International Journal of Innovation and Industrial Revolution
EISSN: 2637-0972
IJIREV
Volume 7 Issue 23 (December 2025) PP. 433-448
DOI 10.35631/IJIREV.723028

INTERNATIONAL JOURNAL OF INNOVATION AND INDUSTRIAL REVOLUTION (IJIREV)
www.ijirev.com

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METABOLOMIC SIGNATURES IN THE PROGRESSION AND TREATMENT OF SUBSTANCE USE DISORDERS: A BIBLIOMETRIC ANALYSIS

Edyham Misnan[1,3], Rusdi Abd Rashid[2,3], Maw Shin Sim[1,3*], Aishah Mohd Shah[4]

[1] Department of Pharmaceutical Life Sciences, Faculty of Pharmacy, Universiti Malaya, 50603 Kuala Lumpur, Malaysia
Email: garethsim@um.edu.my
[2] Department of Psychological Medicine, Faculty of Medicine, Universiti Malaya, 50603 Kuala Lumpur, Malaysia
Email: rusdi@um.edu.my
[3] Universiti Malaya Centre of Addiction Science Studies, Universiti Malaya, 50603 Kuala Lumpur, Malaysia
Email: edyhamisnan@gmail.com
[4] Jabatan Kesihatan Negeri Melaka, 70450 Melaka Malaysia
Email: aisice.shah@gmail.com
[*] Corresponding Author

Article Info:

Article history:
Received date: 22.10.2025
Revised date: 10.11.2025
Accepted date: 01.12.2025
Published date: 21.12.2025

To cite this document:

Misnan, E., Abd Rashid, R., Maw, S. S., & Shah, A. M. (2025). Metabolomic Signatures In The Progression And Treatment Of Substance Use Disorders: A Bibliometric Analysis. *International Journal of Innovation and Industrial Revolution, 7* (23), 433-448.

DOI: 10.35631/IJIREV.723028

Abstract:

Metabolomics has emerged as a promising approach to elucidate the biochemical signatures underlying the onset, progression, and treatment response of substance use disorders (SUDs), yet the research landscape in this field remains fragmented and underexplored. To address this gap, this study applies a bibliometric analysis to map and evaluate the global research trends on metabolomic signatures in SUDs, with a focus on their role in therapeutic development. Data were collected through Scopus advanced searching using the keywords "metabolomic," "signature," "substance use disorder," and "treatment," yielding a total of 1,214 publications. The dataset was processed and harmonized using OpenRefine, analyzed through the Scopus Analyzer for descriptive statistics and trends, and visualized using VOSviewer to generate co-authorship, co-citation, and keyword co-occurrence networks. The results highlight a consistent upward trend in publications over the past decade, with significant contributions concentrated in high-income countries, particularly the United States, China, and European nations. Keyword mapping revealed research hotspots clustered around biomarker discovery, neurobiological mechanisms, and personalized treatment strategies, while co-authorship networks showed a growing yet fragmented collaboration among multidisciplinary teams. Citation analyses identified influential authors and journals driving the field, underscoring the translational potential of metabolomics in bridging laboratory findings with clinical interventions. This

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bibliometric evidence suggests that metabolomic profiling is increasingly recognized as a critical tool for advancing precision medicine approaches in SUDs, though stronger international collaboration and integration with pharmacological research remain needed. Overall, the study provides a comprehensive overview of the intellectual structure and emerging directions in this domain, offering valuable insights for researchers, clinicians, and policymakers working toward improved treatment outcomes in substance use disorders.

Keywords:

Metabolomic, Signature, Substance Use Disorder, Treatment

Introduction

Substance use disorders (SUDs) represent a significant public health challenge, characterized by the compulsive use of psychoactive substances despite adverse consequences. These disorders are associated with a range of social, professional, and familial impairments, and they impose a substantial socio-economic burden on healthcare systems worldwide (Morcuende et al., 2021). The complexity of SUDs is underscored by the high rates of relapse and poor treatment compliance, necessitating a deeper understanding of the underlying biological mechanisms to improve diagnosis and treatment outcomes (Loganathan & Tiego, 2023). Metabolomics, the comprehensive study of metabolites within a biological system, has emerged as a powerful tool to elucidate the biochemical perturbations associated with SUDs. By identifying specific metabolomic signatures, researchers aim to uncover the metabolic pathways involved in the progression and treatment of these disorders, thereby paving the way for personalized therapeutic strategies (Caspani et al., 2022; van de Wetering et al., 2023).

The application of metabolomics in the study of SUDs has provided valuable insights into the biochemical alterations that occur during substance abuse and dependence. Metabolomic studies have highlighted the importance of understanding the dynamic changes in the metabolome as individuals transition from recreational drug use to chronic dependence. These studies have identified key metabolites and metabolic pathways that are disrupted in SUDs, offering potential biomarkers for disease progression and treatment response (Caspani et al., 2022; Mamat et al., 2025). For instance, research on amphetamine-type stimulants (ATS) has revealed significant alterations in energy metabolism, neurotransmitter biosynthesis, and oxidative stress defenses, with specific metabolites such as cholic acid, L-valine, and homovanillic acid being identified as critical biomarkers (Mamat et al., 2025). These findings underscore the potential of metabolomics to guide the development of targeted interventions for SUDs.

