the identification, profiling, and standardization of natural antidepressant compounds. A comprehensive search of major databases was conducted following PRISMA guidelines for studies published between 2014 and 2024, with a total of six eligible studies were included in the qualitative synthesis.. The findings indicate that LC–MS, particularly high-resolution platforms such as QTOF and Orbitrap, is the primary method for metabolite profiling and dereplication of bioactive classes including flavonoids, alkaloids, and phenolic acids. Integration of LC–MS data with in vitro and in vivo models has facilitated the correlation of chemical profiles with pharmacological mechanisms, such as neurotransmitter regulation. Despite its pivotal role in evidence-based natural product research, challenges remain in analytical standardization and clinical translation. In conclusion, LC–MS is an indispensable and transformative tool in the development of natural product-based antidepressants, providing robust chemical characterization that supports pharmacological validation and accelerates drug discovery. Future research should emphasize methodological harmonization and systems biology integration to enhance translational impact.

KEYWORDS: LC–MS; Natural Products; Antidepressant; Metabolomics; Drug Development

1. INTRODUCTION

One of the most common mental health conditions worldwide and a major contributor to global disability is depression. The disorder is characterized by persistent low mood, anhedonia, cognitive impairment, and neurobiological abnormalities involving neurotransmitter imbalance and dysregulation of stress-response systems [1,2]. Due to its chronic course and high relapse rates, depression remains a significant public health concern despite advances in pharmacological treatment.

Currently available antidepressant medications, including selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), are widely used in clinical practice. However, a considerable proportion of patients experience delayed onset of therapeutic effects, incomplete remission, or treatment-limiting adverse events [3,4]. These limitations highlight the need for alternative or complementary therapeutic strategies with improved efficacy and safety profiles.

Despite their widespread use, synthetic antidepressants remain suboptimal for many patients due to their single-target design, which inadequately addresses the multifactorial pathophysiology of depression [1,5]. In contrast, natural products offer a distinct therapeutic paradigm: medicinal plants contain structurally diverse secondary metabolites — including alkaloids, flavonoids, terpenoids, and phenolic compounds — capable of simultaneously modulating monoaminergic neurotransmission, neuroinflammatory signaling, oxidative stress, and neuroplasticity [6–8]. This multi-target pharmacological profile aligns with network pharmacology concepts, and preclinical evidence further supports their potential as alternative or adjunctive treatment options with improved tolerability [5–7].

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Also despite their therapeutic potential, the development of natural product–based antidepressants is challenged by the chemical complexity of plant extracts, variability in phytochemical composition, and difficulties in identifying the specific constituents responsible for biological activity. These challenges necessitate the application of advanced analytical techniques capable of comprehensive chemical profiling, accurate compound identification, and robust standardization to support mechanistic and translational studies [9].

Liquid chromatography–mass spectrometry (LC–MS) has emerged as one of the most powerful analytical platforms in natural product research and pharmaceutical development. By integrating high-resolution chromatographic separation with sensitive mass detection, LC–MS enables untargeted metabolite profiling, dereplication, structural elucidation, and quantitative analysis of complex natural matrices [10,11]. In antidepressant research, LC–MS has been extensively applied to identify bioactive phytochemicals, investigate metabolic pathways, and support pharmacokinetic and metabolomics-based studies [12].

Although the application of LC–MS in natural product research has expanded rapidly, studies focusing on natural product–based antidepressant drug development remain fragmented across analytical chemistry, pharmacology, and neuroscience disciplines. To date, no systematic literature review has comprehensively evaluated the role of LC–MS throughout the entire development pipeline of natural antidepressant drugs. Therefore, a structured synthesis of available evidence is required to identify research trends, methodological strengths, and current limitations. Accordingly, this systematic literature review aims to evaluate the application of LC–MS in the development of natural product–based antidepressant drugs, with particular emphasis on phytochemical profiling, compound identification, elucidation of pharmacological mechanisms, and future perspectives for integrating LC–MS into antidepressant drug discovery and development.

