

Bibliometric approach in comparative review of liposome encapsulated andrographolide for potential anticancer treatment strategies

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Abstract

Andrographolide, a diterpenoid lactone derived from the medicinal plant *Andrographis paniculata*, exhibits a wide range of pharmacological activities, including antioxidant, anticancer, anti-inflammatory, and antihyperglycemic effects. However, its clinical application remains limited due to its low solubility, rapid systemic clearance, and poor bioavailability. This review critically assessed the efficacy of andrographolide encapsulation, particularly focusing on liposomal delivery systems as a promising strategy to enhance therapeutic outcomes in anticancer treatment. Employing a bibliometric analysis of literature from 2013 to 2023 sourced from Google Scholar, ScienceDirect, and Scopus, the study used VOSviewer to conduct a detailed network analysis of keywords, authorship patterns, institutional affiliations, and regional research distribution. The review identified a significant concentration of studies in Asian countries, predominantly China and India, with key contributions from researchers such as Meiwan Chen, Yitao Wang, and Jinming Wang. Despite identifying 302 relevant articles, only 16 specifically addressed the encapsulation of andrographolide for anticancer treatment, with six focusing on liposomal systems. The findings suggested that liposomal encapsulation not only enhances andrographolide's therapeutic efficacy but also mitigates its pharmacokinetic limitations by improving solubility, stability, and targeted delivery. The study underscored the need for further investigation into optimized liposomal formulations and potential clinical applications, positioning liposomal systems as a compelling avenue for advancing andrographolide-based anticancer therapeutics.

1. Introduction

Cancer is a group of diseases that can affect almost any organ or tissue in the body if abnormal cells proliferate or grow beyond their normal limits, triggering them to attack nearby tissues or spread to other organs. In 2024, the United States is expected to report approximately 2,001,140 new cancer cases, including 56,500 cases of ductal carcinoma in situ in women and 99,700 cases of melanoma in situ of the skin. Cancer incidence trends (2020-2024) revealed significant disparities across Human Development Index (HDI) regions, with Very High HDI regions reporting the highest rates at 1,527 cases per 100,000, influenced by better detection and reporting. In contrast, Low HDI regions show the lowest rates at 791 cases per 100,000, likely due to underreporting and limited diagnostic

access. Medium and High HDI regions fall in between, with Medium HDI regions experiencing a sharp increase from 965 in 2020 to 1,085 in 2024, indicating a growing cancer burden (Siegel *et al.*, 2024; Sheikh *et al.*, 2024). Chemotherapy is the current method of treatment for cancer patients. Chemotherapy drugs for cancer currently in use are temozolomide, cisplatin, docetaxel, doxorubicin, and paclitaxel. Meanwhile, drugs under development in the experimental stage are quercetin (Alhakamy *et al.*, 2022), curcumin (Namwan *et al.*, 2022), and andrographolide (Khairiah *et al.*, 2025).

Andrographolide is the main active compound isolated from *Andrographis paniculata* plant. *A. paniculata* is native to India and Sri Lanka but is widespread in China, Cambodia, the Caribbean,

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Indonesia, Laos, Malaysia, Thailand, Taiwan, and Vietnam, where it has been used as a traditional medicine including traditional Chinese and Thai medicine systems in treating various ailments such as fever, headache, and respiratory infections (Nayak *et al.*, 2020; Oseni *et al.*, 2021). Originally sourced from the traditional herb, andrographolide has gained recognition as a potent anticancer agent with diverse mechanisms targeting multiple cancer pathways. It not only boosts the effectiveness and minimizes the toxicity of chemotherapy and radiotherapy but also benefits from advanced drug delivery systems that enhance its bioavailability. Furthermore, structural modifications have further elevated its anticancer treatment strategy, establishing andrographolide as a promising candidate for clinical cancer treatment reinforces its therapeutic potential (Hu *et al.*, 2024).

Andrographolide and its derivatives have been widely applied in disease prevention owing to their broad range of pharmacological effects, including anticancer treatment strategy (Sanati *et al.*, 2020), antiproliferative (Pasha *et al.*, 2021), and hepatoprotective properties (Hazra *et al.*, 2021). Derived from the upper portion of the plant, andrographolide is an active compound characterized by its bitter taste. This compound is a two-dimensional bicyclic lactone, exhibiting multifaceted pharmacological activities. Andrographolide consists of diterpenoid lactones (34.95%) and flavonoids (46.23%), the leading group of chemical components found in *A. paniculata* aerial parts (61.93%). Terpenoids (0.22%), phenolic acids (4.30%), chalconoids (2.15%), xanthenes (2.15%), and volatile chemicals were also found in plant sections (Kumar *et al.*, 2021). The structure of the andrographolide compound and the *A. paniculata* plant are shown in Figure 1.

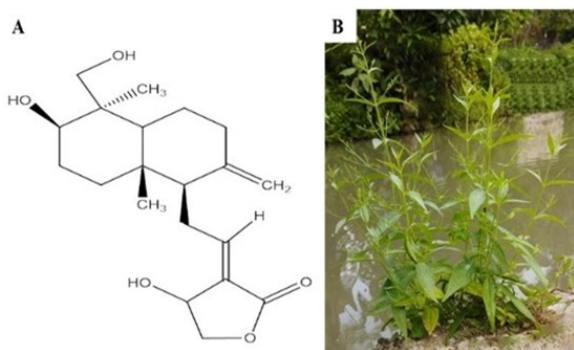


Figure 1. (A) Two-dimensional structure of andrographolide and (B) *Andrographis paniculata* plant.

Andrographolide has low water solubility, poor bioavailability, and a short half-life, reducing its therapeutic activity. It is necessary to design an appropriate delivery system that can significantly increase bioavailability through the encapsulation (Li *et al.*, 2022; Khairiah *et al.*, 2025). Understanding the

physical properties of andrographolide, including its hydrophobicity and molecular structure, is essential for addressing the challenges and strategies involved in optimizing its encapsulation efficacy for improved therapeutic delivery. Encapsulation has the benefits of protecting active compound functionality, facilitating active chemical delivery optimization and controlled release, increasing stability, increasing solubility, extending release time, and directing active compound delivery to target sites in the body (Alu'datt *et al.*, 2022).