In addition to metabolomics, other omics approaches, including genomics, proteomics, and immunomics, have been employed to identify biomarkers and elucidate the molecular mechanisms underlying SUDs. For example, studies have shown that chronic substance use leads to neurochemical disruptions and systemic toxicity, which are reflected in altered metabolic profiles (Peregud & Gulyaeva, 2024; Yang et al., 2023). The integration of metabolomics with other omics data can provide a more comprehensive understanding of the biological processes involved in SUDs. This multi-omics approach has the potential to identify novel therapeutic targets and improve the precision of treatment strategies (Volkow et al., 2015; Yang et al., 2023). Moreover, the use of advanced technologies such as brain imaging and

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human brain organoids has further enhanced our ability to study the neurobiological effects of substance abuse and identify relevant biomarkers (Li et al., 2025).

Despite the progress made in identifying metabolomic signatures associated with SUDs, several challenges remain. One major challenge is the variability in individual responses to substance use and treatment, which can be influenced by genetic and environmental factors. Pharmacogenomics and pharmacomicrobiomics have been explored to address this issue, with studies highlighting the role of genetic variants and gut microbiome diversity in modulating drug metabolism and treatment outcomes (Borrego-Ruiz & Borrego, 2025). However, the interpretation of these findings is limited by the lack of standardized methodologies and the need for large-scale validation studies. Additionally, the complexity of SUDs, which often involve comorbid conditions such as major depressive disorder, further complicates the identification of specific biomarkers (Abé et al., 2013; Valeri et al., 2022). Therefore, ongoing research is needed to refine the methodologies and validate the identified biomarkers in diverse populations.

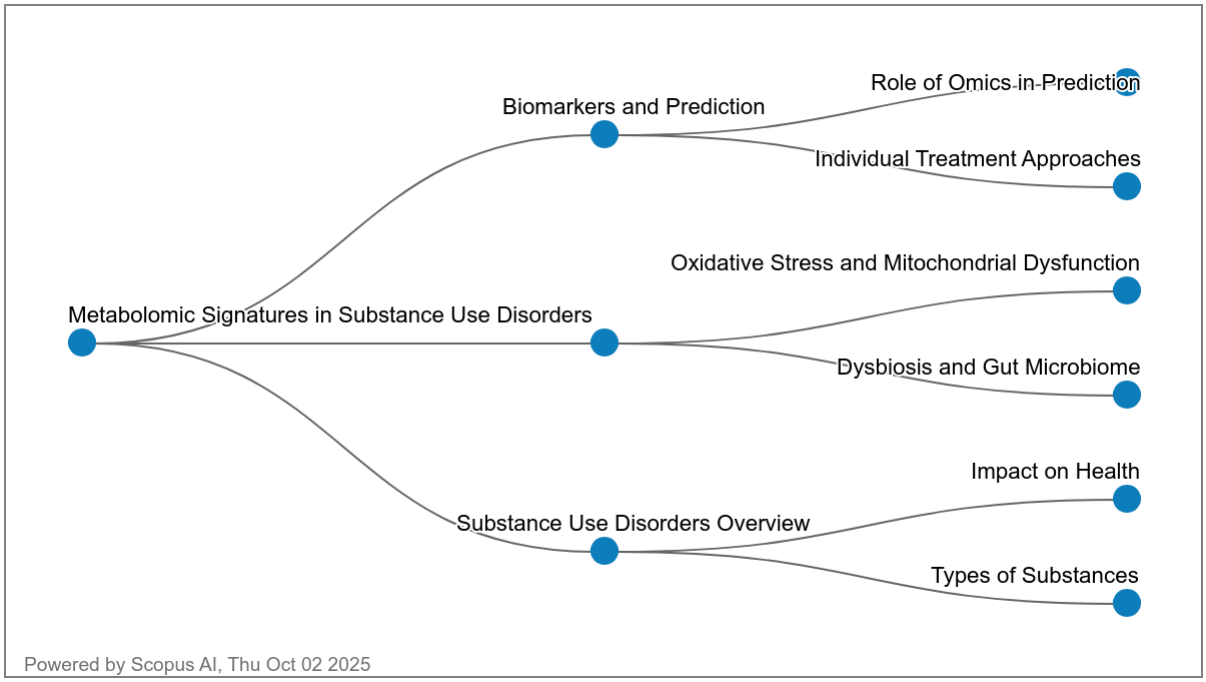

Figure 1: Concept Map of Metabolomic Signatures in the Progression and Treatment of Substance Use Disorders

