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A bibliometric analysis of preclinical trials of *Andrographis paniculata* (Burm.f.) Nees in diabetes mellitus

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ABSTRACT

The prevalence of diabetes mellitus has increased over time. Medicinal plants, including *Andrographis paniculata* (Burm.f) Nees, are recognized for their use to manage hyperglycemia. Nowadays, plenty of papers are published about *A. paniculata* as an antidiabetic; however, no bibliometric study about the topic exists. This study examines the existing papers about the preclinical trial of *A. paniculata* as an antidiabetic agent using bibliometric analysis focusing on countries, institutions, publishers, authors, documents, and keywords. Bibliographic information of relevant research and conference articles were obtained from the Scopus database. In total, 97 articles published between 1994 and 2021 were selected, covering 376 authors and 1270 keywords. Data were analyzed bibliometrically using Vosviewer 1.6.16. A total of 97 published papers occurred from 1994 to 2021 were selected. India, Universitas Gadjah Mada (Indonesia), Journal of Ethnopharmacology, and Agung Endro Nugroho (Universitas Gadjah Mada, Indonesia) were the most productive country, institution, publisher, and author, respectively. The analysis of the most influential papers, co-citation network of the most influential papers, bibliographical coupling network based on authors, and keyword co-occurrence network and overlay demonstrated that the abundance and variety of existing papers about preclinical trials of *A. paniculata* as an antidiabetic were from phytochemistry, pharmacology, and drug formulation. The findings of our analysis have implications for managerial and theoretical aspects on this topic, such as encouraging research collaborations by analyzing the contributions of countries, institutions, publishers, and authors and revealing research gaps (molecular mechanisms, toxicities and side effects, drug formulations, and clinical trials) to accept a phytomedicine as a therapeutic option.

1. Introduction

Lifestyle habits, including an unhealthy diet, inadequate exercise, smoking, and alcohol consumption are rapidly rising and contributing to diabetes mellitus (DM) (Khaltaev and Axelrod, 2021). DM manifests as hyperglycemia due to insufficient insulin production, lack of insulin uptake, or both (Zhang et al., 2018). Its conditions can promote micro- and macrovascular complications mainly in several organs, including the eyes, kidneys, heart, feet, and nerves (Ezhilarasi et al., 2018). The prevalence of DM has consistently risen over time and the cases quadrupled from 108 million to 422 million from 1980 to 2014, along with a percentage increase from 4.7 to 8.5% in the adult population (Ampofo and Boateng, 2020). In 2030, the prevalence of DM was predicted at approximately 25.3% (range, 18.3–32.6%) (Ampofo and Boateng, 2020). DM and its complications lead to multiple organ dysfunctions so that preventive and curative approaches to the disease are still required, including those from natural compounds (Rohman et al., 2020).

Nowadays, many natural compounds control DM patients (Widjajakusuma et al., 2019; Yeung et al., 2020). *Andrographis paniculata* (Burm.f.) Nees is one of the promising plants as a natural source to lower blood glucose (Augustine et al., 2014). The species is a herbaceous plant belonging to the Acanthaceae family and intensively cultivated in some countries including China, India, Indonesia, Thailand, the West Indies, Mauritius, and Malaysia (Valdiani et al., 2012). The plant is traditionally used to treat various diseases in communities, such as diabetes, hypertension, malaria, fever, pain, cough, gastritis,

List of abbreviations: AC, average number of citations per publication; AP-1, activator protein 1; DM, diabetes mellitus; DPP-IV, dipeptidyl peptidase-IV; NF-κB, nuclear factor-κB; PDX-1, pancreatic and duodenal homeobox 1; PI3K, phosphatidylinositol 3′-kinase; PTP-1B, protein tyrosine phosphatase 1B; STZ, streptozotocin; Th, T helper cell; Vosviewer, visualization of similarities viewer.

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an antidote, dermatological ailments, jaundice, muscle pain, wound, rashes, and others (Budiarti et al., 2020; Inta et al., 2013; Mardisiswojo and Rajakmangunsudarso, 1987; Pandikumar et al., 2011). In Indonesia, the herbal recipe suggests washing a half handful of *A. paniculata* leaves boiling in 600 cc water until 75% remains, waiting until cold part, and drinking 2–3 times a day after a meal (Mardisiswojo and Rajakmangunsudarso, 1987). Recently, preclinical studies of *A. paniculata* are not only focused on lowering glucose levels but also elucidating its antidiabetic mechanisms of action, including glucose uptake through the activation of insulin receptor substrate-1 and phosphatidylinositol 3′-kinase (PI3K) pathways (Jin et al., 2011), PI3K/Akt pathway (Lu et al., 2011), activation of peroxisome proliferator-activated receptor-γ (Jin et al., 2012), translocation of glucose transporters-4, and others (Arha et al., 2015; Nugroho et al., 2011).