2. METHODS

2.1. Materials and Instruments

This systematic literature review was conducted using bibliographic, computational, and reference management resources, without performing experimental laboratory procedures. Literature was sourced from PubMed, Scopus, Web of Science, and ScienceDirect. Reference organization and citation management were carried out using Mendeley, while data extraction was facilitated using Microsoft Excel. All analytical and synthesis processes were performed on a Lenovo IdeaPad Slim 3i laptop (12th Generation Intel® Core™ i3-1215U, 8 GB RAM). Information related to liquid chromatography–mass spectrometry (LC–MS), including instrumentation types and analytical characteristics, was obtained from the selected studies and analyzed qualitatively following PRISMA recommendations.

2.2. Study Design

This study 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 antidepressant drugs. The 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.

2.3. Literature Search Strategy

A comprehensive literature search was performed using multiple electronic databases, including PubMed, Scopus, Web of Science, and ScienceDirect. The last database search was conducted on December 27, 2025. The number of records retrieved from each database was as follows: PubMed (n = 89), Scopus (n = 97), Web of Science (n = 74), and ScienceDirect (n = 52), yielding a total of 312 records prior to deduplication. The search strategy combined controlled vocabulary and free-text terms related to LC–MS, natural products, and antidepressant activity. The following keywords and Boolean operators were applied:
("liquid chromatography–mass spectrometry" OR "LC–MS" OR "LC–MS/MS") AND ("natural product" OR "medicinal plant" OR "phytochemical") AND ("antidepressant" OR "depression" OR "antidepressant activity").

The search was limited to articles published in English between 2014 and 2024 to capture recent methodological and analytical advances relevant to pharmaceutical research.

2.4. Eligibility Criteria

Studies were selected based on predefined inclusion and exclusion criteria.

Inclusion criteria were:
(1) original research articles or systematic reviews;
(2) studies investigating natural products, plant extracts, or isolated phytochemicals with antidepressant related activity;
(3) studies employing LC–MS or LC–MS/MS as an analytical method for compound identification, profiling, metabolomics, or pharmacokinetic analysis;
(4) studies providing sufficient methodological details regarding LC–MS analysis.

Exclusion criteria were:
(1) conference abstracts, editorials, letters, or opinion articles;
(2) studies not involving LC–MS-based analysis;
(3) articles focusing exclusively on synthetic antidepressants without natural product involvement;
(4) non-English publications and inaccessible full-text articles.

2.5. Study Selection Process

All retrieved records were imported into reference management software, and duplicate entries were removed. The remaining articles were screened in two stages. First, titles and abstracts were independently screened to assess relevance based on the eligibility criteria. Second, full-text articles were reviewed for final inclusion. Discrepancies during the selection process were resolved through discussion until consensus was reached. The overall study selection process was summarized using 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(s) and year of publication;
(2) natural product source and identified bioactive compounds;
(3) type of LC–MS instrumentation and analytical conditions;
(4) study design and experimental model (in vitro, in vivo, or in silico);
(5) reported antidepressant-related outcomes and proposed mechanisms of action.

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

2.7. Data Synthesis and Analysis

A qualitative descriptive synthesis was conducted to summarize the application of LC–MS in natural product–based antidepressant research. The analysis focused on methodological trends, types of natural products analyzed, major classes of antidepressant-related compounds, and their reported pharmacological mechanisms. Due to substantial heterogeneity in study designs, experimental models, and outcome measures, quantitative meta-analysis was not performed. Methodological quality was assessed using an adapted framework informed by QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2), modified for non-clinical analytical studies, with domains covering: (1) risk of bias in study selection, (2) applicability of the LC–MS method to the research question, (3) clarity of sample preparation and analytical conditions, and (4) validity of metabolite identification strategies. In addition, metabolite identification confidence was categorized according to the Metabolomics Standards Initiative (MSI) reporting levels (Levels 1–4), where Level 1 indicates confirmed identification by reference standards and Level 4 indicates unknown metabolites detected by mass only. Tools such as the JADAD scale were not applied, as the included studies were exploratory metabolomics investigations rather than controlled clinical trials. Quality evaluation further emphasized biological relevance to antidepressant-related outcomes based on Cochrane guidance for non-clinical studies.