The concept map in **Figure 1** outlines the interconnected domains shaping research on metabolomic signatures in substance use disorders (SUDs). At the core, metabolomic profiling provides insights into disease mechanisms, prediction, and treatment strategies. One major branch highlights biomarkers and prediction, emphasizing the role of omics technologies in identifying metabolic signatures that inform individualized treatment approaches. Another key area focuses on pathophysiological mechanisms, such as oxidative stress and mitochondrial dysfunction, which underlie cellular damage and dysbiosis of the gut microbiome, which further influences neurochemical and metabolic pathways. These mechanistic insights connect directly to clinical outcomes, supporting the development of tailored interventions. A complementary branch provides a broader overview of SUDs, including classifications based

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on types of substances and their varying metabolic impacts. This is linked to the overall health consequences of substance misuse, reinforcing the clinical relevance of metabolomic investigations. Together, these domains illustrate how metabolomics can bridge fundamental mechanisms and applied treatment strategies, positioning it as a transformative tool for understanding SUD progression, identifying predictive biomarkers, and informing precision medicine approaches to improve long-term recovery and health outcomes.

In conclusion, metabolomics has emerged as a promising approach to uncover the biochemical underpinnings of SUDs and identify potential biomarkers for disease progression and treatment response. The integration of metabolomics with other omics data and advanced technologies holds great potential for advancing our understanding of SUDs and developing personalized therapeutic strategies. However, further research is needed to address the challenges associated with individual variability and comorbid conditions, and to validate the identified biomarkers in larger and more diverse populations. By continuing to explore the metabolomic signatures of SUDs, researchers can contribute to the development of more effective and targeted interventions for these complex disorders.

Research Question

RQ1: What are the research trends in these studies according to the year of publication?
RQ2: What are the top 10 most cited articles?
RQ3: Where are the top 10 countries based on the number of publications?
RQ4: What are the popular keywords related to the study?
RQ5: What is co-authorship by countries' collaboration?

Methodology

Bibliometrics represents a systematic methodology for mapping and quantifying scientific knowledge by gathering, organizing, and critically analyzing bibliographic data from scholarly publications (Alves et al., 2021; Assyakur & Rosa, 2022; Verbeek et al., 2002). Beyond descriptive indicators such as publication trends, leading journals, and prolific authors (Wu & Wu, 2017), bibliometric analyses employ advanced techniques including co-citation and co-occurrence mapping to uncover intellectual structures and emerging research fronts within a field. A rigorous literature review, therefore, necessitates an iterative and strategic process beginning with the careful selection of keywords, followed by comprehensive database searches, and culminating in in-depth analytical synthesis. Such an approach enables the construction of a robust evidence base while ensuring reliability and reproducibility of findings (Fahimnia et al., 2015). In this study, priority was given to high-impact publications, recognizing their critical role in shaping theoretical frameworks and guiding scientific discourse. To maximize accuracy and coverage, SCOPUS was employed as the primary database (Al-Khoury et al., 2022; di Stefano et al., 2010; Khiste & Paithankar, 2017), given its global reach and established indexing standards. To uphold scientific quality, the dataset was restricted to peer-reviewed journal articles, with books and lecture notes excluded (Gu et al., 2019).

Data Search Strategy

For the retrieval of strategic data, we employed the Scopus advanced search function, which allows for precise Boolean-based query structuring to capture the breadth of metabolomics research in relation to substance use disorders (SUDs). As outlined in **Table 1**, the search string combined multiple concept clusters, including metabolomic-related terms ("metabolomic,"

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"metabolome," "metabolite," "metabolism"), biomarker-related descriptors ("signature," "profile," "pattern," "biomarker"), substance use terminology ("substance use disorder," "addiction," "substance abuse," "dependency"), and specific addictive substances ("alcohol," "drugs," "opioids," "nicotine"), alongside clinical application terms ("diagnosis," "treatment," "intervention," "therapy"). This comprehensive structure ensured the inclusion of studies that integrate metabolomic approaches with both diagnostic and therapeutic perspectives across a wide spectrum of addictive substances. To maintain rigor and reproducibility, the search was further limited to English-language publications and to journal articles (document type "ar"), while excluding conference proceedings, book chapters, and review papers, as detailed in **Table 2**. These exclusion criteria were applied to ensure the dataset consisted solely of original, peer-reviewed research outputs, which offer empirical evidence rather than secondary or non-validated sources. The access date of the search was October 2025, providing an up-to-date capture of the most recent developments while incorporating earlier studies that shaped the field. Following application of these inclusion and exclusion criteria, the final dataset comprised 1,214 publications. This number reflects both the increasing global research interest in metabolomics and the steady integration of omics-based approaches into addiction science. Importantly, the size and scope of this dataset make it sufficiently robust for bibliometric mapping and network analysis, allowing for the identification of influential authors, institutions, journals, and thematic research trends in metabolomic signatures associated with the progression and treatment of substance use disorders.

Table 1

The Search String.

