RESEARCH PAPER

Natural Products and Phytopharmacology in Advanced Drug Delivery Systems: A WoS–Scopus Bibliometric and Thematic Evolution Study

Mohammed Sami Aleid[1], Abdullah Ahmed Alamer[1], Janin Saadi Khalil Younis[1], Ibrahim Albokhadaim[1], Nawal Mohamed Elkhair[1], Aimi Syamima Abdul Manap[1]*

[1]*Department of Biomedical Science, College of Veterinary Medicine, King Faisal University, 31982, Al-Ahsa, Saudi Arabia*

ABSTRACT

Background: Nanotechnology-enabled delivery of plant-derived bioactive has emerged as a rapidly expanding area of pharmaceutical research. Despite increasing publications, a comprehensive understanding of the intellectual structure, thematic evolution, and emerging translational directions of phytopharmaceutical nano delivery remains limited. Objectives: This study aimed to map the global research landscape of plant-based nano delivery systems using bibliometric and science-mapping approaches to identify core themes, leading contributors, and emerging research fronts. Methods: Bibliometric analysis was conducted on publications indexed in major databases covering the period 2005-2025. Analytical tools including Bibliometrix (R), VOSviewer, and CiteSpace were used to evaluate annual scientific production, Bradford's Law source distribution, international collaboration, keyword co-occurrence, thematic evolution, and citation burst detection. Results: Annual output showed exponential growth after 2018, with publications increasing more than five-fold in the last decade, indicating accelerating research interest. Bradford's Law analysis revealed that the core dissemination zone comprised approximately 8–10 journals contributing about 30–35% of total publications, predominantly in drug delivery and nanomedicine fields. The most cited countries included China (>240 citations) and India (>100 citations), reflecting strong Asian research leadership. Keyword co-occurrence and thematic mapping identified three dominant knowledge clusters: (i) engineered nano-drug delivery systems, (ii) plant extract–derived antioxidant and antimicrobial nanomaterials, and (iii) green synthesis of metal nanoparticles. Motor themes with high centrality and density included "green synthesis," "antioxidant," and "anti-bacterial activity," while targeted drug delivery and controlled release systems formed a well-developed translational cluster. CiteSpaceburst analysis highlighted emerging fronts related to plant-derived nanomaterials, exosome-like nanovesicles, and zinc oxide nanoparticles after 2020. Conclusion: The field has transitioned from traditional phytochemical exploration to technology-driven nano formulation and targeted delivery research, with strong interdisciplinary integration across pharmaceutical technology, biomaterials, and nanomedicine. Future directions are expected to focus on standardized green synthesis protocols, advanced targeting strategies, and clinically translatable plant-based nanotherapeutics.

Keywords: Phytopharmaceutical nano delivery; Green synthesized nanoparticles; Targeted drug delivery systems; Plant-derived nanomaterials; Bibliometric analysis

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INTRODUCTION

Natural products have long served as a foundational source of therapeutic agents, contributing significantly to modern pharmacotherapy through their chemical diversity and biological activity [1,2]. However, despite their pharmacological potential, many plant-derived compounds suffer from poor aqueous solubility, low bioavailability, rapid metabolism, and limited target specificity [3], which restrict their clinical translation. In recent years, advances in pharmaceutical technology have provided new opportunities to overcome these limitations through engineered drug delivery systems, particularly nanotechnology-based platforms [4]. Nanocarriers such as polymeric nanoparticles, lipid-based systems, nano-emulsions, and metal nanoparticles have demonstrated the capacity to enhance the stability, controlled release, and targeted delivery of phytochemicals [5]. In parallel, green synthesis approaches utilizing plant extracts have emerged as sustainable alternatives for nanoparticle fabrication, offering both environmental advantages and intrinsic surface functionalization with bioactive molecules [6]. These developments have transformed natural product research from traditional phytochemical exploration into an interdisciplinary field at the interface of nanomedicine, biomaterials science, and advanced drug delivery engineering [7].

The growing integration of plant-derived bioactive into research toward multifunctional, biocompatible, and sustainable therapeutic platforms [8]. Emerging concepts such as bioinspired vesicular systems, plant-derived nanomaterials, and hybrid nano–bio delivery platforms further indicate that natural products are not only therapeutic agents but also structural and functional components of modern delivery systems [4,5,9]. Despite the

**Author for Correspondence: Aimi Syamima Abdul Manap*

rapid expansion of this field, the global research landscape remains fragmented, and a comprehensive understanding of its intellectual structure, thematic evolution, and emerging technological directions is still lacking.

Bibliometric and science-mapping approaches provide powerful tools to systematically analyze research trends, collaboration patterns, and knowledge development [10–13]. By integrating performance analysis with conceptual and thematic mapping, it is possible to identify the core technological drivers, leading contributors, and future research frontiers shaping the evolution of natural product–based drug delivery systems.