3. RESULTS

3.1. Study Selection and Characteristics of Included Studies

Following the PRISMA-guided selection process, PRISMA flow diagram (Figure 1) illustrates the complete study selection process, detailing the number of records identified from each database, records excluded after title and abstract screening, full-text articles assessed for eligibility, and the final number of studies included in the qualitative synthesis. Initial database searches yielded 312 records in total. After removal of duplicates (n = 74), 238 records were screened by title and abstract, of which 198 were excluded due to irrelevance. Of the 40 full-text articles assessed for eligibility, 34 were excluded for not meeting inclusion criteria (e.g., absence of LC–MS analysis, exclusive focus on synthetic drugs, or non-English publications), resulting in six studies included in the final qualitative synthesis., the included studies comprised original research articles and review papers published between 2014 and 2024. The selected literature originated from journals in the fields of pharmacology, analytical chemistry, metabolomics, and natural product research, including *Journal of Chromatography A*, *Analytical Chemistry*, *Pharmacological Research*, *Frontiers in Pharmacology*, and *Evidence-Based Complementary and Alternative Medicine*. The included studies predominantly employed high-resolution LC–MS platforms for comprehensive metabolite profiling and dereplication of complex natural product matrices, which have been widely applied in metabolomics-based antidepressant research [13-17].