Scopus	TITLE-ABS-KEY (("metabolomic" OR "metabolome" OR "metabolite" OR "metabolism") AND ("signature" OR "profile" OR "pattern" OR "biomarker") AND ("substance use disorder" OR "addiction" OR "substance abuse" OR "dependency") AND ("alcohol" OR "drugs" OR "opioids" OR "nicotine") AND ("diagnosis" OR "treatment" OR "intervention" OR "therapy")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (DOCTYPE , "ar")) Access date: October 2025

Table 2
The Selection Criterion Is Searching

Criterion	Inclusion	Exclusion
Language	English	Non-English
Literature type	Journal (Article)	Conference, Book, Review

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Data Analysis

VOSviewer, developed by Nees Jan van Eck and Ludo Waltman at Leiden University, Netherlands (van Eck & Waltman, 2010a, 2017), is a widely recognized bibliometric software designed for the visualization and analysis of scientific literature. Renowned for its capacity to generate intuitive network visualizations, clustering analyses, and density maps, VOSviewer enables researchers to explore co-authorship, co-citation, and keyword co-occurrence networks with remarkable clarity. Its interactive interface, ongoing updates, and adaptability to multiple bibliometric data sources have established it as an indispensable tool for examining complex research landscapes. By transforming intricate datasets into visually interpretable maps and charts, VOSviewer facilitates both novice and expert users in uncovering structural and thematic patterns within scientific domains.

For this study, bibliographic datasets including publication year, title, author, journal, citation, and keywords in PlainText format were retrieved from Scopus, covering the period from 1973 to October 2025. These datasets were analyzed using VOSviewer software version 1.6.20. Leveraging VOS clustering and mapping techniques, the software generated two-dimensional visualizations that reflect the proximity and relatedness of items within low-dimensional space. Unlike Multidimensional Scaling (MDS), which depends on conventional similarity indices such as cosine and Jaccard measures, VOS employs association strength (ASij) as a normalization method (van Eck & Waltman, 2010b), (Appio et al., 2014). Association strength is computed as:

$$AS_{ij} = \frac{C_{ij}}{w_i w_j}$$

where C_ijdenotes the observed co-occurrences of items i and j, while w_iand w_jrepresent their respective total co-occurrence counts (Van Eck & Waltman, 2007). This ratio reflects the extent to which the observed co-occurrences exceed those expected under statistical independence, thereby offering a more robust quantification of relatedness for bibliometric mapping.

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Findings and Discussion

What Are the Research Trends in These Studies According to The Year of Publication?