Encapsulation is the technique of encasing or concealing active substances in a delivery vehicle, such as liposomes (Kang *et al.*, 2018; Hudiyanti *et al.*, 2021), nanophytosomes (Neamatallah *et al.*, 2023), niosomes (Tu *et al.*, 2014), nanoemulsomes (Elsheikh *et al.*, 2021), porous polymer scaffolds (Lavanya *et al.*, 2022), poly [lactide-co-glycolide] (Oseni *et al.*, 2021), and solid lipid nanoparticles (Li *et al.*, 2022). Liposomes are commonly used nanocarriers for both hydrophobic and hydrophilic molecules, owing to their biodegradability, low immunogenicity, and high biocompatibility. They improve drug solubility, facilitate targeted, sustained release, and ensure controlled distribution. Over time, liposomes have advanced from traditional formulations to stimuli-responsive and actively targeted versions. Numerous liposomal drug delivery systems are already clinically approved for treating viral infections, fungal infections, and cancer, with more undergoing advanced clinical trials (Nsairat *et al.*, 2022).

In recent years, there has been a growing body of literature focusing on the formulation of andrographolide, with a particular emphasis on its potential as a key component in anticancer medications (Hu *et al.*, 2024; Khairiah *et al.*, 2025). Given the remarkable pharmacological properties associated with andrographolide, there is a pressing need to assess the viability of encapsulated andrographolide as a feasible strategy for leveraging its anticancer activity. However, no bibliometric studies are yet available to examine the existing publications on the efficacy of encapsulated andrographolide as an anticancer. This approach is especially relevant as it facilitates an objective comparison of different encapsulation methods, aiding in the identification of trends, key research topics, and gaps in the existing literature. Through the quantitative analysis of published studies, bibliometric methods offer valuable insights into the development and influence of encapsulation technologies within the field.

Therefore, this review aimed to identify trends in research output over time, which can reveal patterns of collaboration among researchers, institutions, and countries involved in studying encapsulated andrographolide as an anticancer treatment strategy. This

information can facilitate networking opportunities and enhance knowledge exchange within the research community. This analysis can also highlight areas where research on encapsulated andrographolide as an anticancer agent is lacking or underdeveloped. By identifying knowledge gaps, researchers can prioritize future research directions and allocate resources more effectively to address unanswered questions or unexplored aspects of this topic.

2. Methodology

2.1 Search strategy

Science Direct advanced search, Scopus, and Google Scholar were used for database collection, utilizing Harzing's Publish or Perish (<http://www.harzing.com/pop.htm>) to retrieve and analyze academic papers. Covidence systematic review software was also employed to find and remove literature searches by analyzing keywords in titles and abstracts (www.covidence.org) based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Similarity visualization VOSviewer v.1.6.18 (<https://www.vosviewer.com>) was used to analyze and visualize the data (Van Eck and Waltman, 2014). For data mining of papers related to our investigation, the keywords used are listed in Table 1. The rationale for using 'AND' is to maintain specificity while preventing the inclusion of unrelated studies. The literature search was limited to the previous ten years until March 6, 2024. Table 1 shows the total number of papers from Science Direct's advanced search, Scopus, and Harzing's Publish or Perish. A total of 302 papers were used to build our bibliometric review using the PRISMA strategy by Covidence software.

2.2 Inclusion criteria

The inclusion criteria were: andrographolide encapsulated, dose/IC₅₀, the potential to inhibit cancer cells, and English language articles.

2.3 Exclusion criteria

Exclusion criteria were book chapters, conference papers, editorials, duplicated papers, and unrelated

papers.

2.4 Data extraction

The filtering process followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring a transparent and systematic approach. Studies were screened based on predefined inclusion and exclusion criteria. Over 200 studies were excluded, with reasons such as review papers, book chapters, and irrelevance with keywords to maintain transparency and reproducibility. VOSviewer software was utilized to analyze the keywords' network, occurrence, total link strength, and year of publication (Zakaria et al., 2023). Other analyses regarding the author, country, and publication source were also conducted. Furthermore, we conducted an in-depth analysis of the selected papers based on the encapsulation type, cell line, cancer/cell type, and dose.

3. Results

3.1 Analysis of keywords

From the inclusion and exclusion criteria, 16 papers were selected. The PRISMA flowchart in Figure 2 presents the screening process. VOSviewer software analyzed the keywords, occurrence, total link strength, and year of publication, displayed as bubble maps. The degree of interaction and the number of keywords in publications are reflected by the distance between nodes and the size of the circular nodes. Linkages like co-occurrences or partnerships are indicated by the links between nodes. The bubbles' color indicated the number of citations each publication contained the term, and their proximity indicated how frequently they co-occurred.

Based on VOSviewer analysis, 52 keywords were obtained from the 16 selected papers with five primary clusters. Figure 3 illustrates the network analysis of these keywords. A colored node (red, green, and dark blue) represents each keyword. The largest cluster, indicated in red, comprises 24 nodes or keywords. Following this, the green cluster contains eight keywords, while the dark blue and yellow clusters each contain seven and eight keywords, respectively. Lastly, the purple cluster

Table 1. List of keywords and the number of papers discovered.

Keyword	Quantity	Source	Year
Andrographolide AND Encapsulation AND Liposome* AND Anticancer OR Anticarcinoma OR Antitumor Setting: maximum number of results	200	Google Scholar	Ten years
Andrographolide AND Encapsulation AND Liposome AND Vesicle AND Anticancer OR Anticarcinoma	25	Science Direct	Ten years
Andrographolide AND encapsulation AND Liposome AND Anticancer AND Antitumor	67	Scopus	Ten years
Andrographolide AND Encapsulation AND Liposome AND Anticancer OR Anticarcinoma	10	Manual searching	Ten years
Total	302		