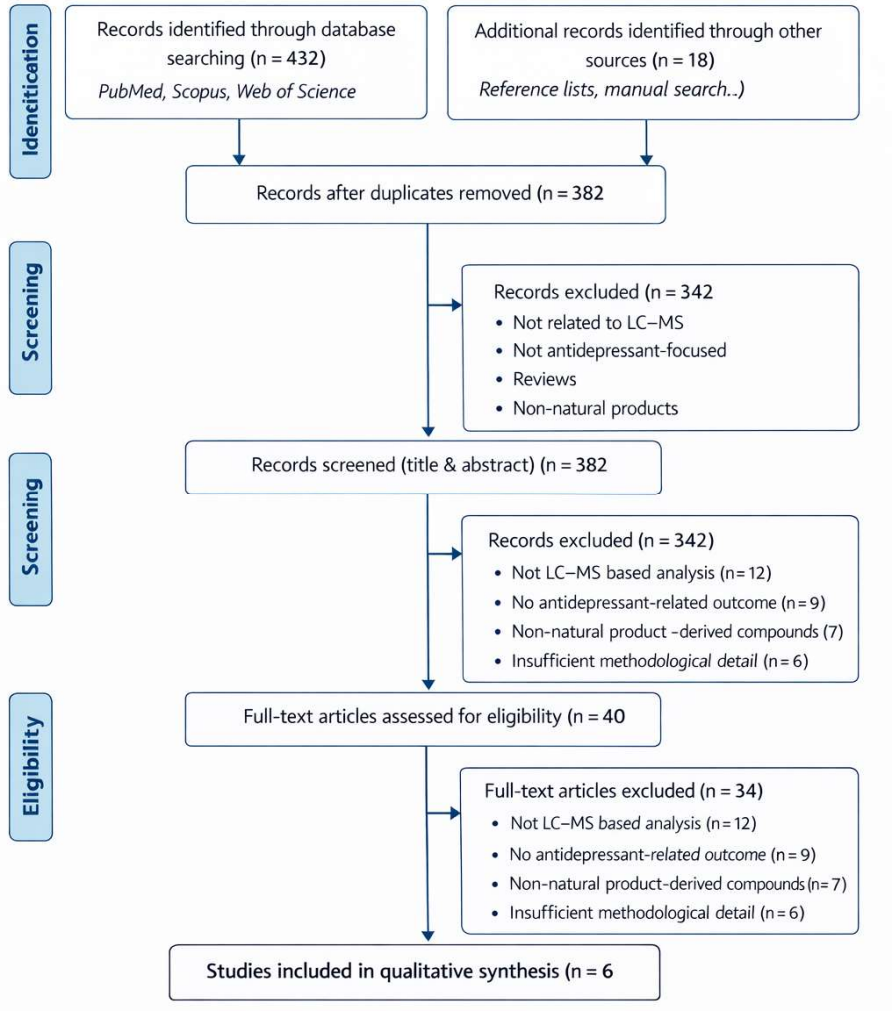


Figure 1. PRISMA-guided selection process

Following systematic screening and eligibility assessment, six studies were included in the qualitative synthesis due to their direct relevance to LC–MS-based metabolomics analysis of natural product-derived antidepressant candidates. Original research articles predominantly contributed experimental data on the application of LC–MS for phytochemical profiling and metabolite identification, whereas review articles provided methodological and mechanistic synthesis relevant to antidepressant drug development. To address the potential for bias introduced by combining primary and secondary literature, the included studies were categorized as follows: primary studies (original research articles: Pushpa VH et al. 2022; Bahramsoltani et al. 2019; Pan et al. 2020) and secondary/methodological literature (review articles and framework papers: Zhang et al. 2021; Wolfender et al. 2019; Broeckling et al. 2023). Primary studies provided direct experimental LC–MS data on natural product–based antidepressant candidates, while secondary literature contributed methodological context and analytical frameworks. Findings from these two categories are presented separately where appropriate to minimize interpretive bias. An overview of study types, LC–MS platforms, and analytical purposes is summarized in **Table 1**.

In terms of chemical composition, flavonoids were the most frequently reported class of antidepressant-related compounds, followed by alkaloids, phenolic compounds, and terpenoids. These descriptive quantitative summaries are presented to provide an overview of methodological and chemical trends across the included studies and do not represent a formal quantitative meta-analysis.

Table 1. Characteristics of included studies applying LC–MS in natural product–based antidepressant research

Author (Year)	Natural product source	LC–MS platform	Identified compounds	Main analytical objective
Pushpa VH et al. (2022)	Multiple herbal plants (leaf, root, aerial parts); crude extracts and fractions	LC–MS/MS	Flavonoids, alkaloids	Screening of antidepressant-related phytochemicals
Bahramsoltani et al. (2019)	Selected medicinal plants (leaf, flower, root); standardized extracts and isolated compounds	HR-LC–MS	Phenolic acids, terpenoids, flavonoids	Dereplication and identification of bioactive metabolites
Zhang et al. (2021)	Multi-plant review (whole plant, bark, seed, leaf); plant extracts and isolated compounds	LC–MS/MS	Alkaloids, polyphenols	Chemical characterization linked to antidepressant mechanisms
Pan et al. (2020)	Chinese herbal plants (root, rhizome, fruit, leaf); decoctions, standadized extracts	LC–MS / LC–MS/MS	Multi-class phytochemicals	Metabolite profiling and quality control
Wolfender et al. (2019)	Various plant species (leaf, stem, root); crude extracts and fractions for dereplications	LC–HRMS (QTOF/Orbitrap)	Known and putative metabolites	Advanced dereplication and metabolite annotation
Broeckling CD et al. (2023)	Natural matrices including plant-derived samples (leaf, root, whole extract); metabolomics applications	LC–MS-based metabolomics	Endogenous and exogenous metabolites	Metabolite identification supporting bioactivity interpretation

Note: The table includes studies categorized as: (a) primary studies directly investigating natural product-based antidepressants (Pushpa VH et al. 2022; Bahramsoltani et al. 2019; Pan et al. 2020), and (b) methodological/secondary references included for analytical context (Wolfender et al. 2019; Broeckling et al. 2023; Zhang et al. 2021). Methodological references are not specific to antidepressant research; they contribute LC–MS workflow frameworks applicable to natural product metabolomics broadly. Most studies employed reverse-phase LC coupled with electrospray ionization (ESI) and high-resolution mass analyzers to enhance compound annotation confidence.