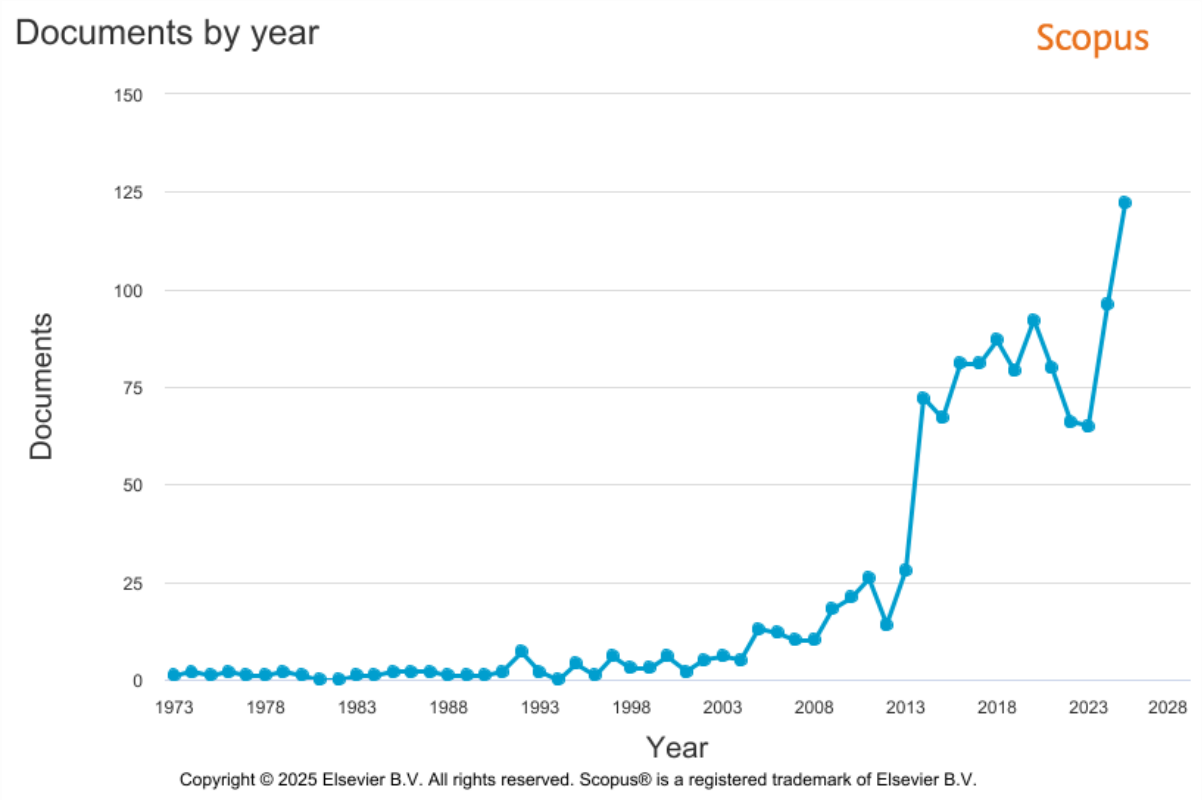

Figure 2: Number of Documents Based on Year of Publication

Figure 2 demonstrates the publication trend from 1973 to October 2025 demonstrates three distinct phases in the evolution of metabolomic research applied to substance use disorders (SUDs). Between 1973 and the late 1990s, the number of publications was minimal, rarely exceeding 2–3 papers per year. This reflects both the limited technological capacity of that era and the early stage of metabolomics as a scientific discipline, with biochemical profiling still largely focused on traditional clinical chemistry rather than system-level investigations. A modest rise appears in the early 2000s (2000–2006), where annual outputs grew to 5–13 papers, coinciding with the increasing adoption of mass spectrometry (MS) and nuclear magnetic resonance (NMR) technologies, as well as the broader integration of "omics" frameworks into biomedical sciences. This period marks the first wave of metabolomics being applied to addiction research, primarily in exploratory studies and small-scale biomarker discovery efforts.

From 2010 onward, the growth became more pronounced, with annual publications rising from 18 in 2009 to 67 in 2015 and reaching a consistent range of 70–92 papers annually between 2016 and 2020. The sharp acceleration after 2013 corresponds with global research priorities that emphasized precision medicine and the systems biology approach to complex disorders, alongside increased funding for SUD-related studies during the opioid crisis. Notably, the most

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dramatic surge occurs after 2021, with publications reaching 96 in 2024 and peaking at 122 in 2025, suggesting an exponential trajectory. This can be explained by the convergence of factors: advancements in high-throughput metabolomics, stronger interdisciplinary collaborations, open-access data initiatives, and a clinical demand for biomarker-driven approaches in addiction treatment. Together, these forces have transformed metabolomics from a niche application into a mainstream methodology for investigating progression and therapeutic monitoring in SUDs

What Are the Top 10 Most Cited Articles?

Table 3: Most Cited Author and Article

No	Authors	Year	Source title	Cited by
1	Ghandi et al., (2019)	2019	Nature	2245
2	(Jonklaas et al., 2014)	2014	Thyroid	1355
3	Pergolizzi et al. (2008)	2008	Pain Practice	748
4	Johnson et al. (2014)	2014	Journal of Psychophar macology	722
5	Škrott et al., (2017)	2017	Nature	657
6	de Sousa E Melo et al., (2017)	2017	Nature	618
7	Zuccato et al., (2008)	2008	Environment al Health Perspectives	564
8	Italiano et al., (2018)	2018	The Lancet Oncology	526
9	Rathert et al. (2015)	2015	Nature	429
10	Robinson et al. (1988)	1988	Brain Research	422

Table 3 shows the citation landscape of the top 10 most cited articles, highlighting the interdisciplinary scope of metabolomic and addiction-related research, bridging oncology, psychiatry, pharmacology, and methodological innovation. The most cited article, Ghandi et al. (2019) in Nature with 2,245 citations, reflects the pivotal role of large-scale genomic and metabolomic characterization (Cancer Cell Line Encyclopedia) in shaping biomarker discovery and precision medicine. Similarly, Jonklaas et al. (2014), with 1,355 citations, demonstrate the translational weight of consensus guidelines, in this case for hypothyroidism, which are widely referenced in both clinical and basic science contexts. Articles like Pergolizzi et al. (2008) on opioid management in elderly patients (748 citations) and Johnson et al. (2014) on psilocybin for tobacco addiction (722 citations) represent clinically oriented works that align

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closely with the scope of substance use and pain management research, explaining their high visibility and enduring impact.

The inclusion of articles such as Škrott et al. (2017) and de Sousa E Melo et al. (2017), both published in Nature and cited over 600 times, underscores the influence of mechanistic cancer biology research with direct implications for therapeutic strategies. Likewise, Zuccato et al. (2008) on wastewater analysis (564 citations) exemplifies the rise of population-level metabolomics, offering a novel epidemiological tool for drug monitoring that has gained global traction. High-impact clinical studies, such as Italiano et al. (2018) in Lancet Oncology and Rathert et al. (2015) in Nature, further illustrate the importance of integrating metabolomics into cancer therapy and resistance research. Notably, Robinson et al. (1988) in Brain Research remains influential decades later due to its foundational contribution to understanding dopaminergic sensitization, a central mechanism in addiction neurobiology. Collectively, the dominance of articles published in top-tier journals (Nature, Lancet Oncology, Environmental Health Perspectives) explains their broad citation reach, reflecting how methodological novelty, translational guidelines, and clinical relevance drive sustained academic influence.