Therefore, the present study aims to provide a comprehensive bibliometric and thematic evaluation of research on phytopharmaceutical nano delivery systems over the past two decades. By elucidating how natural product research has transitioned toward advanced delivery technologies, this work offers strategic insights into the maturation of the field and highlights directions that may accelerate the translation of plant-derived therapeutics into clinically relevant drug delivery platforms.

METHODOLOGY

Data Sources and Search Strategy

A bibliometric analysis was conducted using records retrieved from Scopus and Web of Science Core Collection (WoS) to ensure comprehensive coverage of peer-reviewed literature. The search strategy combined keywords related to natural products, phytochemicals, and advanced drug delivery systems, including nanocarriers, controlled release, and targeted delivery platforms. Only articles published in English between 2005 and 2025 were included. The complete search strings and Boolean operators used for each database are provided in the Supplementary Materials.

Data Extraction and Cleaning

Retrieved records were exported with full bibliographic information, abstracts, author keywords, and cited references. Duplicate entries between databases were identified and removed based on DOI, title matching, and author information. To enhance thematic accuracy, non-scientific index terms (e.g., “human,” “animal,” “article”) were excluded, and keyword normalization was performed by merging synonyms and singular/plural variants. The complete data cleaning workflow is detailed in the Supplementary Materials.

Bibliometric and Science Mapping Analysis

Descriptive bibliometric performance indicators were generated to assess annual scientific production, source productivity, institutional contribution, country impact, and collaboration networks. Bradford’s Law was applied to identify core journals within the research domain

Conceptual and thematic structures were analyzed using Bibliometrix (Biblioshiny, R package), VOSviewer, and CiteSpace. Keyword co-occurrence networks and thematic maps were used to identify major research clusters and their developmental status. Multiple correspondence analysis (MCA) and hierarchical clustering were employed to explore conceptual relationships among research themes. Citation burst detection and timeline visualization were conducted using CiteSpace to reveal emerging research fronts and temporal evolution patterns. Detailed parameter settings for each software tool are provided in the Supplementary Materials.

Visualization and Interpretation

Network visualizations were interpreted based on node size (frequency), link strength (co-occurrence or collaboration intensity), and cluster structure. Thematic maps were evaluated according to centrality and density metrics to classify themes as motor, basic, niche, or emerging. Temporal trends were interpreted in relation to technological advancement in drug delivery systems.

RESULTS

Annual Scientific Production

The temporal distribution of publications demonstrates a clear evolution of research activity in natural product–based advanced drug delivery systems. From 2005 to approximately 2014, annual output remained low and relatively stable, indicating an exploratory phase dominated by preliminary phytochemical and nanoparticle biosynthesis studies. A gradual increase became evident after 2015, corresponding with the expansion of nano formulation strategies and the integration of plant bioactive into drug delivery platforms.

A pronounced surge occurred after 2019, with exponential growth observed between 2022 and 2025. This rapid acceleration reflects the maturation of the field and its convergence with nanomedicine, biomaterials, and targeted delivery research. The steep rise in the most recent years indicates sustained global interest and technological consolidation around nano-enabled phytopharmaceutical systems.

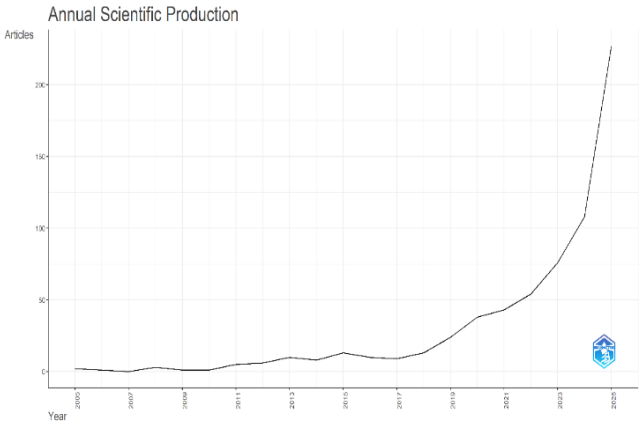

Figure 1. Annual scientific production showing the progressive increase in publications from 2005 to 2025, with a marked post-2019 growth phase

Core Sources According to Bradford’s Law

Bradford’s Law demonstrated a pronounced concentration of publications within a limited number of highly productive journals. The core Bradford zone contained approximately 8–10 journals, accounting for nearly 30–35% of the total research output in the field. These core sources were predominantly specialized in drug delivery, nanomedicine, biomaterials, and pharmaceutical formulation sciences, including *Journal of Drug Delivery Science and Technology*,

International Journal of Nanomedicine, *International Journal of Pharmaceutics*, and *International Journal of Biological Macromolecules*. Individual core journals contributed between 10 and 15 articles each, whereas journals in the subsequent Bradford zones showed a steep decline in productivity, often contributing fewer than five publications.