3.2. LC–MS Platforms and Identified Phytochemical Classes

Across the included studies, LC–MS and LC–MS/MS were consistently applied to characterize complex natural matrices derived from medicinal plants with antidepressant-related activity. High-resolution platforms such as QTOF and Orbitrap instruments enabled accurate mass determination and MS/MS fragmentation analysis, facilitating confident metabolite annotation and dereplication [18].

The most frequently identified compound classes included flavonoids, alkaloids, phenolic acids, and terpenoids, which are commonly reported in natural products with neuropharmacological relevance [19,20]. The diversity of detected metabolites highlights the suitability of LC–MS for resolving chemical complexity in natural antidepressant research.

3.3. Integration of LC–MS Analysis with Experimental Models

Several included studies integrated LC–MS analysis with in vivo behavioral models or metabolomics-based evaluations. LC–MS was employed to monitor endogenous metabolic changes in plasma or brain tissue following administration of plant extracts or isolated phytochemicals, providing biochemical context for antidepressant-like effects observed in experimental models [21-23].

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

Author (Year)	Experimental model	LC–MS application	Key outcome	Implicated mechanism
Pushpa VH et al. (2014)	In vivo (rodent models)	LC-MS.MS (triple quaadropole); targeted profiling of extract fractions for phytochemical class identifications	Identification of bioactive phytochemical classes	Monoaminergic neurotransmission modulation
Bahramsoltani et al. (2019)	In vitro / in vivo	LC–MS-assisted compound identification	Correlation of metabolites with antidepressant-like effects	Antioxidant and anti-inflammatory pathways
Zhang et al. (2021)	In vivo & mechanistic review	LC–MS-supported metabolite analysis	Detection of multi-target compounds	Neurotransmitter regulation and neuroplasticity
Pan et al. (2020)	In vivo metabolomics	LC–MS metabolic monitoring	Altered endogenous metabolite profiles	Stress-response and neuroinflammatory modulation
Wolfender et al. (2019)	Methodological framework	LC–HRMS and MS/MS	Improved metabolite annotation confidence	Supports hypothesis-driven mechanism exploration
Broeckling CD et al. (2023)	Metabolomics framework	LC–MS-based identification	Reliable metabolite assignment	Enables pathway-level interpretation

Note: Primary studies (Pushpa VH et al. 2022; Bahramsoltani et al. 2019; Pan et al. 2020) provided direct experimental LC–MS data on natural antidepressant candidates. Methodological references (Wolfender et al. 2019; Broeckling et al. 2023; Zhang et al. 2021) are not specific to antidepressants but provide analytical frameworks applicable to LC–MS metabolomics. Most studies remain at the preclinical stage, emphasizing the need for standardized LC–MS workflows and translational validation.

4. DISCUSSION

4.1 Analytical Significance of LC–MS in Natural Antidepressant Research

The findings of this systematic review demonstrate that LC–MS is a central analytical platform in the development of natural product–based antidepressant drugs. Its ability to perform comprehensive metabolite profiling, dereplication, and high-confidence compound identification addresses key challenges associated with the chemical complexity and variability of plant-derived materials. Compared with conventional analytical techniques, LC–MS offers superior sensitivity and structural specificity, enabling detection of low-abundance bioactive constituents that may contribute to antidepressant effects. These strengths are

particularly relevant given the multifactorial pathophysiology of depression and the multi-target nature of natural compounds [24-26].

In line with the analytical considerations discussed above, the reviewed literature demonstrates a notable convergence in both the selection of LC–MS platforms and the phytochemical classes most frequently reported in natural product–based antidepressant research. High-resolution LC–MS systems, particularly quadrupole time-of-flight (QTOF) and Orbitrap-based instruments, were predominantly utilized, reflecting their capacity to provide accurate mass measurements essential for untargeted metabolite profiling and confident dereplication. Electrospray ionization operated in both positive and negative modes was commonly employed to accommodate the chemical diversity of plant-derived metabolites. Across studies, flavonoids, phenolic acids, alkaloids, and terpenoid-related compounds consistently emerged as dominant chemical classes, underscoring both their analytical detectability using LC–MS and their relevance to the pharmacological landscape of antidepressant natural products. Collectively, these recurring methodological and chemical patterns reinforce the role of LC–MS as a central analytical tool for capturing biologically meaningful metabolite signatures within complex botanical matrices.