Where Are the Top 10 Countries Based on The Number of Publications?

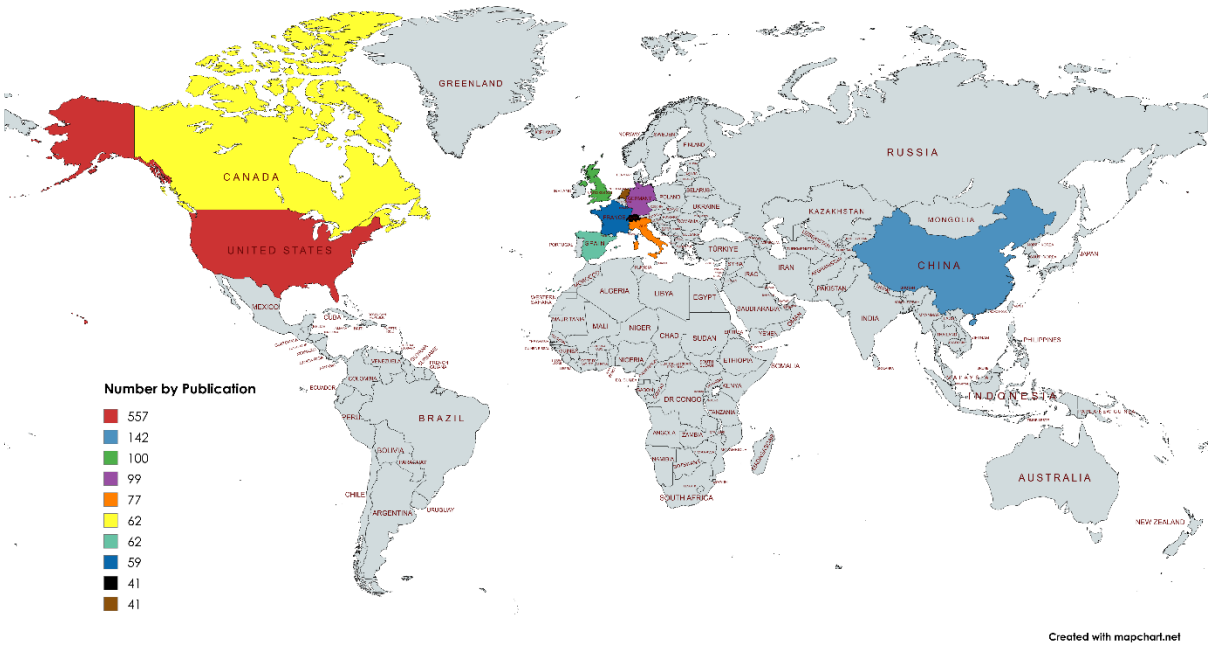

Figure 3: Country Mapping on Number of Publications

Figure 3 shows the distribution of publications reveals a clear dominance of the United States, which accounts for 557 papers, far exceeding the second-ranking country, China (142). This disproportionate leadership is not surprising given the U.S.'s long-standing investment in addiction research, its advanced metabolomics infrastructure, and the significant funding directed toward addressing the opioid crisis. Institutions such as the National Institutes of Health (NIH) and the National Institute on Drug Abuse (NIDA) have prioritized biomarker

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EISSN: 2637-0972
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discovery and translational research, enabling metabolomics to be applied extensively in substance use disorder (SUD) studies. China (142) and the United Kingdom (100) follow as emerging leaders, reflecting both their expanding biomedical research capabilities and strong international collaborations, particularly in precision medicine and psychiatry.

European countries, including Germany (99), Italy (77), Spain (62), France (59), the Netherlands (41), and Switzerland (41) also contribute substantially, showing that Europe is a major hub for metabolomic applications in SUDs. These countries benefit from strong public health agendas, pan-European research networks such as Horizon Europe, and interdisciplinary collaborations integrating clinical, pharmacological, and systems biology expertise. Canada (62) similarly stands out due to its active engagement in addiction and mental health research, supported by institutions like CIHR. The regional variation can largely be explained by differences in funding priorities, the burden of substance use, infrastructure for omics technologies, and global collaboration networks, with high-income countries leading due to greater resources and stronger integration of metabolomics into clinical research frameworks.

What Are The Popular Keywords Related To The Study?