This strong source concentration indicates that research on natural product–based nano delivery systems is firmly anchored in pharmaceutical technology and delivery science, rather than traditional pharmacognosy or phytochemistry outlets. The pattern reflects a disciplinary evolution from descriptive phytochemical studies toward engineered nano formulations, controlled release platforms, and translational therapeutic delivery systems, highlighting the technological maturation of the field.

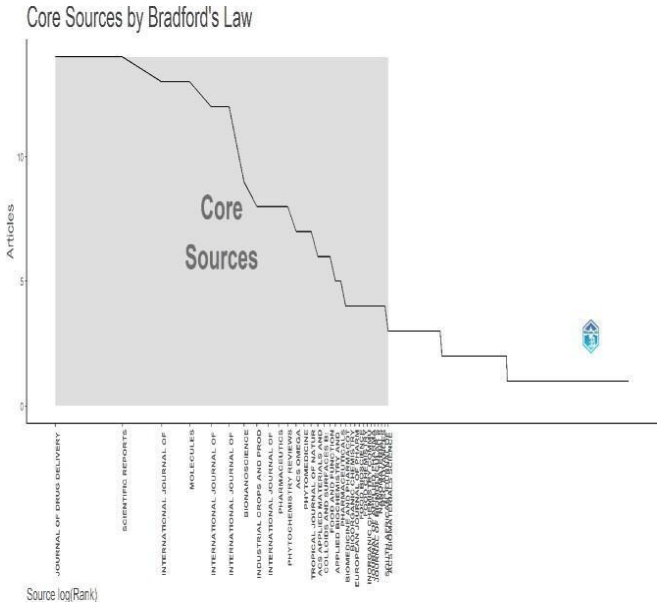

Figure 2. Bradford's Law distribution illustrating the concentration of publications within a limited number of core journals.

Author Collaboration Network

The co-authorship network reveals several distinct collaboration clusters, indicating regionally concentrated research groups with strong internal connectivity but relatively limited inter-cluster interaction. Prominent author clusters are associated with nanomedicine, green synthesis of nanoparticles, and bioinspired delivery systems.

The presence of multiple independent clusters suggests parallel research trajectories worldwide, with emerging opportunities for greater international integration. Notably, leading clusters are centered on nanocarrier development, metal nanoparticle biosynthesis, and extracellular vesicle–based delivery systems

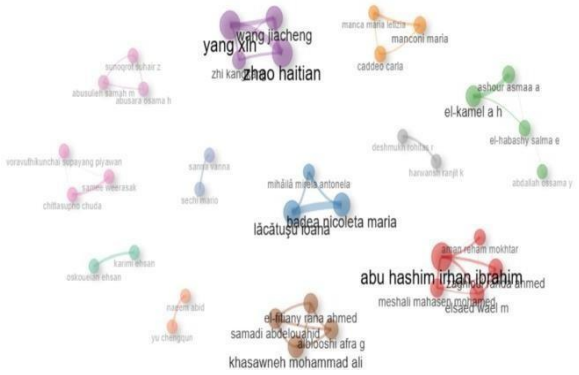

Figure 3. Author collaboration network showing distinct research clusters and key contributing investigators in nano-phytopharmaceutical delivery.

Most Cited Countries

Citation impact analysis indicates that research influence is geographically concentrated. China leads by a substantial margin, followed by India, Turkey, and Iran, reflecting strong contributions from Asia and the Middle East in phytogenic nanotechnology and delivery system development. European countries such as Italy and Egypt also demonstrate notable impact, while emerging contributions are visible from Saudi Arabia, Brazil, and Kenya.

This distribution highlights the global diffusion of research activity, with developing regions playing an increasingly important role in green synthesis and plant-based nanomaterials for drug delivery.

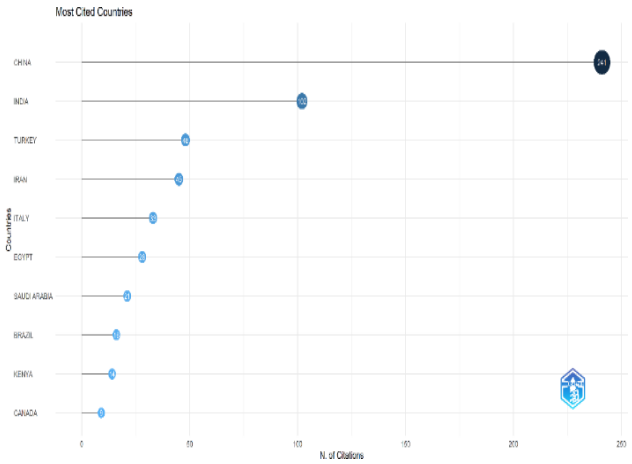

Figure 4. Most cited countries ranked by total citation counts, indicating global research impact in phytopharmaceutical nano delivery.