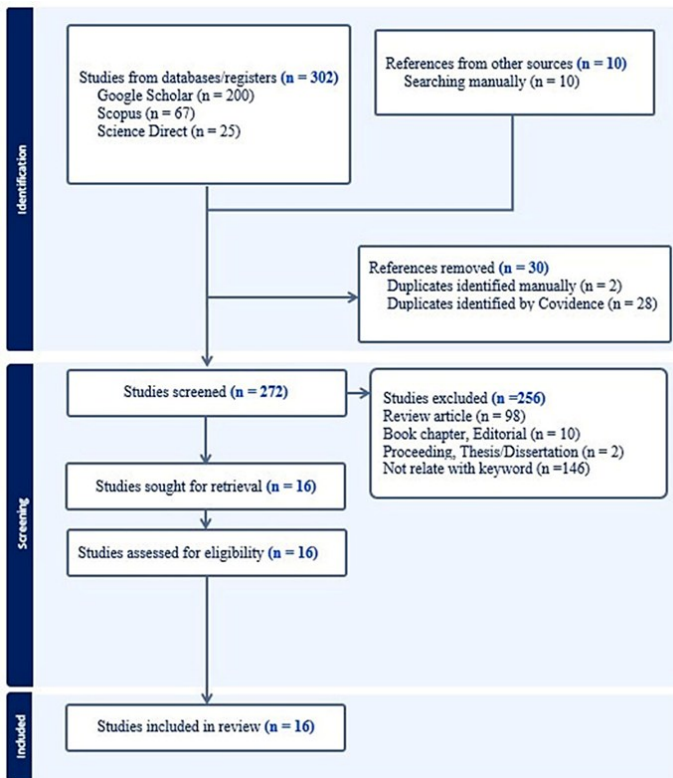


Figure 2. PRISMA flow chart.

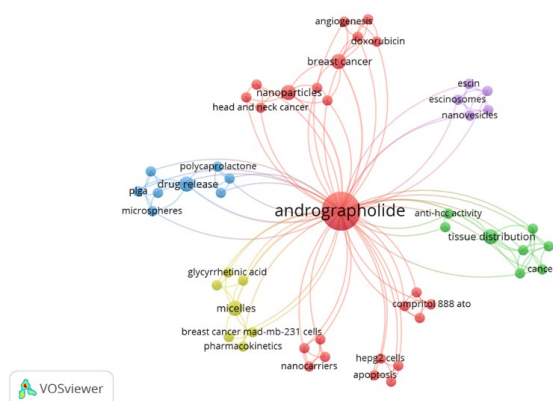


Figure 3. Network visualization of keywords analysis.

encompasses five keywords. Each node is unique, with the largest one being the “andrographolide” node. Every node is linked to the “andrographolide” node by a solid red line. The color of the line corresponds to the color of the cluster.

Thus, the keyword network in Figure 3 confirms that the 16 selected papers focus on the andrographolide topic with five main topics. The topics comprise the types of encapsulations of andrographolide for the treatment of various types of cancer (red cluster), niosomes encapsulation andrographolide for anti-HCC activity in HepG2 cells treatment (green cluster), polycaprolactone encapsulation andrographolide for cervical cancer cells treatment (dark blue cluster), PLGA-PEG-PLGA micelles encapsulation andrographolide for breast cancer (yellow cluster), escinosom encapsulation andrographolide for colorectal cancer with simulation in vivo in rat model of oxaliplatin-induced neuropathy

(purple cluster). Table 2 presents the details of the clusterization of keywords and thematic interpretation.

Meanwhile, Figure 4 represents the quantification of the network from occurrences and total link strength between keywords' points of view. Andrographolide was the most popular keyword with 56 total link strengths and 13 occurrences, breast cancer with nine total link strengths and two occurrences, and drug release with nine total link strengths and two occurrences. Figure 5 illustrates the visualization of the keyword occurrence with a timeframe. The color difference represents the publication date in the ten-year range (2013-2023). Blue represents publications published between 2014 and 2017, green represents articles published between 2018 and 2022, and yellow represents articles published in 2023. A liposome encapsulation investigation was started in 2018 for the treatment of 4T1 cell breast cancer. Based on the occurrence analysis of keywords, research discussing andrographolide encapsulation has been detected since 2014, using niosomes and polymers as encapsulants, with a total occurrence of four. Research on andrographolide encapsulation has increasingly developed over time with variations. The occurrence of 12 articles in 2018-2023 indicates the various applications of encapsulants.

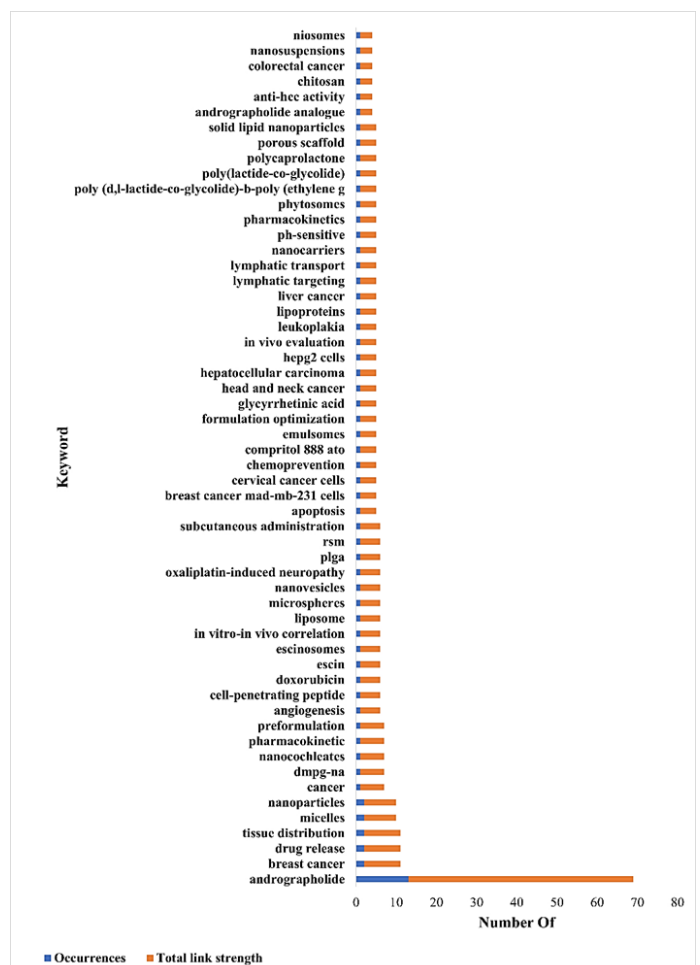


Figure 4. Quantification of occurrences and total link strength of keywords.

Table 2. The primary findings of the examination of all keywords' co-occurrence networks.