Recently, several preclinical scientific publications of *A. paniculata* are being used to treat diabetes, including several literature reviews of the topic; however, no bibliometric studies focusing on the antidiabetic action of *A. paniculata*. A similar bibliometric study of *A. paniculata* has been published but focuses on global publications during 2003–2018 (Gupta et al., 2019). Therefore, a comprehensive bibliometric analysis on *A. paniculata* must be performed to understand scholarly preclinical studies of DM to determine the future direction of research progress. Bibliometric analysis is used to recognize a backbone in a citation about mapping knowledge over time, such as to assess studies of published literature quantitatively to describe and evaluate the results, authors, institutions, and journals published within specific areas of knowledge, and subsequently analyze the dissemination of knowledge within topic areas (Elisha and Viljoen, 2021; Melo et al., 2021; Rodríguez-Rojas et al., 2019).

Findings from the bibliometric analysis provide significant contributions to the existing literature, play fundamental roles in decision making regarding policy formations, assist funding agencies and policymakers in decisions on the prioritization of funding, the direction of future trends, and collaboration opportunities with other institutions (Elisha and Viljoen, 2021; Musa et al., 2021). This information makes it possible to understand the publication trends and potential future applications of *A. paniculata* as an antidiabetic based on available information. The present study provides a quantitative overview of the scientific literature, frequently investigated *A. paniculata* as an antidiabetic to shed light and correlate the previous research on this plant. It will update suggestions for further research directions.

2. Materials and methods

2.1. Data sources

Literature data about *A. paniculata* as an antidiabetic were extracted from the Scopus database because it has a wide coverage of scientific literature and is a more comprehensive and extensive database, including the Web of Science (Bamel et al., 2020; Khitous et al., 2020). Moreover, Google Scholar was not used because it does not provide detailed information demanded by network analysis, like the bibliometric approach (Bamel et al., 2020). We searched the Scopus database using the following keywords: "*Andrographis paniculata*" OR andrographolide AND diabet* OR "diabetes mellitus" OR dm OR insulin OR glucose. The searched scientific literature contained any of these keywords, terms, or phrases in their title, abstract, or keywords. Full texts that met the eligibility criteria from the inclusion and exclusion requirements would be analyzed. The inclusion criteria included literature from the Scopus database, original articles or conference papers, the use of the English language only, and preclinical trials of *A. paniculata* as antidiabetic terms. Scientific literature with the following requirement was excluded, *i.e.*, irrelevant terms such as diagnosis, public policy, risk factor, epidemiology, and other terms (extraction process, analytical methods, and others), least and biased information, unavailable full-text, and repetitions.

Toxicological issues also assessed in this study. We searched the Scopus database using the following keywords: "*Andrographis paniculata*" AND toxicity OR toxicology OR "adverse effect" OR "side effect". The inclusion criteria included literature from the Scopus database, original articles or conference papers, the use of the English language only, and toxicological assessments terms. The exclusion criteria included inadequate information or articles without full-text and studies with similar topic meanwhile were older than other studies. Additionally, the structures of important identified phytochemical compounds were drawn using MarvinSketch.

2.2. Data extraction and analysis

Data extraction and analysis were defined the research scope and generated the papers to be used as subsequent inputs, which are described in Fig. 1. Then, the eligible literature collected from the database was saved as the ".CSV" and exported to the visualization of similarities viewer (Vosviewer) 1.6.16 for further bibliometric analysis (van Eck and Waltman, 2020). The following parameters were assessed for the results, including publication trends, analysis of contributing countries, analysis of contributing institutions, analysis of contributing publishers, analysis of authors and their bibliographical coupling network, analysis of the most influential paper and their co-citation network, keyword co-occurrence network and overlay, and toxicological aspects.

2.3. Term map

VOSviewer software extracted and analyzed the words that appeared in the title, abstract, and keywords of eligible literature, then visualized the results as bubble maps that represented a term or phrase (Yeung et al., 2018). The manual inspection was conducted to exclude generic or irrelevant terms (Yeung et al., 2018). The bubble size indicated the number of words that appeared in the literature. The bubble color indicated the citations per publication containing the term and the proximity of two bubbles if two terms co-appeared more frequently (Yeung et al., 2020, 2018).