Most Relevant Affiliations

Institutional productivity analysis shows that a limited number of universities and research centers contribute repeatedly to this field. Institutions from Iran, Thailand, Egypt, Brazil, India, and China are prominently represented, aligning with regions where plant-derived nanomaterials and green nanotechnology are actively developed.

The relatively small publication counts per institution suggest a distributed research landscape rather than dominance by a single center, consistent with the interdisciplinary and emerging nature of the field.

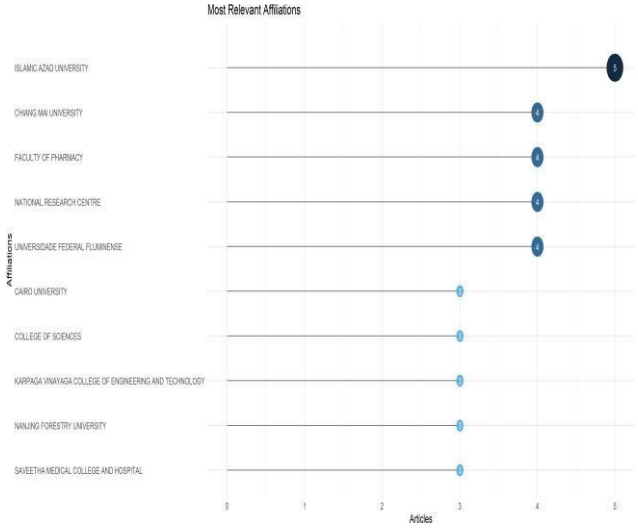

Figure 5. Most relevant affiliations ranked by number of publications in natural product–based advanced drug delivery research.

Most Relevant Sources

The leading journals include *Journal of Drug Delivery Science and Technology*, *Scientific Reports*, *International Journal of Biological Macromolecules*, *Molecules*, *International Journal of Nanomedicine*, and *International Journal of Pharmaceutics*. These sources collectively represent the intersection of nanotechnology, biomaterials, and pharmaceutical formulation science.

The prominence of journals focused on polymer science, nanomedicine, and drug delivery systems confirms that research on natural products has transitioned toward advanced formulation engineering and carrier design.

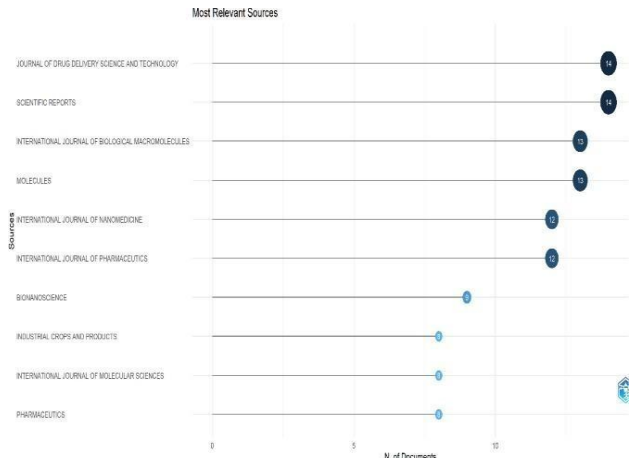

Figure 6. Most relevant sources based on document counts, highlighting the dominance of drug delivery and nanomedicine journals

Source Dynamics Over Time

Longitudinal source analysis demonstrates that early publications were scattered across general pharmacology and natural product journals. However, after 2015, specialized nanomedicine and drug delivery journals increasingly dominated output. A sharp rise in contributions from journals dedicated to pharmaceutical nanotechnology is evident after 2020.

This shift underscores the technological evolution of the field from phytochemical exploration to nano-enabled delivery system engineering.

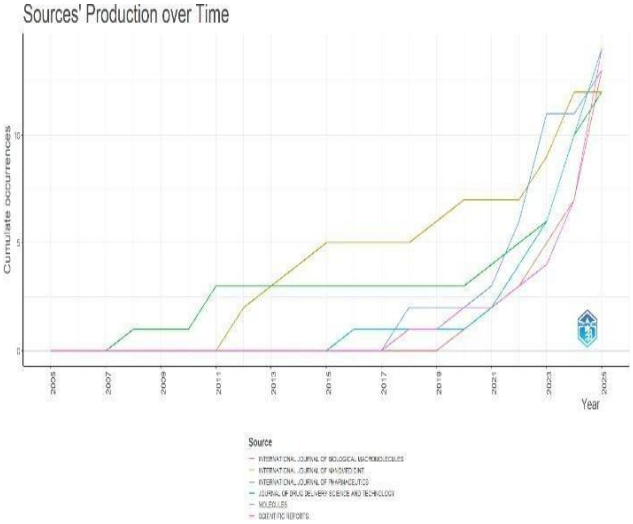

Figure 7. Source production over time showing the transition toward specialized nanomedicine and drug delivery journals.