Clusters	Keywords	Thematic interpretation
Cluster 1 (Red Nodes/24 items)	Andrographolide, angiogenesis, apoptosis, breast cancer, cell-penetrating peptide, chemoprevention, Compritol 888 ato, doxorubicin, emulsomes, formulation optimization, head and neck cancer, HepG2 cells, in vivo evaluation, leukoplakia, lipoproteins, liposome, liver cancer, lymphatic targeting, lymphatic transport, nanocarriers, nanoparticles, phytosomes, poly(lactide-co-glycolide), solid lipid nanoparticles.	This cluster shows the potential of andrographolide with variations in encapsulation methods (such as phytosomes, SLN, and others) and pharmacological tests on variations in cancer types, such as breast cancer, liver cancer, neck cancer, and others.
Cluster 2 (Green Nodes/8 Items)	Anti-HCC activity, cancer, dmpg-na, nanocochleates, niosomes, pharmacokinetic, preformulation, tissue distribution.	This cluster shows the correlation between preformulations anticancer with the encapsulation method that influences the pharmacokinetics, such as in the tissue distribution.
Cluster 3 (Dark Blue Nodes/8 Items)	Cervical cancer, drug release, in vitro-in vivo correlation, microspheres, PLGA, polycaprolactone, porous scaffold, RSM.	Cluster reveals the type of matrix used for andrographolide encapsulation in anti-cancer assay on cervical cancer cell lines.
Cluster 4 (Yellow Nodes/7 Items)	Breast cancer mad-mb-231 cells, glycyrrhetic acid, hepatocellular carcinoma, micelles, pH-sensitive, pharmacokinetics, poly(d,l-lactide-co-glycolide)	Cluster reveals the type of matrix used for andrographolide encapsulation in anti-cancer assay on breast cancer and hepatocellular carcinoma cell lines.
Cluster 5 (Purple Nodes/5 Items)	Escin, escinosomes, nanovesicles, oxaliplatin-induced neuropathy, subcutaneous administration	This cluster shows the nanovesicle used in vivo study.

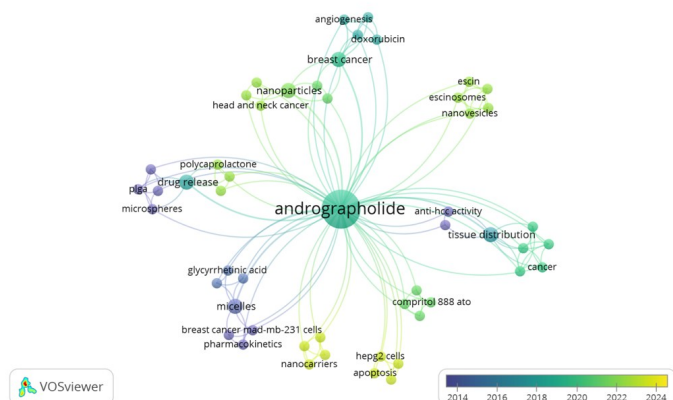


Figure 5. Overlay visualization of keyword occurrence based on publication year.

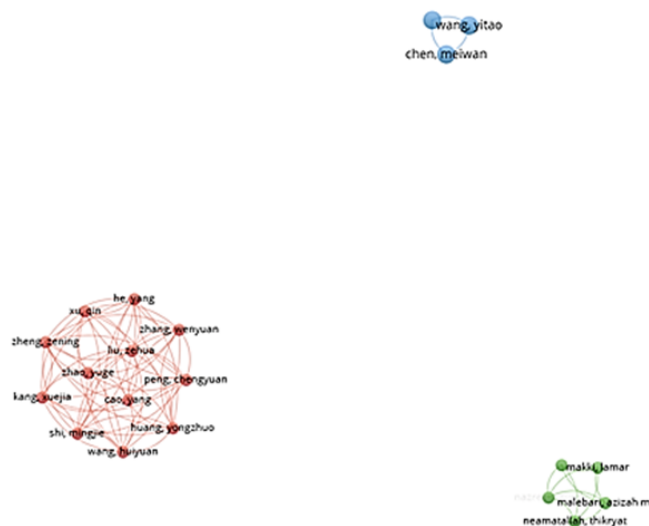


Figure 6. Network visualization for the author analysis.

3.2 Analysis of the author, organization and country

Meiwan Chen, Yitao Wang, and Jinming Zhang stand out as the most prolific authors, each contributing two publications. Notably, they are clustered together within the same blue node, as depicted in Figure 6, which represents the largest node among all others. This clustering underscores their significant output, evidenced by their high number of articles. Moreover, these authors are affiliated with the Institute of Chinese Medical Sciences, University of Macau, China, which is identified as the most productive organization. Their collective works have received a total of 52 citations, as indicated in Table 3, further emphasizing their cohesion within a single cluster.

China and India are the most productive countries in

the research of andrographolide encapsulation on anticancer treatment, with seven and four articles, respectively (Figure 7). All of the publications are from high-impact journals. India, renowned for its biodiversity and diverse traditional medical practices including Ayurveda, Unani, Siddha, and Homeopathy, reflects its distinctive cultural heritage (Nayak *et al.*, 2020). Additionally, countries such as the United States, Thailand, Saudi Arabia, Italy, and Egypt have emerged as key contributors to this field, underscoring the importance of scientific collaboration among them.

Table 3. The most prominent organization.

Organization	Citation
School of Pharmaceutical Sciences, Sun Yat-Sen University, China	52
Institute of Chinese Medical Sciences, University of Macau, China	52
Chinese Academy of Sciences, China	48
Nanchang University, China	48
Faculty of Pharmacy, King Abdul-Aziz University, Saudi Arabia	12
Faculty of Pharmacy, Pharos University in Alexandria, Egypt	9
Faculty of Sciences, King Abdul-Aziz University, Saudi Arabia	4
Faculty of Science, Albaha University, Saudi Arabia	4
Faculty of Pharmacy, Cairo University, Egypt	4
Manipal Academy of Higher Education, India	1

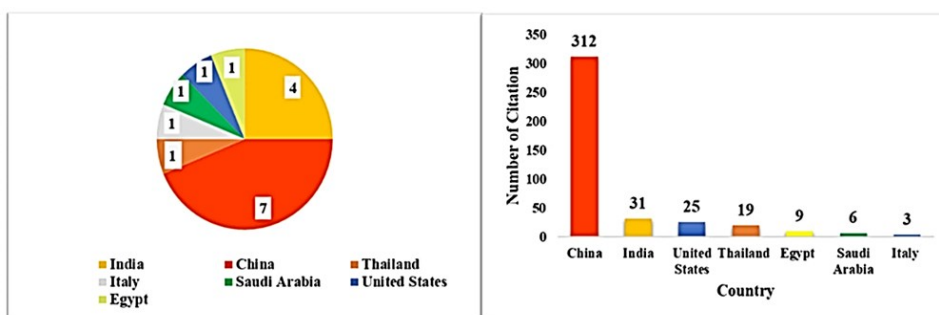


Figure 7. Number of publications and citations of each country.

