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Analyzing the Potential of Herbal Plant Research for Alzheimer's Disease in Diabetes: A Bibliometric Approach

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ABSTRACT

Alzheimer's disease is a progressive neurologic dementia disorder and the fifth leading cause of death among elderly individuals. Its pathogenesis is closely linked to diabetes-induced brain insulin resistance, which accelerates beta-amyloid accumulation, exacerbating disease severity. This condition significantly impacts quality of life and healthcare costs, necessitating effective treatment strategies. Medicinal plants offer a promising avenue, with bibliometric analysis identifying trending active compounds for potential development as therapies for diabetic Alzheimer's. This study analyzed 200 articles from the Scopus database, employing Scopus and VOSviewer 1.6.20 to visualize bibliometric trends by publication, country/territory, subject area, and keyword co-occurrence. Results indicate a recent decline in research activity, with China leading in publications across pharmacology, medicine, and biochemistry. Notably, flavonoids like "quercetin," "kaempferol," and "gallic acid" emerged as prominent topics.
Keywords: Alzheimer's diabetes; Bibliometrics; Herbal medicine; Extracts

INTRODUCTION

The World Health Organization (WHO) reports that approximately 55 million people worldwide have dementia, with 40 million of these cases being Alzheimer's disease. The prevalence of Alzheimer's is projected to rise to 78 million by 2030 and to 139 million by 2050. In Indonesia, the prevalence of Alzheimer's dementia is significantly higher, reaching approximately 27.9%, with the highest rates occurring in Java and Bali (Directorate General of Health Services KEMENKES, 2023).

Type 2 diabetes has a strong association with Alzheimer's. Alzheimer's disease, characterized as a progressive neurological disorder and the most prevalent form of dementia worldwide, affects over 10 million individuals and ranks as the fifth leading cause of death among the elderly population (John et al., 2022). The incidence of Alzheimer's has grown significantly alongside the rising number of diabetic patients, posing a significant public health challenge in recent years.

The pathophysiology of Alzheimer's disease involves the gradual accumulation of amyloid beta peptide (Aβ), leading to hyperphosphorylation of tau proteins and the formation of neurofibrillary tangles, which contribute to brain degeneration and atrophy. Additionally, alterations in glucose metabolism and insulin signaling in the brain indicate insulin resistance among Alzheimer's patients (Hamzé et al., 2022). Studies have highlighted hyperglycemia as a potential risk factor for Alzheimer's development, linking it to increased beta amyloid accumulation, heightened oxidative stress, neuroinflammation, and neurodegeneration (Lee et al., 2018., Chatterjee & Mudher, 2018).

Medicinal plants have historically been utilized across various medical systems to treat diverse ailments, and their popularity as an alternative to conventional therapies is rising. Research on herbal medicine for Alzheimer's and diabetes, however, remains fragmented and lacks cohesion, necessitating integrative analysis methods such as bibliometrics. Jallow et al., (2024) identified 120 relevant English-language publications across 19 journals, with the Journal of Alzheimer's Disease being the most prominent.

Bibliometrics, as described by Hawkins, offers a quantitative assessment of bibliographic attributes in literature (Kokol et al., 2021). Its application is increasingly prevalent in medical research, yet a comprehensive bibliometric analysis specific to Alzheimer's and diabetes remains lacking (Meng et al., 2024). This study aims to elucidate evolving research trends in effective herbal therapies for diabetic Alzheimer's, potentially identifying novel research avenues and fostering interdisciplinary collaboration to address global health challenges.

METHODS

To ensure high-quality research data, in June 2024, a selection of English articles from the internationally recognized Scopus database (www.scopus.com) was conducted using the keywords: (Herbal AND medicine OR Extract AND Alzheimer's AND Diabetic OR Hyperglycemia). A total of 327 articles were found and screened based on their titles and abstracts, adhering to the inclusion criteria of research articles published in the last five years (2020-2024). From this screening, 200 articles were selected. These articles were downloaded and analyzed for keyword information using Zotero. Subsequently, a bibliometric analysis was conducted using Scopus to analyze relevant publication trends and distribution based on country/territory and subject area. The VOSviewer 1.6.20 application was then employed to visualize the data obtained based on keyword co-occurrence.