Conceptual Structure and Thematic Relationships

Hierarchical clustering and multiple correspondence analysis (MCA) revealed the conceptual organization of research on natural products in advanced drug delivery systems. The dendrogram identifies three major thematic domains. The first domain encompasses nanoparticle synthesis and green chemistry, including metal nanoparticles, silver and gold nanoparticles, and green synthesis, representing the foundational stage of phytogenic nanomaterial development. The second domain centers on formulation and delivery engineering, linking encapsulation, controlled and targeted drug delivery, release, solubility, stability, and pH, reflecting the technological maturation of plant-derived materials into engineered delivery platforms. The third domain includes biological and therapeutic evaluation, characterized by terms such as cellular uptake, apoptosis, cytotoxicity, proliferation, and anticancer activity, indicating the progression toward mechanistic and functional validation. The MCA map supports this structure by positioning drug delivery technologies as a central and well-developed theme, while phytochemicals and plant extracts form the biochemical foundation feeding into nano formulation research. Green synthesis and metal nanoparticles appear as the technological bridge between natural products and nanocarrier engineering. Biological activity terms occupy intermediate positions, highlighting

the translational pathway from material fabrication to therapeutic application. Notably, emerging themes such as extracellular vesicles and exosome-like nanovesicles indicate a shift toward bioinspired and biomimetic delivery systems.

Together, these analyses confirm that the field is structured around three interconnected pillars: phytochemical bioactive, nano formulation engineering, and biomedical validation, with recent movement toward biologically derived nanocarriers.

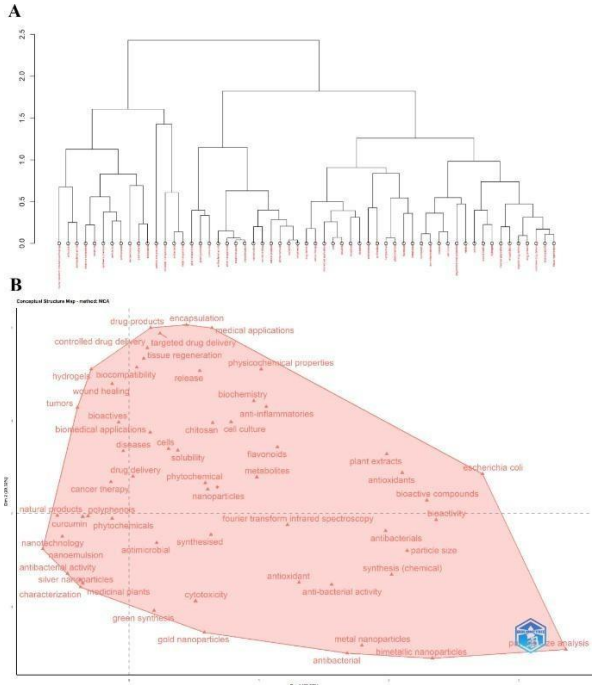

Figure 8. Combined conceptual structure analysis. (A) Hierarchical clustering dendrogram showing relationships among major thematic domains, including nanoparticle synthesis, delivery engineering, and biological evaluation. (B) Multiple correspondence analysis (MCA) conceptual map illustrating the spatial distribution and interconnections of research themes in natural product–based advanced drug delivery systems.

Keyword Co-occurrence Network and Thematic Evolution

Keyword co-occurrence analysis revealed the intellectual backbone of research on natural products in advanced drug delivery systems. The network structure shows nanoparticles and drug delivery as the most central and highly connected nodes, confirming their role as the technological core of the field. Surrounding this hub, targeted drug delivery and controlled drug delivery form a dense cluster linked with biocompatibility, medical applications, hydrogels, and tissue regeneration, indicating strong emphasis on functional nanocarrier design.

A second major cluster is centered on plant extracts, antioxidants, and bioactive compounds, which connect directly to antibacterial activity and cytotoxicity, highlighting the role of phytochemicals as therapeutic payloads and functional nanomaterial precursors. The presence of terms such as curcumin, flavonoids, and metabolites reflects increasing integration of specific phytochemicals into nano formulation strategies. A distinct technological cluster is driven by green synthesis, silver nanoparticles, metal nanoparticles, and Fourier transform infrared spectroscopy (FTIR), emphasizing the rapid expansion of eco-friendly synthesis and material characterization approaches. This cluster acts as a bridge between phytochemistry and nanotechnology, illustrating how plant-derived reducing and stabilizing agents facilitate nanoparticle fabrication.