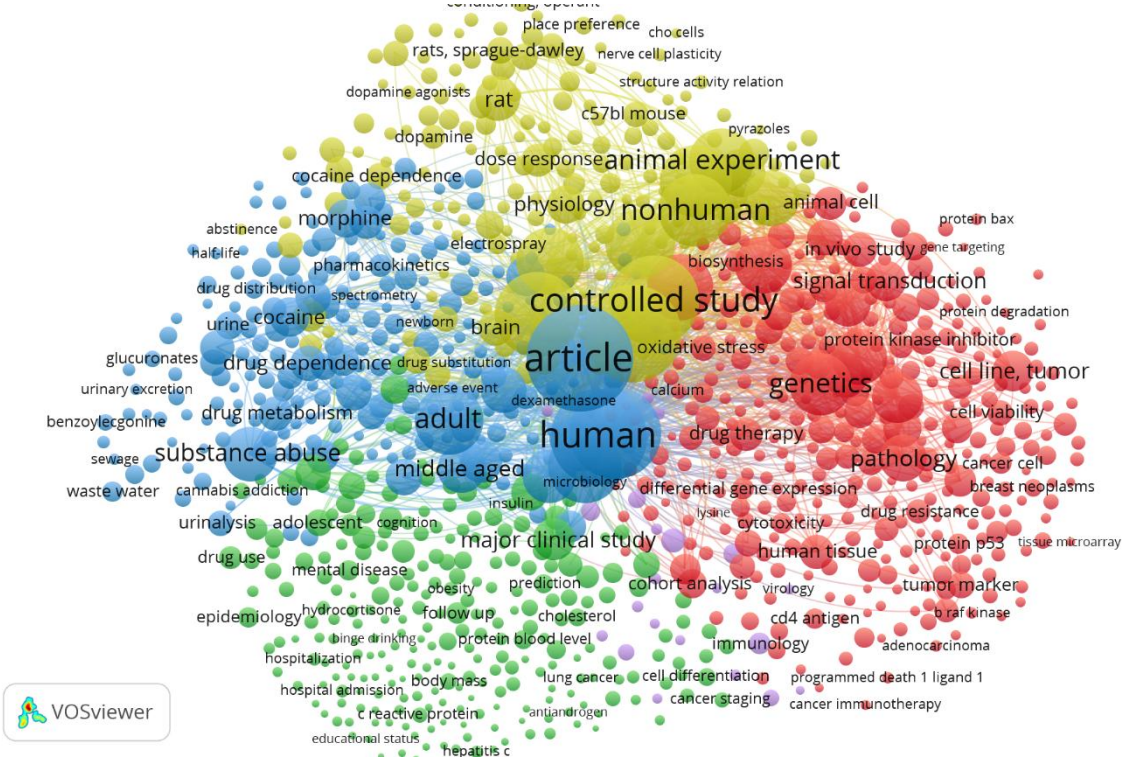

Figure 4: Network Visualization Map of Keywords' Co-Occurrence

The co-occurrence analysis of author keywords using VOSviewer is a bibliometric technique that identifies and maps the relationships between frequently co-mentioned keywords in scientific literature. By visualizing these associations, researchers can detect major research themes, emerging topics, and the structure of a research field. In this study, keywords from a dataset of 7,717 terms were analyzed, and those appearing at least five times (1,921 keywords) were included in the network as show in **Figure 4**. The full counting method was applied,

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which counts each co-occurrence equally regardless of frequency in a single document, providing a comprehensive view of keyword interconnections. A minimum cluster size of five was set, resulting in five distinct clusters, each representing a thematic grouping of related research topics within the field.

The resulting visualization highlights the dominant areas of focus in the literature, with high-frequency terms such as “article,” “metabolism,” “human,” “controlled study,” and “male” indicating central themes in biomedical or clinical research. The map demonstrates how closely linked certain biological and clinical terms are, such as “gene expression,” “animal model,” and “drug effect.” These patterns suggest the field is heavily concentrated on preclinical and translational research involving human and animal studies, drug metabolism, and biomolecular pathways. Such findings contribute to the body of knowledge by revealing not only the scope and focus of existing research but also by identifying possible gaps or underexplored areas, which can inform future investigations and interdisciplinary collaboration strategies.

What Is Co-Authorship by Countries’ Collaboration?