RESULTS AND DISCUSSION

Diabetes mellitus can exacerbate or precipitate Alzheimer's disease through mechanisms such as insulin resistance, metabolic dysfunction, inflammation, and oxidative stress. Insulin regulates blood sugar levels throughout the body, including the brain. Insulin resistance in the brain leads to impaired cognitive function, characterized by the formation of beta-amyloid plaques and neurofibrillary tangles, which are the hallmark features of Alzheimer's disease. Chronic inflammation and oxidative stress further accelerate neurodegeneration by increasing the production of beta-amyloid and tau proteins, closely linked to the onset of plaques and tangles in Alzheimer's disease. Herbal medicines or plant extracts are rich in antioxidant, anti-inflammatory, antidiabetic, and neuroprotective compounds that show potential in improving the condition of Alzheimer's disease.

Scopus analysis results illustrate publication trends over the past five years (Figure 1). The year 2021 saw the highest number of publications, with a total of 53 documents. However, the subsequent three years exhibited a downward trend. As of June 13, 2024, 27 documents had been submitted, with this number expected to increase by the end of the year.

The use of herbal medicines or extracts for the treatment of Alzheimer's diabetes has been extensively researched across various countries. Based on Figure 3, China leads this field with a total of 59 publications, followed by India with 48 publications. This prominence is due to several factors, including historical and cultural influences, a diverse array of plant resources, governmental and financial support, market demand, and international collaborations. China has a rich tradition of Traditional Chinese Medicine (TCM), while India has long practiced Ayurveda and Unani medicine (Verma & Singh, 2008; Wu et al., 2021; Musa et al., 2023).

Indonesia, however, did not make it into the top 10, with only two publications. Among ASEAN countries, Indonesia ranks third, following Malaysia (6 publications) and Vietnam (3 publications). The two Indonesian publications are an article titled "Effect of *Garcinia mangostana Pericarp* Extract on Glial NF-κB Levels and Expression of Serum Inflammation Markers in an Obese-Type 2 Diabetes Mellitus Animal Model" (Muniroh et al., 2021) and a review titled "Potential Pharmacokinetics and Pharmacodynamics (PK-PD) Drug-Herbs Interactions (DHI) from Metformin and Traditional Medicines" (Pramesthi et al., 2022).

Research on herbal medicines or extracts for the treatment of Alzheimer's disease and diabetes is concentrated in three primary subject areas: pharmacology, toxicology, and pharmaceutics (31.5%); medicine (19.2%); and biochemistry, genetics, and molecular biology (16.2%) (Figure 4). The subsequent ranks, with a percentage of 8.4%, are occupied by agricultural and biological sciences and chemistry. Agricultural and biological sciences emphasize research on plant benefits and extraction methods (Fan et al., 2023; Liu et al., 2024; Ntemafack et al., 2023). Chemistry, on the other hand, focuses more on chemical profiling using LC-MS instruments or in silico research (Astuti et al., 2021, 2021; Bai et al., 2024; Güven et al., 2024; Guven et al., 2023).

