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Folic Acid Conjugated Poly(propylene imine) Dendrimer as a Nanomedicine Tool for Targeted Drug Delivery: Bibliometric Analysis Using Google Scholar Indexed VOSViewer

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ABSTRACT

By using bibliometric analysis and data mapping with the help of the VOSViewer program, this study aims to examine the breadth of research on the subject of folic acid-conjugated PPI dendrimers for targeted drug delivery. Data was collected from the Google Scholar scientific document database using the Harzing Publish or Perish 8 application. Journal articles containing the keywords "dendrimer," "PPI," "folic acid," and "drug delivery" that were published in the years 2018 through 2023 were used as the selection criteria for the data. The selection results in the form of 221 journal articles were analyzed and mapped. The total number of research publications has increased from 2018-2021 with the highest number of publications being 64 articles (in 2021). Research publications related to the topic experienced a decline in 2022-2023 due to the global COVID-19 pandemic. The items that are very closely related to the topic have the keywords drug delivery system, treatment, cancer, and ligand. This bibliometric analysis is expected to help researchers identify research trends and recommend future research prospects.

1. Introduction

In recent years, dendrimers have emerged as a promising nano polymer tool for drug delivery and targeting. Dendrimers are mono-dispersed, three-dimensional, highly branched, macromolecular nanocarriers (1-100 nm) (Sohail *et al.*, 2020, Torabi Fard et al., 2022). Dendrimer has distinct advantages over other carrier molecules such as higher drug loading capacity, easy synthesis, high stability, specific functionality and great transdermal capability (Pedziwiatr-Werbicka *et al.*, 2019). Dendrimers have been effectively used to assist insoluble drug solubilization, diagnosis, as well as controlled and sustained transdermal drug delivery approaches for other non-medical purposes (Mendes *et al.*, 2017).

The poly(propyleneimine) dendrimer, commonly known as the PPI dendrimer, is one type of dendrimer that is the most frequently studied dendrimer with promising potential in the fields of biomedicine, drugs, and gene carriers (Pedziwiatr-Werbicka *et al.*, 2019). The term PPI dendrimer is used to refer to a group of dendrimers with a diaminobutane (DAB) center or an ethylene diamine (EDA) center with 1, 2, 3, 4, or 5 generations of propyleneimine molecules attached (Singh *et al*., 2021).

The surface of the PPI dendrimer is composed of cationic amine groups which can bind to a variety of negatively charged drug molecules via electrostatic forces (Kohli *et al.*, 2007). The drug molecule can be encapsulated non-covalently in the interior of the PPI dendrimer (Tripathi & Tripathi, 2019). The number of molecules adsorbed is affected by the size and shape of the drug molecule and the size and shape of the internal dendrimer cavities (Lisuzzo *et al.*, 2019; Pedziwiatr-Werbicka *et al.*, 2019). PPIs can form complexes with peptides, drugs, and nucleic acids, so PPIs are considered as promising carriers of biomolecules in vitro and in vivo (Merritt *et al.*, 2020). The dendrimer surface can be specially modified to increase the functionality and specificity of the dendrimer (Mignani *et al.*, 2020).

According to several studies, dendrimer surfaces can be designed specifically for the targeting of anticancer, anti-HIV, antibiotic, antibacterial, anti-inflammatory, and antitumor drugs (Chen *et al.*, 2021; Dib *et al.*, 2019; Kandi *et al.*, 2019; Namivandi-Zangeneh *et al.*, 2021; Singh *et al.*, 2021). Targeting and targeting efficiency can both be improved by engineering the dendrimer surface with biocompatible ligands (Pooresmaeil & Namazi, 2021). Ligand engineering, for example using folic acid on the dendrimer surface, can help deliver drugs to targets with low toxicity (Gupta *et al.*, 2010; Li *et al.*, 2022). Folic acid conjugates are anticipated to lessen toxicity brought on by cationic charges on dendrimers and target dendrimer conjugates to tumors more precisely (Fatima *et al.*, 2022; Gupta *et al.*, 2010).

Currently, various reports have been published on folic acid-conjugated PPI dendrimers and their application as nanocarriers for anticancer and antitumor drugs (Kaur *et al.*, 2017; Kesharwani *et al.*, 2015; Mandal, 2021; Thakur *et al.*, 2013). However, systematic reviews that provide information on research trends as well as topic mapping of folic acid-conjugated PPI dendrimers for targeted drug delivery are inadequate. Therefore, we conducted a bibliometric analysis using the VOSViewer application using literature related to PPI dendrimers and their application as a nanomedicine tool for targeted drug delivery.