3.3 Document analysis

The findings presented in Table 4, which showcase selected papers based on the inclusion criteria established through PRISMA analysis, offer valuable insights into the landscape of research on the topic under consideration. Among the selected articles, those authored by Jiang *et al.* (2014), Kang *et al.* (2018), and Zhang *et al.* (2015) have garnered significant academic attention, as reflected in their high citation counts.

4. Discussion

Andrographolide shows considerable potential in cancer chemoprevention by targeting multiple molecules and signaling pathways across various cancer types (Malik *et al.*, 2021). It exerts its anticancer effects through several mechanisms, including the inhibition of cell proliferation and differentiation, induction of apoptosis, disruption of the cell cycle, and enhancement of the immune response against cancer cells (Naomi *et al.*, 2022). The mechanism of action involves arresting the cell cycle at different stages, along with the upregulation of pro-apoptotic genes and proteins such as Bax, P53, P21, P16, and reactive oxygen species (ROS), while downregulating anti-apoptotic regulators like Bcl-2, as well as the activity of cell cycle proteins Cyclin D1/CDK4 and Cyclin A/CDK2. A more detailed analysis of andrographolide's anticancer mechanisms has been provided by Malik *et al.* (2020).

However, treatment with free andrographolide has disadvantages, namely low water solubility, poor bioavailability, short half-life, and accumulation in non-target organs. By encapsulating the andrographolide, the above obstacles can be overcome. The encapsulated andrographolide has good solubility, greater cell penetration ability, sustained release time, and increased accumulation in target organs compared to free andrographolide. Liposomes represent one of the promising drug delivery options. To prepare encapsulations, it is crucial to select the appropriate materials and methods, as their interdependent relationships must be considered holistically. Encapsulation processes can be classified based on various criteria, such as the use of organic solvents, the nature of the dispersing medium, the type of polymers or lipids, and the method of associating the molecule with the encapsulating material. These processes are typically categorized into mechanical methods (e.g., spraying, droplet formation, extrusion), physico-chemical methods (involving solubility control, precipitation, or changes in state), and chemical methods (where the encapsulating material is formed in situ through polymerization) (N'guessan-Gnaman *et al.*, 2024).

Based on the document analysis in Table 4, the application of andrographolide as an anticancer using various encapsulation methods was further analyzed as in Table 5. This in-depth analysis emphasized the application of various encapsulation types on different cancer cell lines. As shown in this table, breast cancer

Table 4. Document analysis of encapsulated andrographolide in cancer studies.

No.	Title	Country	Source	Authors	Citation
1	Development of andrographolide-loaded PLGA microspheres: Optimization, characterization and in vitro-in vivo correlation.	China	International Journal of Pharmaceutics, 2014	Jiang, Y., Wang, F., Xu, H., Liu, H., Meng, Q. and Liu, W.	69
2	Liposomal Codelivery of Doxorubicin and Andrographolide Inhibits Breast Cancer Growth and Metastasis.	China	Molecular Pharmaceutics, 2018	Kang, X., Zheng, Z., Liu, Z., Wang, H., Zhao, Y., Zhang, W., Shi, M., He, Y., Cao, Y., Xu, Q., Peng, C. and Huang, Y.	57
3	Glycyrrhetic Acid-Mediated Polymeric Drug Delivery Targeting the Acidic Microenvironment of Hepatocellular Carcinoma.	China	Pharmaceutical Research, 2015	Zhang, J., Zhang, M., Ji, J., Fang, X., Pan, X., Wang, Y., Wu, C. and Chen, M.	56
4	Andrographolide-loaded PLGA-PEG-PLGA micelles to improve its bioavailability and anticancer efficacy.	China	Expert Opinion on Drug Delivery, 2014	Zhang, J., Li, Y., Gao, W., Repka, M.A., Wang, Y. and Chen, M.	53
5	Preparation and characterisation of andrographolide niosomes and their anti-hepatocellular carcinoma activity.	China	Journal of Microencapsulation, 2014	Tu, Y.S., Sun, D.M., Zhang, J.J., Jiang, Z.Q., Chen, Y.X., Zeng, X.H., Huang, D.E. and Yao, N.	46
6	Encapsulation of Andrographolide in poly[lactide-co-glycolide] Nanoparticles: Formulation Optimization and In vitro Efficacy Studies.	United States	Frontiers in Bioengineering and Biotechnology, 2021	Oseni, B.A., Azubuike, C.P., Okubanjo, O.O., Igwilo, C.I. and Panyam, J.	25
7	Andrographolide-loaded solid lipid nanoparticles enhance anticancer activity against head and neck cancer and precancerous cells.	China	Oral Diseases, 2022	Li, H., Qu, X., Qian, W., Song, Y., Wang, C. and Liu, W.	22
8	Investigation of 1,2-Dimyristoyl-sn-Glycero-3-Phosphoglycerol-Sodium [DMPG-Na] Lipid with Various Metal Cations in Nanococheate Preformulation: Application for Andrographolide Oral Delivery in Cancer Therapy.	India	AAPS PharmSciTech, 2020	Ahiwale, R.J., Chellampillai, B. and Pawar, A.P.	19
9	Fabrication and characterization of andrographolide analogue [3A.1] nanosuspensions stabilized by amphiphilic chitosan derivatives for colorectal cancer therapy.	Thailand	Journal of Drug Delivery Science and Technology, 2019	Kansom, T., Sajomsang, W., Saeeng, R., Rojanarata, T., Ngawhirunpat, T., Patrojanasophon, P. and Opanasopit, P.	19
10	Nanoemulsomes for Enhanced Oral Bioavailability of the Anticancer Phytochemical Andrographolide: Characterization and Pharmacokinetics.	Egypt	AAPS PharmSciTech, 2021	Elsheikh, M.A., Rizk, S.A., Elnaggar, Y.S.R. and Abdallah, O.Y.	9
11	Andrographolide-loaded silk fibroin nanoparticles.	China	RSC Advances, 2018	Zhongyu, X., Jiangmeng, R., Qiufang, J., Fuzheng, R., Mengting, H., Wenrui, D. and Buling, Z.	9

Table 4 (Cont.). Document analysis of encapsulated andrographolide in cancer studies.