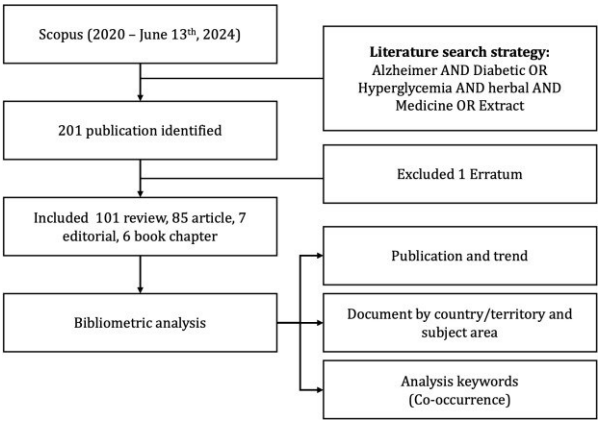


Figure 1. Flow chart of literature search and bibliometric analysis

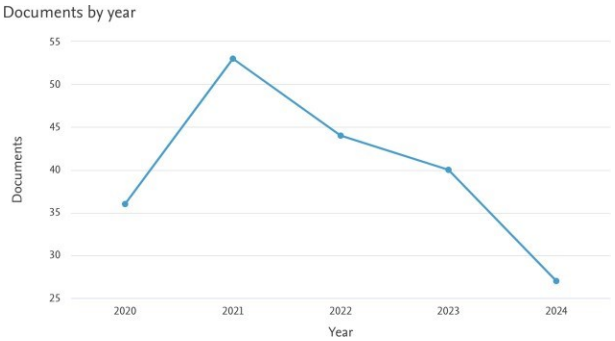


Figure 2. Publication and trend data for the last 5 years based on Scopus analyze results

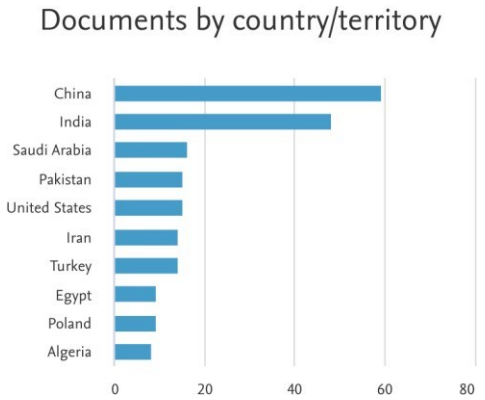


Figure 3. Document by country/territory for the last 5 years based on Scopust analyze result

Bibliometric analysis using VOSviewer, through a keyword analysis approach, provides an overview of the development and ongoing studies on herbal medicines or extracts that have the potential to improve the condition of Alzheimer's disease caused by diabetes. From the 200 articles reviewed, a total of 5521 keywords were identified. A minimum threshold of 16 occurrences was applied to obtain meaningful results, resulting in 151 keywords. After excluding unrelated keywords, 96 keywords were ultimately included in the analysis.

Network visualization or network analysis (Figure 5) illustrates the relationships between the obtained keywords. Based on this analysis, four clusters were identified, each marked with a different

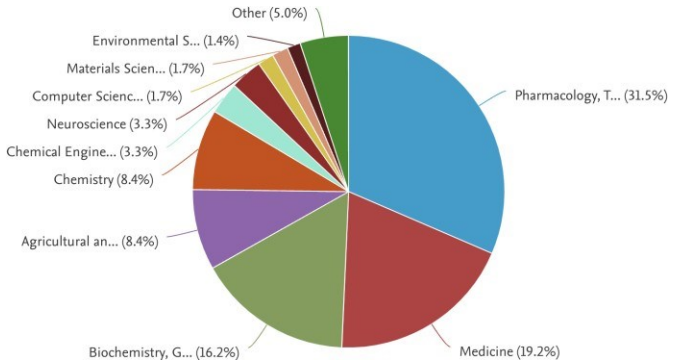


Figure 4. Document by subject area for the last 5 years based on Scopust analyze result