Bibliometric analysis is used to derive quantitative analysis, obtaining distribution patterns of articles relating to a topic, field, author, institution, or country by developing objective criteria used to select, review, and track published research (Nandiyanto *et al.*, 2023; Ragadhita & Nandiyanto, 2021). VOSViewer analysis is very important in determining the quantity and current state of a topic (Nandiyanto *et al.*, 2021; Nandiyanto & Al Husaeni, 2022).

The aim of this study was to conduct a research bibliometric study of folic acid-conjugated PPI dendrimers using mapping analysis on the VOSViewer application. This study can provide information for researchers in considering and developing PPI dendrimer research, especially to see the prospects for this research in the future. This study examines the level of research development from 2018-2022), a list of articles based on Google Scholar Rank, as well as topic mapping (cluster analysis, network and

mapping) using 221 relevant journal articles. This article also reviewed future prospects related to folic acid-conjugated PPI dendrimer research.

2. Methods

Bibliometric analysis was carried out in three stages: data collection, data screening, and data analysis and visualization.

i. Data collection

Analysis of research trends was carried out using Publish or Perish 8 Software. Google Scholar was used to search and collect documents related to the topic. Google Scholar is used as a database for bibliometric analysis Due to the large user base of the free and openly available scientific article database. Google Scholar can be compared with two other expensive scientific article databases such as Web of Knowledge (edited by ISI/Thomson) and Scopus (developed by Elsevier) (Nandiyanto *et al.*, 2023).

Data was collected on April 25, 2023 with a publication period from 2018-2023 (5 years). The keywords used are 'dendrimer', 'PPI', 'folic acid', and 'drug delivery' with only journal articles are utilized as sources. The search results show a total of 221 relevant journal articles from 500 articles. The articles were then processed using Microsoft Excel software.

ii. Data screening

Journal articles that have been collected was then selected based on article's title, topic relevance, and year of publication. Articles having titles and publication dates unrelated to the criteria were discarded and not used. The selected data was then further processed using Microsoft Excel and VOSViewer.

iii. Data analysis and visualization

Using Microsoft Excel, the chosen data is prepared and sorted by year and Google Scholar Ranking (GSRank). Additionally, bibliometric analysis of the data was performed using VOSViewer. Article data was mapped and visualized based on network and density. More detailed information about the data analysis and visualization using VOSViewer and Publish or Perish has been described in our previous work (Fitria *et al.*, 2021).

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3. Results and Dicussions

3.1 Research Development on the Topic of Dendrimer Poly(propyleneimine) Conjugated Folic Acid for Targeted Drug Delivery

Figure 1 shows the quantity of relevant articles over the previous five years (2018-2023) was shown in Figure 1. The total number of research publications related to the topic has increased from 2018 to 2021. The rice in research publication number demonstrates the interest among scientists in developing a folic acid-conjugated PPI dendrimer as a drug substance. The highest number of publications was obtained in 2021 with a total of 64 journal articles.

The number of research publications on the subject declined between 2022 and 2023. The worldwide COVID-19 epidemic is the root reason of this drop in publications. The COVID-19 pandemic has had a considerable impact on laboratory access, raw material distribution for synthesis, and the implementation of strict regulations for physical distancing (Durant et al., 2020).

After processing, journal articles are arranged according to Google Scholar Ranking (GSRank). This score is determined by how closely journal articles match the search terms used in the dataset. Based on Table 1, the three journal articles with the highest GSRanks were published in the journals European Polymer Journal, International Journal of Pharmaceutics, and Journal of Materials Chemistry B.