No.	Title	Country	Source	Authors	Citation
12	Development of andrographolide-loaded solid lipid nanoparticles for lymphatic targeting: Formulation, optimization, characterization, in vitro, and in vivo evaluation.	India	Drug Delivery and Translational Research, 2023	Shrivastava, S. and Kaur, C.D.	8
13	Andrographolide nanophytosomes exhibit enhanced cellular delivery and pro-apoptotic activities in HepG2 liver cancer cells.	Saudi Arabia	Drug Delivery, 2023	Neamatallah, T., Malebari, A.M., Alamoudi, A.J., Nazreen, S., Alam, M.M., Bin-Melaih, H.H., Abuzinadah, O.A., Badr-Eldin, S.M., Alhassani, G., Makki, L. and Nasrullah, M.Z. Nasrullah, Mohammed Z.	6
14	Escinosomes: Safe and Successful Nanovesicles to Deliver Andrographolide by a Subcutaneous Route in a Mice Model of Oxaliplatin-Induced Neuropathy.	Italy	Pharmaceutics, 2022	Vanti, G., Capizzi, M., Di Cesare Mannelli, L., Lucarini, E., Bergonzi, M.C., Ghelardini, C. and Bilia, A.R.	3
15	Mannosylated-Chitosan-Coated Andrographolide Nanoliposomes for the Treatment of Hepatitis: In Vitro and In Vivo Evaluations.	India	Membranes, 2023	Metkar, S.P., Fernandes, G., Nikam, A.N., Soman, S., Birangal, S., Seetharam, R.N., Joshi, M.B. and Mutalik, S.	2
16	Sustained delivery of andrographolide from 3D porous scaffolds imparting anticancer activity.	India	Journal of Drug Delivery Science and Technology, 2022	Lavanya, S.K., Kamath, M., Rao, K., Rajapriya, P., Patil, S. and Sundaresan, S.	2

Table 5. List of variations of andrographolide encapsulation methods for various anticancer applications.

Encapsulation types	Cell line	Cancer type	IC ₅₀ /Dose	Finding	Reference
Scaffolding polycaprolactone [PCL]	Hela cells	Human cervical cancer	16.11 µm and 17.08 µm	Significant decrease in cell viability for three days.	Lavanya <i>et al.</i> (2022)
Nanophytosomes	Hepg2	Liver cancer	4.02±0.14 µm	Termination of the G2-M cell cycle phase and increased apoptotic cells in the pre-G1 phase.	Neamatallah <i>et al.</i> (2023)
Silk fibroin nanoparticles	Hela cells and MDA-MB-231 cells	Human cervical cancer and Human breast cancer	50 mm and 100 mm	Negligible cytotoxicity to cells and antiproliferative activity.	Zhongyu <i>et al.</i> (2018)
Poly[lactide-co-glycolide]	LM2	Breast cancer	16.80 µm	Inhibition of cell proliferation in triple-negative LM2 breast cancer.	Oseni <i>et al.</i> (2021)
Nanocochleate	MCF-7	Breast cancer	40.46 µg/ml	Cytotoxicity in ER/PR positive/Her2 negative breast cancer cells, MCF-7.	Ahiwale <i>et al.</i> (2020)
Liposomal	4T1 cells	Breast cancer	5 mg/kg	Significantly arrested the tumor growth.	Kang <i>et al.</i> (2018)
Nanoliposom	Sel hepg2	Treatment of Hepatitis	50 mg/kg	The cytotoxicity of the drug is reduced when introduced into nanocarriers.	Metkar <i>et al.</i> (2023)
Solid lipid nanoparticles [SLN]	HIOEC, Leuk1, HN6, dan HN30	Neck cancer and precancerous cells	0.3371, 0.717, 6.087, and 11.74 µg/mL	Advanced anticancer activity against head and neck cancer and precancerous cells compared to free ADG.	Li <i>et al.</i> (2022)
Solid lipid nanoparticles	Hepatic cells	Lymphatic	160.5 µg h/ml	Have higher bioavailability and specificity.	Shrivastava and Kaur (2023)

Table 5 (Cont.). List of variations of andrographolide encapsulation methods for various anticancer applications.

Encapsulation types	Cell line	Cancer type	IC ₅₀ /Dose	Finding	Reference
Emulsome [EML-AG]	Intestinal lymphatic transport	Lymphoma	25 mg/kg	EML-AG significantly enhanced the rate and extent of AG absorption compared with free AG.	Elsheikh <i>et al.</i> (2021)
Escinosomes	Rat model of oxaliplatin-induced neuropathy	Colorectal cancer	10 mg/kg	AG-loaded escinosomes effectively reduced the thermal allodynia characteristic of chemotherapy-induced neuropathy, enhancing and prolonging the effect of the natural compound.	Vanti <i>et al.</i> (2022)
PLGA-PEG-PLGA micelles	MAD-MB-231 cells	Human breast cancer	7.45±1.21 µm	ADG-loaded PLGA-PEG-PLGA micelles exhibited higher proliferation inhibition, cell cycle arrest at the G2/M phase and pro-apoptosis effects in MAD-MB-231 cells.	Zhang <i>et al.</i> (2014)
Niosomes	Cell line HepG2 was	Human liver cancer	25.0 mM	The tissue distribution in mice demonstrated that the AG niosomes were absorbed in the liver much more than the free AG.	Tu <i>et al.</i> (2014)
Poly [ethylene glycol]-poly [lactic-co-glycolic acid] [GA-PEG-PHIS-PLGA, GA-PPP] micelles	Human Hep3B liver cells	Hepatocellular carcinoma	6.12 µM	AGP/GA-PPP mi-celles significantly inhibited tumor growth and provided better therapeutic outcomes compared to free AGP.	Zhang <i>et al.</i> (2015)
PLGA microspheres	Healthy male Sprague-Dawley [SD] rats	Cancer therapy	10 mg/kg	Sustained release of AG from the PLGA microspheres, PLGA microspheres might be a promising formulation for AG used for cancer therapy.	Jiang <i>et al.</i> (2014)
Nanosuspensions with chitosan derivatives	[HCT116] cells.	Colorectal cancer	0.541± 0.041 µg/mL	Efficiently inhibit the growth of tumor cells	Kansom <i>et al.</i> (2019)