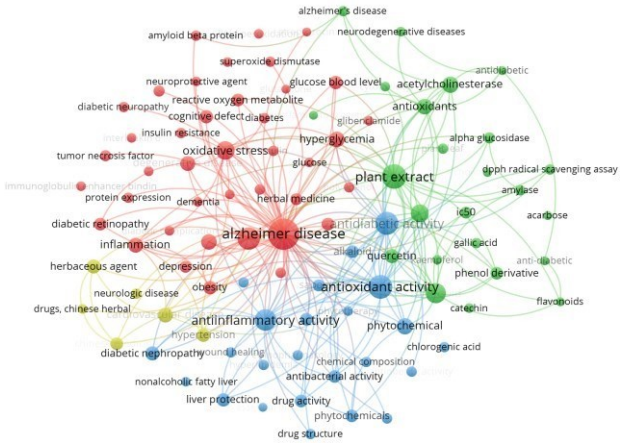


Figure 5. Network Visualization of Keyword Analysis of 200 articles

color. The naming of clusters in the network is based on the most dominant keywords, indicated by larger node sizes. The clusters are as follows: first, the red cluster, labeled “Alzheimer’s disease,” indicates a close relationship between diabetes, oxidative stress, inflammation, and Alzheimer’s disease. Second, the green cluster, labeled “plant extract,” focuses on plant compounds that can improve Alzheimer’s disease. Third, the blue cluster, with three main keywords: “antioxidant activity,” “anti-inflammation activity,” and “antidiabetic activity,” links all three to Alzheimer’s disease. Fourth, the yellow cluster highlights the relationship between “cardiovascular disease” and Alzheimer’s disease.

The interpretation of the relationship between variables in different clusters is based on the connecting lines between clusters. Variables with thick nodes and short distances indicate a strong relationship between their words. For example, in Figure 6, when focusing on the keyword “plant extract,” the bibliometric results show that the compounds “quercetin,” “flavonoids,” and “phenol derivatives” have pharmacological effects such as “antioxidant activity,” “anti-inflammatory activity,” and “antidiabetic activity.” These effects can potentially improve Alzheimer’s disease caused by diabetes (Adem et al., 2024).

Overlay visualization of 200 articles from the last five years (Figure 7) reveals the temporal trend of different keywords connected in the research. The color coding represents the publication year, with blue indicating earlier publications (2021) and yellow indicating more recent publications (2022). Keywords such as "Alzheimer's disease," "plant extract," "anti-inflammatory activity," and "antioxidant activity" are shown in darker colors, indicating these studies were commonly conducted before 2022. In contrast, keywords like "quercetin," "acetylcholinesterase," and "gallic acid" are shown in lighter colors, highlighting increased attention to these topics in more recent years.

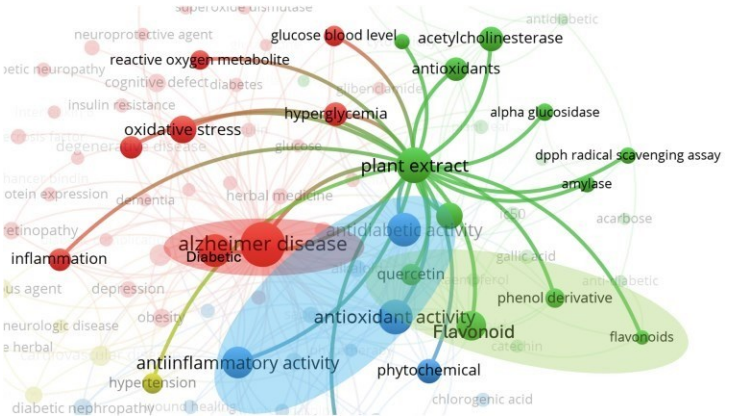


Figure 6. Relationship between variables in different cluster

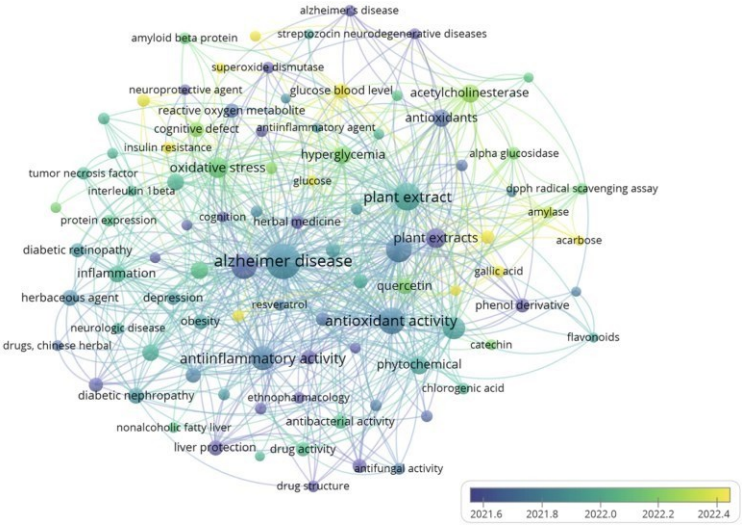
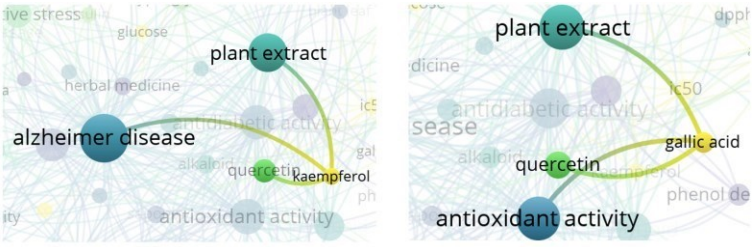