3. Results

3.1. Publication trends

Up to the date that the data were collected and screened on June 10, 2021, for preparing our bibliometric analysis, 97 research and conference papers had been published from 1994 to 2021 about preclinical trials of *A. paniculata* as an antidiabetic that included 75 publishers and 376 authors. Fig. 2 shows the trends of the number of publications every year. The oldest document was published in 1994 in the *Bangladesh Medical Research Council Bulletin* about the hypoglycemic test in non-diabetic rabbits (Borhanuddin et al., 1994). The number of publications rose and fell in subsequent years. Then, the largest number of publications occurred in 2020, when 10 studies were published. Before 2000, the number of publications per year on the topic was very low and reported preliminary studies of antidiabetic effects in rats.

A summary of preclinical trials of *A. paniculata* on antidiabetic research can be found in Table S1. From 2000 to 2005, supporting evidence was provided from *in vitro*, and *in vivo* experiments of aqueous extract, ethanolic extract, and andrographolide using myoblast C2C12 cells and streptozotocin (STZ) as an inductor of DM elucidated the mechanisms related to antioxidants, increased glucose metabolism, and enhanced glucose uptake. From 2006 through 2010, 19 papers discussed aqueous, ethanolic, chloroform, and methanolic extracts, combined with other plant extracts, phytochemical

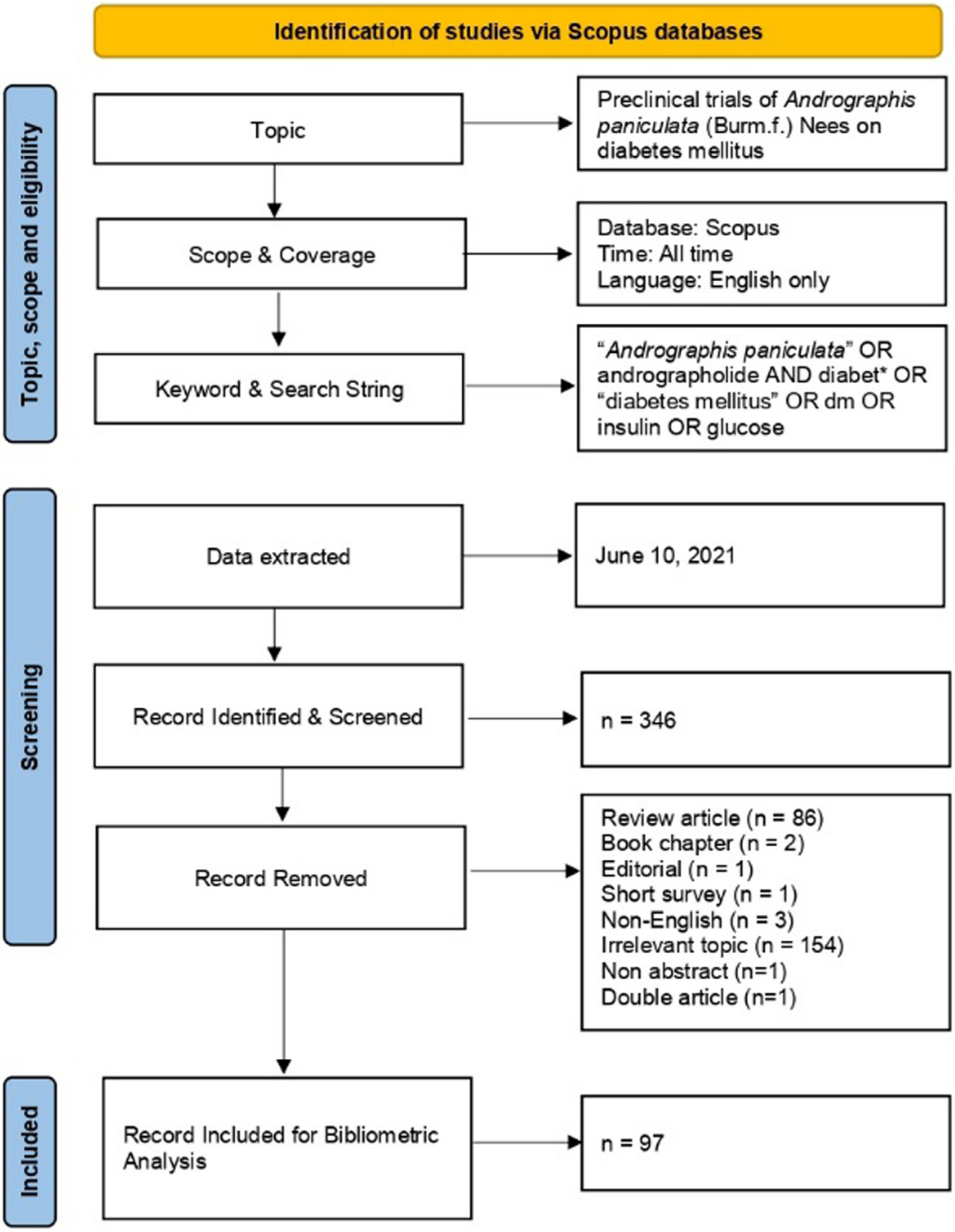

Fig. 1. Flow diagram of the search strategy.