cells are the most common type of cancer cell used in this area of the topic, as indicated by the five papers that addressed andrographolide encapsulation in breast cancer cells. Expansion of the study was also conducted by testing on other cancer cell types, such as neck cancer, hepatocellular carcinoma, liver cancer, hepatitis, colorectal cancer, cervical cancer, and precancerous cells. The results of cytotoxicity testing showed that andrographolide had cytotoxicity in various cancer cells and inhibited cell proliferation. An effective IC₅₀ and dose was obtained for each type of cell tested based on variations of the andrographolide encapsulation method used. The results revealed that encapsulating materials can increase bioavailability and specificity in the target organ and show superior anticancer activity compared to free andrographolide (Zhang *et al.*, 2015; Ahiwale *et al.*, 2020).

Research conducted by Ahiwale *et al.* (2020) reported that andrographolide formulations encapsulated with nanocochleates (NCs) could reduce the IC₅₀ value of andrographolide by 26.99 times compared to free andrographolide based on the MTT assay. The advantage of encapsulating andrographolide with nanocochleates (NCs) is that it can increase the oral bioavailability of andrographolide in andrographolide nanocochleates (ANDNCs) by 1.81-fold compared to free andrographolide, based on *in vivo* pharmacokinetic studies in female Wistar rats. Another advantage of encapsulation is that it can minimize the dosage of the encapsulated formulation in non-target organs such as the liver, kidney, and spleen based on tissue distribution tests carried out on Wistar rats. Encapsulated

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andrographolide did not show significant changes in particle size, encapsulation efficiency, and zeta potential during short-term studies at a temperature of 4°C for six months. The encapsulation of andrographolide with nanocochleates is physically stable.

Research conducted by Oseni *et al.* (2021) reported that encapsulating andrographolide in poly (lactide-co-glycolide) (PLGA) nanoparticles can overcome solubility problems and enable sustained drug release based on the influence of formulation parameters such as polymer composition, polymer molecular weight, polymer to drug ratio, the concentration of surfactant and organic solvent used affects the properties of the nanoparticles, resulting in better therapeutic efficacy. The study showed that encapsulated andrographolide was better than the free drug with an IC_{50} of 16.80 μ M and 27.68 μ M, respectively, based on the acute viability test with the MTS assay.

Research reported by Neamatallah *et al.* (2023) showed that andrographolide encapsulated with phytosomes (AG-PTMs) can increase cellular absorption of andrographolide by HepG2 cells compared to free andrographolide. It is related to favorable cellular penetration due to nano-sized particles with a larger surface area, so that andrographolide quickly enters cancer cells to provide its pharmacological effects. Conner reports that the cellular uptake of polymer nanoparticles is enhanced by endocytosis (Conner and Schmid, 2003; Zhang *et al.*, 2014). Andrographolide encapsulated with phytosomes (AG-PTMs) significantly suppressed the growth of HepG2 liver cancer cells with an IC_{50} value of 4.02 ± 0.14 μ M compared with free andrographolide.

Phytosomes used as encapsulant materials can increase the cytotoxicity of phytochemical compounds such as sinigrin (Mazumder *et al.*, 2016), quercetin (Alhakamy *et al.*, 2022), and curcumin (Al-Rabia *et al.*, 2022). Andrographolide encapsulated with phytosomes provides an increase in its antiproliferative effect. AG-PTM and AG-loaded PLGA-PEG-PLGA micelles caused the arrest of the G2-M phase of the cell cycle and increased the fraction of apoptotic cells in the pre-G1 phase significantly compared to free andrographolide (Zhang *et al.*, 2014; Neamatallah *et al.*, 2023). These effects are associated with the induction of oxidative stress and mitochondrial dysfunction. AG-PTM significantly upregulated BAX mRNA expression and downregulated BCL2. AG-PTM significantly increased the concentration caspase-3 compared with free AG (Neamatallah *et al.*, 2023). Research conducted by Lavanya *et al.* (2022) reported that andrographolide encapsulated with polycaprolactone (PCL) scaffolds

showed sustained release of andrographolide for eight days. Jiang *et al.* (2014) contributed to this discourse with their study titled “Development of andrographolide loaded PLGA microspheres: Optimization, characterization and in vitro-in vivo correlation.” Their research focused on the development and characterization of andrographolide-loaded PLGA microspheres, aiming to optimize their formulation and establish an in vitro-in vivo correlation. The study explores the encapsulation of andrographolide, a bioactive compound with potential therapeutic applications, within PLGA microspheres, offering insights into controlled drug delivery systems. The encapsulation process provides sustained release and is suitable for cancer therapy (Jiang *et al.*, 2014).

Liposomes are artificially spherical vesicles formed by self-assembly of amphiphilic lipid molecules in solution. Liposomes consist of one or more lipid bilayers (lamellae) arranged around an internal water core, with polar head groups oriented towards the inner and outer water phases. Liposomes have been widely developed for various pharmaceutical and biomedical applications with the unique ability to trap hydrophilic (polar) and hydrophobic (nonpolar) compounds as they have amphiphilic characteristics in aqueous media. Hydrophobic compounds will be trapped in the bilayer membrane, while hydrophilic compounds will be encased in the aqueous phase (Olusanya *et al.*, 2018). One of the components of liposomes is cholesterol. Cholesterol is a critical component of liposomes that plays an important role in the stability and properties of liposome membranes. Cholesterol has an impact by controlling fluidity, permeability, membrane strength, elasticity and stiffness, transition temperature (T_m), drug retention, phospholipid packing, and plasma stability. Based on the andrographolide lipophilicity property, we predict that andrographolide will be in the liposome membranes, as illustrated in Figure 8. Incorporating cholesterol into liposome formulations can significantly enhance membrane stability, reduce leakage, and improve drug retention, making it a critical component in optimizing the efficacy of encapsulated therapeutic agents (Hudiyanti *et al.*, 2023; Hudiyanti *et al.*, 2025).