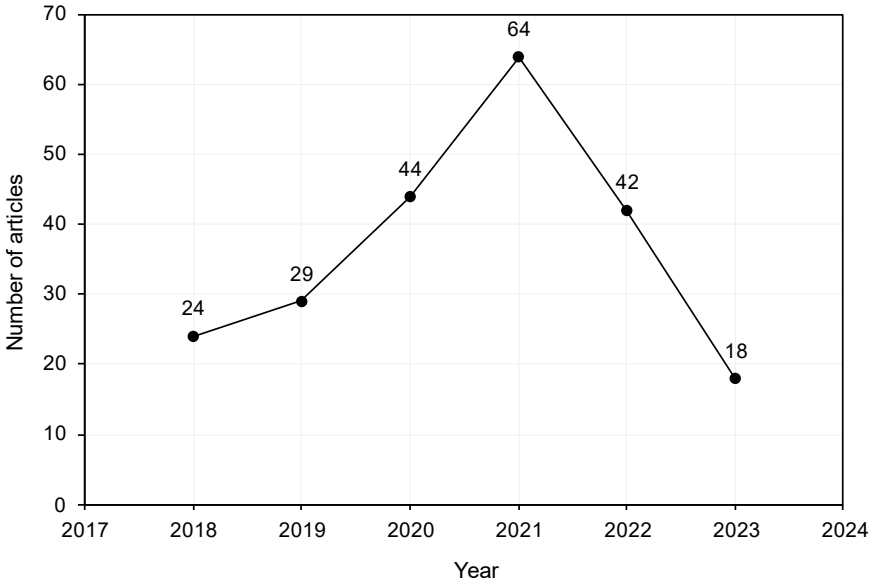

Figure 1. Research development of folic acid-conjugated PPI dendrimers for drug delivery.

Table 1. List of articles based on GSRank.

GSRank	Author	Year	Title	Journal	Citations
1	V Singh, A Sahebkar, P Kesharwani	2021	Poly (propylene imine) dendrimer as an emerging polymeric nanocarrier for anticancer drug and gene delivery	European Polymer Journal	51
2	AP Sherje, M Jadhav, BR Dravyakar, D Kadam	2018	Dendrimers: A versatile nanocarrier for drug delivery and targeting	International Journal of Pharmaceutics	213
3	SR Barman, A Nain, S Jain, N Punjabi, S Mukherji, J Satija	2018	Dendrimer as a multifunctional capping agent for metal nanoparticles for use in bioimaging, drug delivery and sensor applications	Journal of Materials Chemistry B	58
4	M Fatima, A Sheikh, N Hasan, A Sahebkar, Y	2022	Folic acid conjugated poly (amidoamine) dendrimer as a smart nanocarriers for tracing, imaging, and	European Polymer Journal	22

GSRank	Author	Year	Title	Journal	Citations
	Riadi, P Kesharwani		treating cancers over-expressing folate receptors		
5	RS Ambekar, M Choudhary, B Kandasubramanian	2020	Recent advances in dendrimer-based nanoplatform for cancer treatment: A review	European Polymer Journal	72
6	M Pooresmaeil, H Namazi	2021	Advances in development of the dendrimers having natural saccharides in their structure for efficient and controlled drug delivery applications	European Polymer Journal	37
7	JK Patra, G Das, LF Fraceto, MDP Rodriguez-Torres, LS Acosta-Torres, LA Diaz-Torres, R Grillo, MK Swamy, S Sharma, S Habtemariam, HS Shin	2018	Nano based drug delivery systems: recent developments and future prospects	Journal of Nanobiotechnology	3368
8	AK Mandal	2021	Dendrimers in targeted drug delivery applications: A review of diseases and cancer	International Journal of Polymeric Materials and Polymeric Biomaterials	44
9	P Tagde, GT Kulkarni, DK Mishra, P Kesharwani	2020	Recent advances in folic acid engineered nanocarriers for treatment of breast cancer	Journal of Drug Delivery Science and Technology	48
10	V Arora, MAS Abourehab, G ModI, P Kesharwani	2022	Dendrimers as prospective nanocarrier for targeted delivery against lung cancer	European Polymer Journal	13
11	MR Carvalho, RL Reis, JM Oliveira	2020	Dendrimer nanoparticles for colorectal cancer applications	Journal of Materials Chemistry B	62
12	AP Dias, S da Silva Santos, JV da Silva, R Parise-Filhom, E Igne Ferreira, OE Seoud, J Giarolla	2020	Dendrimers in the context of nanomedicine	International Journal of Pharmaceutics	127