The thematic map further clarifies the maturity and relevance of these research streams. Green synthesis, antioxidants, and antibacterial activity appear as motor themes, demonstrating both high centrality and high development, and therefore represent the driving forces of the field. Targeted and controlled drug delivery with chitosan also emerges as a well-developed and strategically important theme. In contrast, plant extracts and antimicrobial activity occupy the basic theme quadrant, suggesting that while highly relevant, these areas still offer opportunities for deeper mechanistic and translational exploration. Niche themes such as phytochemical characterization and FTIR analysis of silver nanoparticles indicate specialized but technically advanced research directions, whereas traditional nanoparticle–drug delivery–disease combinations appear as established but less rapidly evolving themes.

Overall, the field is transitioning from simple nanoparticle fabrication toward biofunctionalized, plant-derived nanocarriers with enhanced therapeutic activity, supported by greener synthesis routes and improved physicochemical characterization.

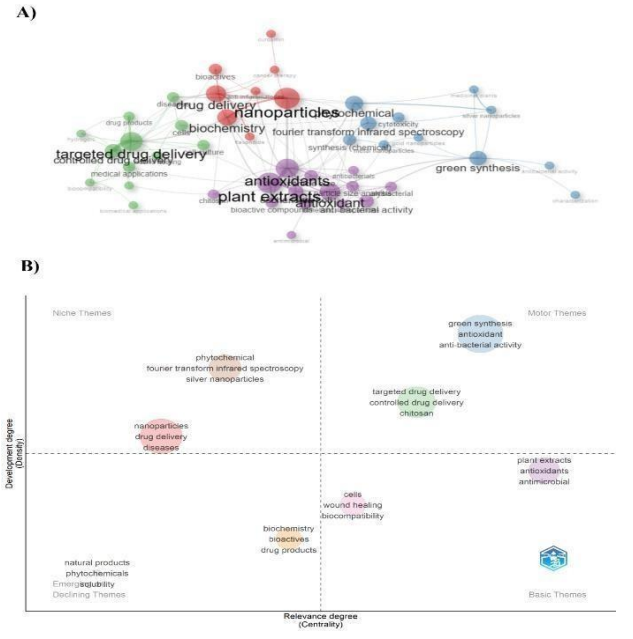

Figure 9. (A) Keyword co-occurrence network showing major clusters linking nanotechnology, phytochemistry, and drug delivery; node size indicates frequency and link thickness reflects co-occurrence strength. (B) Thematic map identifying motor, basic, niche, and emerging/declining themes in natural product–based advanced drug delivery research.

Citation Burst and Temporal Evolution of Research Fronts

Citation burst detection and timeline visualization revealed the dynamic progression of research themes in natural product–based advanced drug delivery systems. Early research phases (2008–2014) were dominated by silver nanoparticles and green synthesis, which exhibited strong citation bursts and formed the foundational methodological framework for plant-mediated nanomaterial fabrication. These early themes reflect the initial emphasis on eco-friendly nanoparticle production using phytochemical reducing and stabilizing agents.

During the intermediate phase (2015–2019), research activity expanded toward antioxidant activity, antibacterial applications, and bioactivity evaluation, indicating a transition from material synthesis to functional biological validation. This period marks the integration of phytochemical-rich extracts with nanoparticle platforms aimed at therapeutic enhancement.

In recent years (2020–2025), citation bursts shifted toward plant-derived nanomaterials, zinc oxide nanoparticles, and bioinspired nano formulations, reflecting diversification beyond traditional silver-based systems. Notably, the emergence of plant-derived exosome-like nanovesicles and nanovesicle-based delivery systems signals a new research frontier focused on biologically derived and biomimetic carriers. These trends indicate a maturation trajectory in which the field moves from basic nanoparticle fabrication toward multifunctional, bioactive, and biologically integrated delivery platforms.

The temporal network density observed in the later years further demonstrates increased interdisciplinarity, with stronger interconnections between phytochemistry, nanotechnology, and therapeutic application domains. Overall, the citation burst profile confirms that the field is entering a phase characterized by green, plant-based nanomaterials with advanced therapeutic functionality, alongside the rise of bioinspired nanocarrier systems that may define the next generation of natural product–based drug delivery research

Keyword Density Mapping and Research Hotspots (VOSviewer Analysis)

The VOSviewer keyword density visualization revealed the intensity and concentration of research activity within the field of natural products–based advanced drug delivery systems. Areas with warmer color gradients (yellow to green) indicate higher co-occurrence frequency and thematic prominence.