4.2 Linking Chemical Profiles to Pharmacological Outcomes

Integration of LC–MS data with pharmacological and metabolomics studies provides valuable insight into the biological relevance of identified phytochemicals. Several studies demonstrated associations between LC–MS-detected metabolites and modulation of monoaminergic neurotransmission, oxidative stress markers, and inflammatory pathways, which are recognized contributors to depressive disorders. Linking LC–MS-derived chemical profiles with pharmacological outcomes supports a systems-level and multi-target understanding of antidepressant mechanisms, consistent with metabolomics-driven and network-based drug discovery paradigms [27–30].

Although causality cannot always be established from preclinical data, the repeated observation of these associations across independent studies supports the utility of LC–MS as a bridging tool between chemical composition and antidepressant-related outcomes.

4.3 Methodological Limitations and Future Directions

Despite its advantages, the reviewed literature revealed notable methodological heterogeneity in LC–MS workflows, including differences in sample preparation, chromatographic conditions, mass analyzers, and data processing strategies. Such variability limits cross-study comparability and highlights the need for standardized protocols and integration of advanced bioinformatics approaches to enhance translational relevance [31-34]. It is also important to contextualize LC–MS within the broader analytical landscape. While LC–MS provides unparalleled sensitivity and compound identification capacity for complex plant matrices, complementary platforms offer distinct advantages: nuclear magnetic resonance (NMR) spectroscopy enables unambiguous structural elucidation without reference standards and is particularly valuable for novel compound characterization; gas chromatography–mass spectrometry (GC–MS) offers superior resolution for volatile and thermostable phytochemicals such as terpenoids and fatty acids; and capillary electrophoresis–mass spectrometry (CE–MS) provides high separation efficiency for polar and charged metabolites. Integration of LC–MS with these complementary platforms in a multi-modal analytical strategy would strengthen metabolite coverage, improve structural annotation confidence, and enhance the overall translational relevance of natural antidepressant research.

Future research should prioritize standardization of LC–MS protocols and the integration of advanced bioinformatics, systems biology, and network pharmacology approaches to enhance mechanistic interpretation and translational relevance. These efforts are essential to advance LC–MS-supported natural antidepressant discovery toward clinical application.

5. CONCLUSION

This systematic literature review demonstrates that liquid chromatography–mass spectrometry (LC–MS) appears to serve as a central analytical platform in the development of natural product–based antidepressant drugs, based on current preclinical evidence. Across the reviewed studies, LC–MS consistently enabled comprehensive phytochemical profiling, accurate metabolite identification, and effective dereplication of

complex natural matrices, addressing key challenges associated with chemical diversity and variability of medicinal plant sources.

The integration of LC–MS analysis with pharmacological and metabolomics-based experimental models provided meaningful biochemical context for antidepressant-like effects observed in preclinical studies. By linking chemical profiles with biological outcomes, LC–MS supports mechanistic interpretation and strengthens the evidence base for multi-target actions of natural antidepressant candidates.

Despite these advantages, the current evidence remains largely preclinical and is characterized by methodological heterogeneity in LC–MS workflows. Standardization of analytical protocols and data processing strategies is therefore essential to enhance reproducibility and cross-study comparability. Future research should emphasize integrative approaches combining LC–MS with advanced bioinformatics, systems biology, and translational studies to facilitate the progression of natural product–based antidepressants toward clinical application.

Overall, the findings suggest that LC–MS appears to be a pivotal analytical platform for evidence-based discovery and development of natural antidepressant drugs, based on current preclinical evidence. Continued research and methodological standardization will be necessary to confirm and extend these findings toward clinical application.

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