GSRank	Author	Year	Title	Journal	Citations
13	S Hossen, MK Hossain, MK Basher, MNH Mia, MT Rahman, MJ Uddin	2019	Smart nanocarrier-based drug delivery systems for cancer therapy and toxicity studies: A review	Journal of Advanced Research	624
14	M Nikzamir, Y Hanifehpour, A Akbarzadeh, Y Panahi	2021	Applications of dendrimers in nanomedicine and drug delivery: a review	Journal of Inorganic and Organometallic Polymers and Materials	46
15	AS Chauhan, M Kaul	2018	Engineering of “critical nanoscale design parameters”(CNDPs) in PAMAM dendrimer nanoparticles for drug delivery applications	Journal of Nanoparticle Research	10
16	F Najafi, M Salami-Kalajahi, H Roghani-Mamaqani	2020	Synthesis of amphiphilic Janus dendrimer and its application in improvement of hydrophobic drugs solubility in aqueous media	European Polymer Journal	21
17	J Wang, B Li, L Qiu, X Qiao, H Yang	2022	Dendrimer-based drug delivery systems: history, challenges, and latest developments	Journal of Biological Engineering	16
18	V Singh, P Kesharwani	2021	Dendrimer as a promising nanocarrier for the delivery of doxorubicin as an anticancer therapeutics	Journal of Biomaterials Science, Polymer Edition	24
19	BF Grześkowiak, D Maziukiewicz, A Kozłowska, A Kertmen, E Coy, R Mrówczyński	2021	Polyamidoamine dendrimers decorated multifunctional polydopamine nanoparticles for targeted chemo-and photothermal therapy of liver cancer model	Journal of Biomaterials Science, Polymer Edition	9
20	X Yan, Y Yang, Y Sun	2021	Dendrimer applications for cancer therapies	Journal of Physics: Conference Series	7

3.2 VOSViewer Visualization on the Topic of Conjugated Folic Acid Dendrimer Poly(propyleneimine) for Targeted Drug Delivery

Based on the VOSViewer mapping analysis, the studies relevant to the topic can be divided into 4 clusters:

i. Cluster 1 is marked by a red color containing 11 items, namely antibody, aptamer, drug release, formulation, gene delivery, generation, group, ligand, nanomedicine, peptide, and polymer.

ii. Cluster 2 marked by green color contains 8 items, namely biomedical applications, carbosilane dendrimers, cells, dendrimers, drug delivery applications, properties, synthesis, and targeted delivery.

iii. Cluster 3 marked in blue contains 7 items, namely cancer, diagnosis, folate receptor, nanotechnology, polypropyleneimine, recent advances, and treatment.

iv. Cluster 4 is marked by a yellow color containing 3 items, namely drug delivery system, liposome, and micelle.

3.3 VOSViewer Network Visualization on the Topic of Folic Conjugated Folic Acid Dendrimer Poly(propyleneimine) for Targeted Drug Delivery

The relationship between items in the four clusters is illustrated in the network visualization shown in Figure 2. The lines that link one item to another depict their connection and proximity. Table 2 displays the total strength of the association between the items and the frequency of occurrence of the items.

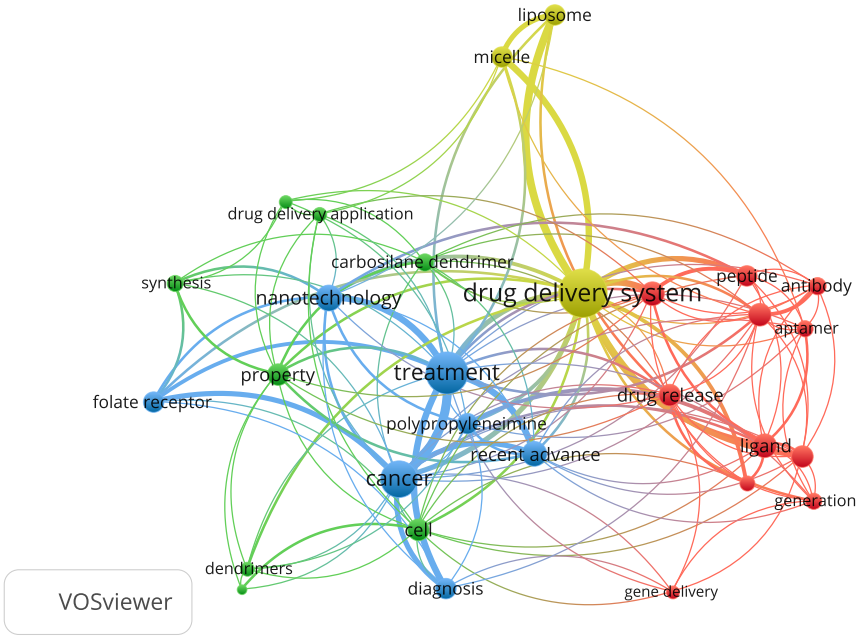

Figure 2. Network visualization on the topic of folic acid-conjugated PPI dendrimers for targeted drug delivery.