Figure 7. Overlay Visualization of Keyword Analysis for the Last 5 Years



(a) (b)

Figure 8. Potential future research based on overlay visualization analysis. Potential research development on variables (a) "kaempferol", (b) "gallic acid" and "quercetin"

The mapping conducted in the overlay visualization analysis highlights the potential for future research based on past trends. As shown in Figure 8 (a), there is a growing research interest in the compound "kaempferol" found in plant extracts for the treatment of "Alzheimer's disease." Additionally, Figure 8 (b) indicates that the compounds "gallic acid" and "quercetin" in plant extracts have significant potential for "antioxidant activity." Brighter and smaller nodes represent variables with substantial potential for future research.

Table I. The Most Researched Active Compounds

Keywords	Occurrences
flavonoid	56
quercetin	30
alkaloid	24
phenol derivative	22
saponin	20
curcumin	17
resveratrol	16
polyphenol	15
gallic acid	15
kaempferol	14

Based on the analysis of 96 inclusion keywords, certain limitations were identified that hindered the identification of the most researched herbal plants in studies conducted over the past five years. However, the potential of herbal plants is represented by the ten most frequently researched active compounds. Expanding studies to include a larger number of keywords could enhance the likelihood of discovering additional herbal plants with potential therapeutic benefits for Alzheimer's diabetes.

Table presents the results of bibliometric analysis focusing on the top 10 most studied active compounds over the past five years for treating Alzheimer's disease in diabetic patients. The compound "flavonoids" ranks highest with 56 occurrences, indicating its predominant use in therapy for diabetic Alzheimer's. Momina and Gandla (2023) demonstrated that the *Alterna pungen* fraction, rich in flavonoids, improves memory dysfunction induced by hyperglycemia in diabetic rats.

Table highlights an intriguing trend where "quercetin," "gallic acid," and "kaempferol," identified as emerging keywords in 2022 based on data from Figure and Figure , are featured among the top 10 most studied compounds. This suggests increasing research focus on these compounds as novel therapeutic avenues. Recent studies employing LC-MS/MS for phytochemical profiling of *Onobrysis argyrea* extracts have identified quercetin, gallic acid, and kaempferol, known for their antioxidant, antidiabetic, and Alzheimer's disease-related activities (Yeniçeri et al., 2024). Additionally, Türkan et al., (2020) investigated secondary metabolites in *Achillea schischkinii* plants, revealing the presence of gallic acid and quercetin with potent antioxidant properties, capable of inhibiting enzymes involved in diabetic Alzheimer's disease formation.

CONCLUSION

Bibliometric analysis of diabetic Alzheimer's disease reveals substantial progress and serves as a crucial knowledge source for future researchers. This analysis utilizes data on herbal treatments for diabetic Alzheimer's to explore extensively researched herbs and those that warrant further investigation. The findings indicate a recent decline in research trends over the past five years, with China and India leading in publication contributions. Research is predominantly concentrated in pharmacology, toxicology, and pharmaceutics (31.5%), followed by medicine (19.2%) and biochemistry, genetics, and molecular biology (16.2%). Co-occurrence analysis highlights flavonoid compounds as the most studied, with an emerging focus on specific compounds like "quercetin," "kaempferol," and "gallic acid." These insights aim to support future investigations into herbal remedies that mitigate the long-term effects of diabetic Alzheimer's and enhance recovery and life expectancy among diabetic patients affected by Alzheimer's disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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