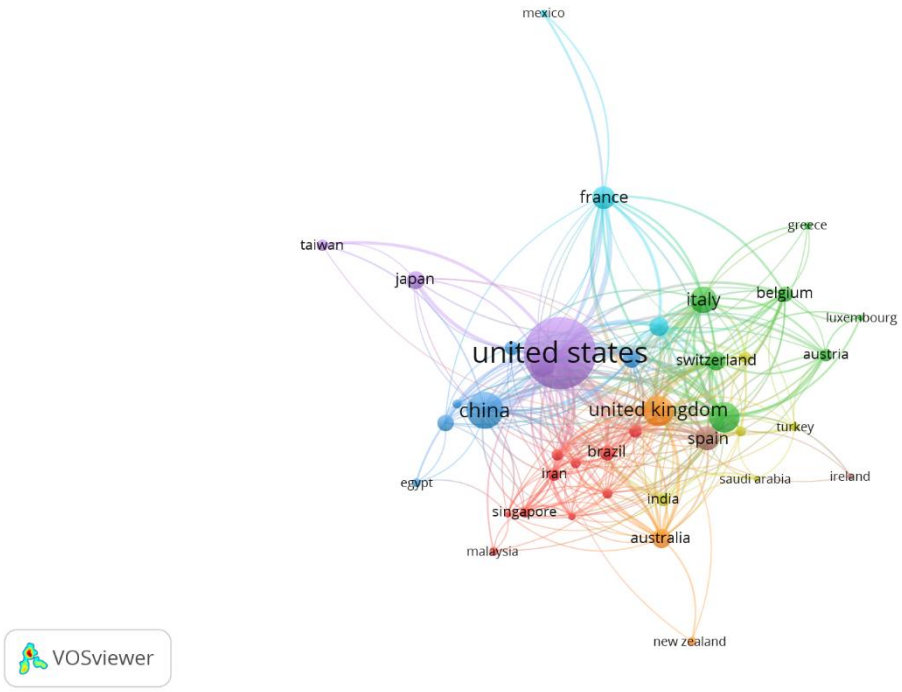

Figure 5: Network Visualization Map Co-Authorship by Countries

The co-occurrence analysis of countries using VOSviewer visualizes the relationships between countries based on the number of collaborative documents they have in common, illustrating how frequently countries work together in published research illustrated in **Figure 5**. By analyzing the frequency and co-occurrence of publications from different countries, the tool generates a network where countries that have a higher number of shared publications are placed closer together, while those with fewer shared publications are positioned farther apart. This method is useful for understanding global research collaboration patterns and how different countries contribute to the scientific landscape.

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EISSN: 2637-0972
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In this specific analysis, the full counting method was employed, counting each document equally regardless of how often it appears in a particular country's output. The minimum threshold of five documents was set, resulting in 40 countries meeting this threshold from a total of 76 countries. A minimum cluster size of five was used, which resulted in the formation of eight distinct clusters, each representing different regional or thematic research collaborations. The findings suggest that countries like the United States, the United Kingdom, and China are central hubs in global research, with high document counts and strong co-occurrence links. These results contribute to the body of knowledge by highlighting the importance of international collaboration in advancing research and identifying the dominant research centers around the world, which can inform funding and strategic partnerships in future scientific endeavors.

Conclusion

This bibliometric study was conducted to explore the global research landscape on metabolomic signatures in the progression and treatment of substance use disorders, with the aim of identifying prevailing trends, influential contributions, and collaborative patterns within this domain. The analysis addressed key research questions concerning publication growth, citation impact, geographic distribution, keyword dynamics, and international co-authorship networks. The findings revealed a steady increase in scholarly output over the past two decades, with a marked surge in recent years, reflecting growing recognition of metabolomics as a valuable approach for understanding substance use disorders. High-income countries, particularly the United States, China, and several European nations, emerged as leading contributors, while keyword analysis highlighted biomarker discovery, neurobiological mechanisms, and personalized treatment as dominant themes. Network mapping demonstrated the presence of influential authors and journals, yet also indicated that collaboration remains fragmented, suggesting opportunities for strengthening international partnerships and interdisciplinary integration.

This study contributes to the field by offering a systematic overview of how metabolomic research is shaping the discourse on substance use disorders. The analysis underscores the importance of metabolomics in bridging basic science and clinical applications, thereby informing precision medicine strategies and advancing the search for reliable biomarkers. In practical terms, the results may guide policymakers, funding bodies, and researchers in prioritizing future investigations and fostering more effective collaborative frameworks. Several limitations must be acknowledged, including the exclusive reliance on a single database, the restriction to English-language publications, and the exclusion of non-article document types, all of which may narrow the scope of coverage. Future studies should expand to multiple databases, incorporate gray literature, and explore multi-omics integration to provide a more comprehensive understanding of the field.

In summary, this research demonstrates the growing significance of metabolomics in the study of substance use disorders and highlights bibliometric analysis as a valuable tool for mapping scientific progress. Strengthening international collaboration and advancing methodological approaches will be essential for consolidating this field and translating metabolomic findings into meaningful clinical outcomes.

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Acknowledgement
The authors wish to thank Universiti Malaya for institutional support during the preparation of this manuscript.

Funding
The author(s) reported that there is no funding associated with the work featured in this article.

Competing Interests
The authors declare no conflicts of interest related to this work.

Data Availability Statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contributions
- Edyham: Writing – Review & Editing, Methodology, Formal Analysis, Software.
- Maw Shin: Validation, Formal Analysis.
- Rusdi: Methodology, Formal Analysis
- Aishah: Writing – Review & Editing.

ORCID
Edyham Misnan https://orcid.org/0009-0008-6370-8731
Rusdi Abd Rashid https://orcid.org/0000-0002-1295-7382
Maw Shin Sim https://orcid.org/0000-0002-7848-0775
Aishah Mohd Shah https://orcid.org/0009-0000-3155-4661

Declaration Of Generative AI and AI-Assisted Technologies
The authors used ChatGPT to assist with paraphrasing and preliminary data interpretation. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Volume 7 Issue 23 (December 2025) PP. 433-448
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