Table 2. The strength and frequency of occurrence of the term.

Cluster	Total strength	Occurrence
Cluster 1	157	114
Cluster 2	84	71
Cluster 3	181	94
Cluster 4	94	66

3.4 VOSViewer Density Mapping on Conjugated Folic Acid Dendrimer Poly(propyleneimine) Topics for Drug Delivery

Figure 3 shows density mapping of the topic. The items closest to the topic are those with a strong yellow background. Items in green, meanwhile, show that they are not closely related to one another. The topics of folic acid-conjugated PPI dendrimers for drug delivery and treatment, cancer, and ligands had the strongest correlations.

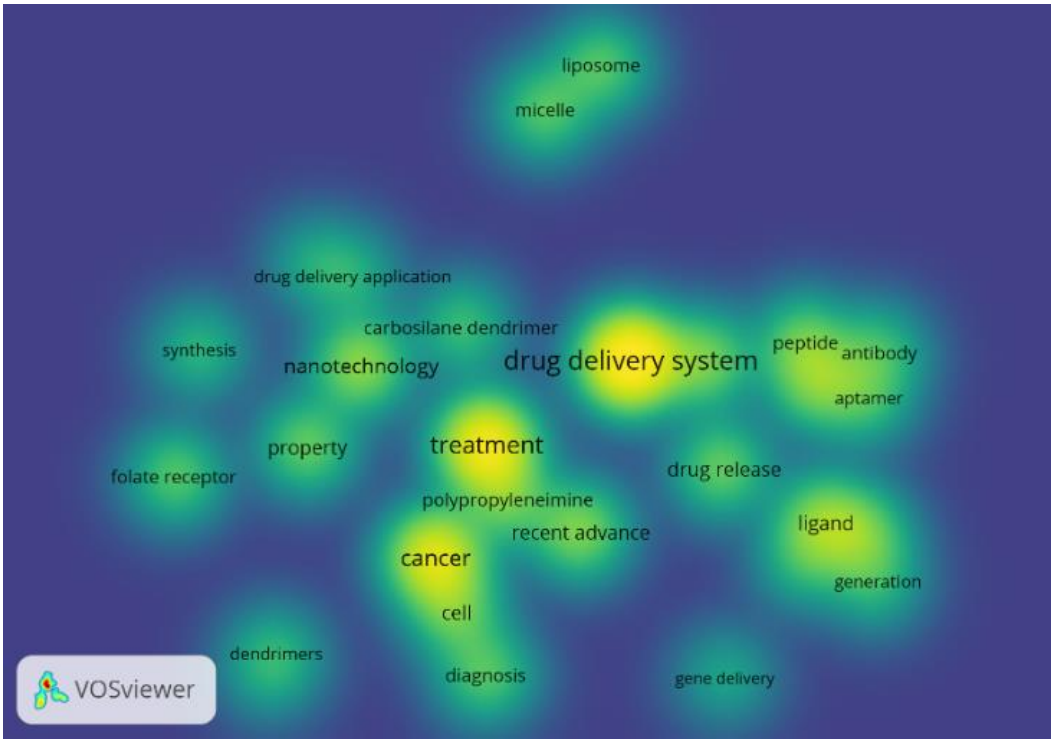

Figure 3. Density map of folic acid-conjugated PPI dendrimer for drug targeted delivery topic.

4. Conclusion

Bibliometric analysis and mapping of journal articles related to the topic of folic acid-conjugated PPI dendrimers for drug delivery in 2018-2023 have been carried out with the results of 221 relevant journals. The number of research publications increased between 2018 and 2021, showing a high level of interest in the subject among scientists. The highest number of publications was obtained in 2021 with a total of 64 journal articles. From 2022 to 2023, research publications related to the topic have decreased due to the global COVID-19 pandemic. The items that are very closely related to the topic are located in clusters 3 and 4 with the keywords drug delivery system, treatment, cancer, and ligand. It is hoped that this bibliometric analysis can be used as an objective consideration for selecting, assessing, and tracking research studies of folic acid-conjugated PPI dendrimers for drug delivery.

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