Liposomes are the most widely utilized nano-carriers

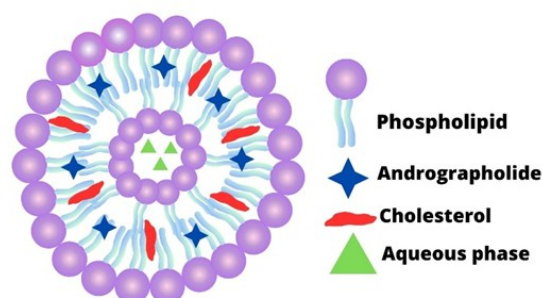


Figure 8. Structure of liposome-encapsulated andrographolide.

due to their low immunogenicity, good biocompatibility, and biodegradability for a wide range of hydrophilic and hydrophobic compounds. It has been proven that liposomes improve drug solubility, control drug distribution, and surface modification ability for extended or sustained targeted release (Nsairat *et al.*, 2022). Several liposome-based drug delivery systems have been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of diseases on the market, and only 14 types are available on the market. It indicates that the advantages of liposomes are still not fully explored (Bulbake *et al.*, 2017; Liu *et al.*, 2022). Liposomes are spherical lipid vesicles that are usually 50-500 nm in particle size (Nsairat *et al.*, 2022). For example, in liposomes, the size of the liposome determines the efficiency of distribution and cleaning after use. The increase in liposome size increases the absorption rate by the reticuloendothelial system (RES). The smaller size of the liposome (≤ 100 nm) can increase the activity of antitumor drugs encapsulated in the liposome, provide more effective delivery properties, longer retention in the tumor, and more targeted drug release (Jiang *et al.*, 2014; Zhang *et al.*, 2015). Various theories in liposome cell interaction, such as adhesion (Oda *et al.*, 2020), specific targeted mediated by receptor (Ismail *et al.*, 2022), fusion (Yang *et al.*, 2016), and lipid exchange (Agarwal *et al.*, 2016). The liposomes cell interaction is illustrated in Figure 9. The encapsulation aspect utilizing coconut-derived phospholipid-based liposomes has been investigated *in silico* by Hudiyanti *et al.* (2025). Using molecular docking and molecular dynamics simulations, the study revealed that the encapsulation process enhances the stability and binding efficiency of liposomal andrographolide complexes targeting human papillomavirus. This encapsulation strategy was simulated using variations in phospholipid types as the primary liposome component. The type of phospholipid significantly influenced the analyzed values and interaction sites obtained. The findings underscore that liposomes exert a synergistic effect on the encapsulation and release of andrographolide, as evidenced by docking scores, interaction sites, potential energy, binding energy, and RMSD, highlighting their potential as a promising anticancer strategy (Hudiyanti *et al.*, 2025).

et al., 2025).

Recent investigations of nanoliposomes encapsulated with temozolomide (TMZ) provide an enormous opportunity for the treatment of glioblastoma (GBM), a disease that presents major challenges because of resistance and the blood-brain barrier, tested *in vivo* and *in vitro*. The modified nanoliposomes have a synergistic effect on enhancing DNA damage and inducing apoptosis. The result showed that the combination of liposomes reduces the effective dose of TMZ and lowers systemic TMZ-induced toxicity. It is suggested that the preclinical potential of new integrative techniques for combination therapy in brain tumors (Ismail *et al.*, 2022).

Research conducted by Kang *et al.* (2018) showed that andrographolide and doxorubicin encapsulation using liposomes have higher cytotoxicity than the free drug based on the cytotoxicity test results using the MTT assay. Using modified liposomes as encapsulant material provides advantages in drug biodistribution, such as higher cellular uptake and deeper tumor infiltration, and can improve the accumulation of liposomes in tumor cells. Treatment with encapsulated andrographolide and doxorubicin with liposomes showed significant tumor shrinkage results of 80.1%, while the treatment with the free combo drug was 36.7%. Based on previous reports have shown that encapsulated andrographolide provides better efficacy compared to free drug andrographolide on various cancer cells. This is promising for the development of anticancer formulations. Investigations and research collaborations on an animal and clinical scale are needed; it is hoped that encapsulated andrographolide can become a resource in anticancer treatment. Of the total encapsulation methods used, the liposome is a method that is still little explored compared to polymers, so it is a great opportunity to continue to be developed and investigated based on the properties and characteristics of liposomes that have potential as encapsulant materials.

5. Conclusion

Over the past decade (2013-2023), a bibliometric analysis of research on andrographolide encapsulation as an anticancer agent has revealed a significant concentration of studies in the Asian region, particularly in China, followed by India. The primary topics of interest included andrographolide, breast cancer, and drug release, with andrographolide being the most frequently studied compound. The research indicates that andrographolide encapsulation has progressed significantly, offering better drug efficacy compared to the free form of andrographolide. However, there remains a notable gap in this area, highlighting

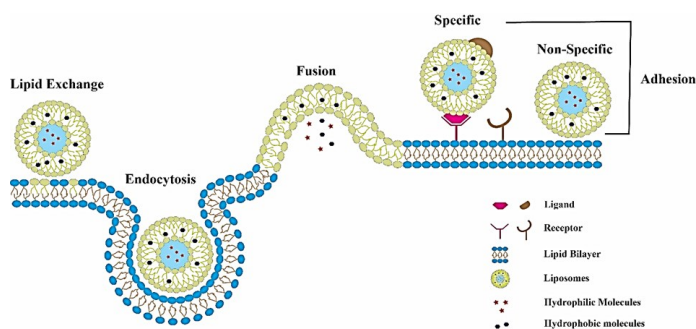


Figure 9. The liposome-cell interaction.

considerable potential for future research, especially in exploring liposomes as encapsulating materials for enhanced anticancer treatment. Moving forward, it would be valuable to examine recent clinical trials and compare them with earlier studies to determine whether the focus should remain on andrographolide encapsulation or shift towards other delivery systems.

Conflict of interest

The authors declare no conflict of interest.

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