The most intense hotspot was centered on “nanoparticles”, confirming its role as the structural and technological core of the research domain.

Closely connected high-density nodes included “drug delivery,” “targeted drug delivery,” and “controlled drug delivery,” highlighting that the primary application focus remains precision delivery of therapeutics using nano-enabled carriers.

A second major hotspot cluster was formed around “plant extracts,” “antioxidants,” and “phytochemical,” indicating the strong integration of natural bioactive compounds into nanocarrier systems. This cluster bridges traditional phytopharmacology with modern formulation science.

The green synthesis and metallic nanoparticle region emerged as another dense thematic zone, with “green synthesis,” “silver nanoparticles,” and “medicinal plants” forming a tightly connected group. This confirms the

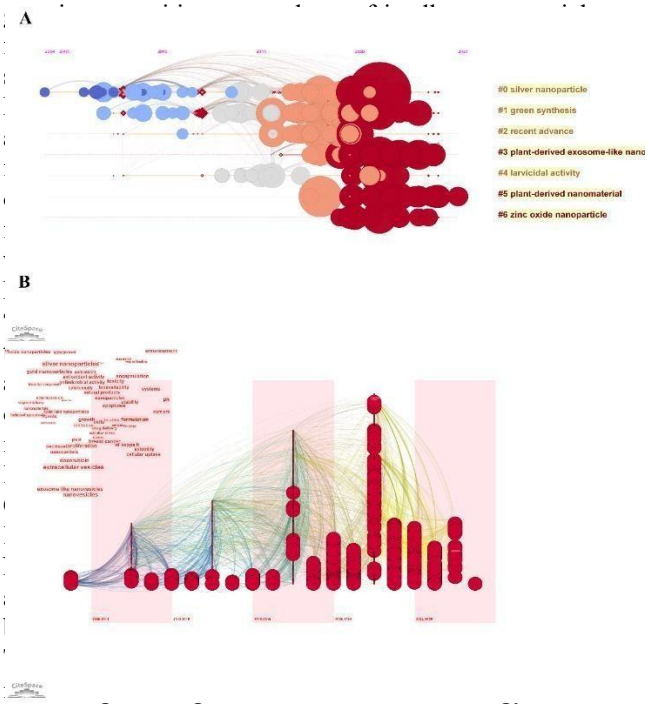

Figure 10. Temporal evolution of research fronts in natural product–based advanced drug delivery systems. (A) CiteSpace citation burst timeline showing early focus on silver nanoparticles and green synthesis, shifting to plant-derived nanomaterials and bioinspired vesicle-like systems. (B) Timeline network visualization showing growing theme interconnections and a shift from material fabrication to multifunctional, biologically integrated delivery platforms.

product pharmacology, and sustainable material synthesis, underscoring the multidisciplinary evolution of the field. These findings demonstrate that natural product research is no longer limited to phytochemical discovery but is increasingly integrated into nanoengineered drug delivery platforms, aligning with the technological priorities of advanced delivery system development.

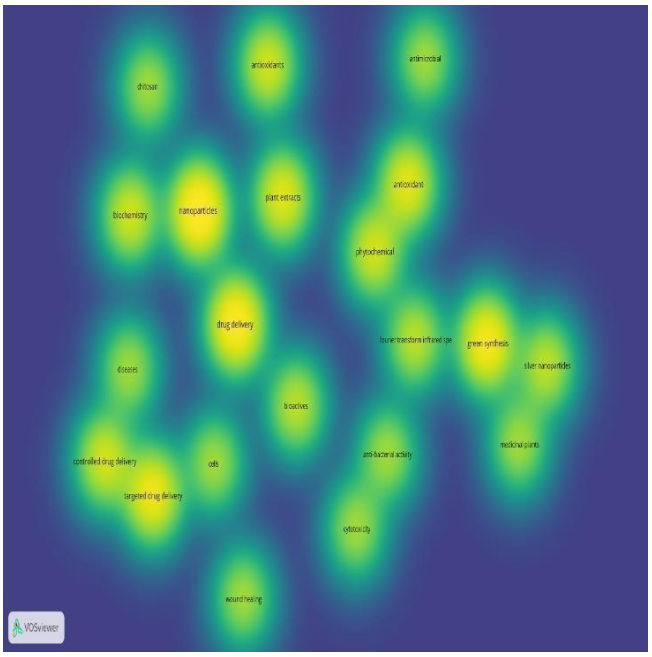

Figure 11. Keyword density visualization generated using VOSviewer.

Color intensity represents the frequency and strength of keyword co-occurrence. Yellow regions indicate high research concentration (hotspots), while green areas represent moderate thematic density. Major hotspots are centered on nanoparticles, drug delivery systems, plant extracts, antioxidants, and green synthesis approaches, illustrating the dominant research directions in natural product–based advanced drug delivery.

DISCUSSION

This bibliometric and knowledge-mapping analysis demonstrates that research on natural products has undergone a clear transformation from traditional phytochemical discovery to the development of technologically engineered drug delivery platforms. The steady growth in publication output and thematic consolidation indicates that plant-derived compounds are now embedded within mainstream nanomedicine and delivery research rather than confined to pharmacognosy. Nanocarrier systems such as polymeric nanoparticles and lipid-based carriers have been widely reported to improve the solubility, stability, and bioavailability of poorly soluble phytochemicals, enhancing therapeutic efficiency and controlled release capabilities in various preclinical models [4,14]. The prominence of green synthesis strategies observed in thematic analyses aligns with literature showing that plant extracts can act as eco-friendly reducing and stabilizing agents for nanoparticle fabrication, yielding biocompatible materials with intrinsic bioactivity [6,15,16]. The clustering of phytochemicals, antioxidants, and plant extract terms with delivery and nanotechnology concepts reflects the convergence of phytopharmacology and nanomedicine, where natural products serve both as therapeutic payloads and functional components in carrier design [5,8,17]. Expanding therapeutic applications such as antibacterial, antimicrobial, and wound healing effects support previous reports that nanoscale plant-based formulations can address infection control and oxidative stress-related diseases [7,18]. Emerging topics identified through citation burst analysis, including plant-derived nanomaterials and exosome-like nanovesicles, corroborate recent reviews highlighting the potential of plant-derived extracellular vesicles as innovative carriers in drug delivery due to their inherent biocompatibility, cellular uptake, and ability to ferry bioactive cargoes [9,19]. Together, these trends suggest that research is advancing toward sustainable, multifunctional, and biologically integrated nanocarriers, with natural product chemistry now directly informing delivery engineering. Future progress will be driven by efforts to standardize plant-derived materials, deepen mechanistic understanding of nano–bio interactions, and accelerate translation of laboratory innovations into clinically viable delivery systems, reinforcing the role of natural product-based nanotechnology as a continuing driver of innovation in advanced drug delivery systems.

Implications for Drug Delivery Technology

The evolution observed in this study underscores that natural product research is now deeply embedded in the development of advanced drug delivery technologies. Rather than serving only as therapeutic agents, plant-derived materials increasingly contribute to carrier design, green nanomanufacturing, and multifunctional formulation strategies. This integration aligns with the strategic goals of modern drug delivery, which seeks safer, more efficient, and biologically adaptable therapeutic platforms.

Overall Perspective

The field is progressing toward multifunctional, sustainable, and biologically integrated nanocarriers that leverage the chemical diversity of natural products. Collectively, these trends suggest that natural product–based nanotechnology will remain a key driver of innovation in advanced drug delivery systems.

Future Directions and Research Gaps

Despite rapid advancements, several gaps remain in translating natural product–based nanocarriers into clinically viable drug delivery systems. A major challenge lies in the lack of standardization of plant extracts, which affects nanoparticle reproducibility and scalability. Furthermore, mechanistic understanding of nano–bio interactions, including cellular uptake, biodistribution, and long-term safety, remains insufficient. Although targeted and controlled drug delivery is a dominant theme, true precision delivery with validated in vivo performance is still limited. Most studies remain at the preclinical level, highlighting the need for robust pharmacokinetic, toxicological, and clinical investigations, as well as clearer regulatory frameworks for plant-derived nanomaterials. Emerging interest in bioinspired systems such as plant-

derived exosome-like vesicles suggests a promising future direction, but their biological behavior and therapeutic efficiency require deeper exploration. Addressing these gaps will be critical for advancing sustainable, biocompatible nanocarriers from experimental concepts to real-world therapeutic applications.

CONCLUSION

This bibliometric and knowledge-mapping study demonstrates that natural products have evolved from traditional phytochemical resources into central components of advanced drug delivery technology. The research landscape has shifted toward nanoparticle-based delivery systems, green synthesis approaches, and multifunctional plant-derived nanomaterials. Temporal analyses indicate a transition from simple nanoparticle fabrication to bioactive, targeted, and biologically integrated nanocarriers, while density and thematic mapping highlight the convergence of nanotechnology, phytopharmacology, and sustainable material science. The findings confirm that natural product research is increasingly aligned with the technological priorities of modern drug delivery, particularly in the development of biocompatible, eco-friendly, and multifunctional therapeutic platforms. Overall, natural product–based nanotechnology represents a rapidly advancing frontier poised to play a transformative role in the future of drug delivery systems.

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