compounds (andrographolide and 14-deoxy-11,12- didehydroandrographolide in the Fig. 3), and andrographolide analogs. Several pharmacological models to test antidiabetic effects were used. For instance, *in vitro* BRIN-BD11 cells, MES-13 cells, RIN-m cells, and α-amylase and α-glucosidase assays were used, also *in vivo* diabetogenic agents (STZ, alloxan, and a combination of STZ-nicotinamide) and the combination of a high-fat diet and STZ. Several mechanisms were elucidated, including inhibiting glucose absorption, inhibiting hepatic gluconeogenesis and lipogenesis, inhibiting nuclear factor-κB (NF-κB), antioxidants, repairing endothelial dysfunction, inhibiting apoptosis related to diabetic nephropathy, also antidiabetic mechanisms related to the reproductive system in women. However, many published papers did not study molecular mechanisms.

From 2011 to 2015, the total number of papers was dramatically higher than the previous period, *i.e.*, 33 documents. The plants were tested in the form of extracts, such as ethanolic, aqueous, methanolic, and ethyl acetate extracts, combined with other plant extracts, various fractions of ethanolic extracts, water-soluble polysaccharides, flavonoid fractions, phytochemicals compounds (andrographolide, deoxyandrographolide, and 5,2-dihydroxy-7-methoxyflavanone in the Fig. 3), moreover, andrographolide derivative to enhance the efficacy of andrographolide. This period had *in silico, in vitro*, and *in vivo* studies. *In silico* studies used molecular docking, whereas *in vitro* studies using cell lines (3T3-L1 cells, L6 cells, mesangial cells, RIN-m cells, 1.1B4 cells, WRL-68 cells, H9c2 cardiomyocytes cells, and PANC-1 cells) and non-cell lines (α-amylase, aldose reductase,

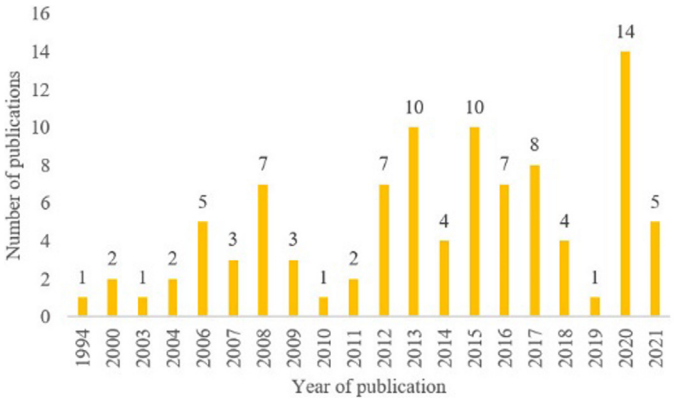

Fig. 2. Publishing trends of *A. paniculata* on diabetic preclinical trials.

dipeptidyl peptidase-IV (DPP-IV), pancreatic lipase, lipoprotein lipase, lipase, glucose uptake, and glucokinase assays). *In vivo* test models used four approaches involving genetic animal models (db/db mice, NOD mice, and ICR mice), diabetogenic agents (alloxan, STZ, and STZ-nicotinamide), nutritional induction (galactose, sucrose, and a high-fat diet, also high fructose and a high-fat diet) and the combination of a high-fat diet and STZ. Several targets of action have been studied including enhancing glucose uptake, antioxidants, maintaining T helper cell (Th)1/Th2/Th17 homeostasis, inhibiting glucose absorption, the protein tyrosine phosphatase 1B (PTP-1B) pathway, the activator protein 1 (AP-1) pathway, and the NF-κB pathway.

From 2016 to 2020, 34 papers were published that used water, ethanolic, and methanolic extracts, bound and free phenolic extracts, various fractions, a combination of ethanolic extracts of several plants, phytochemical compounds (andrographolide and 14-deoxy-11,12-didehydroandrographolide in the Fig. 3), andrographolide derivative, and nanoparticles of extracts or phytochemical compounds (polycaprolactone nanoparticles, chitosan nanoparticles, zinc oxide nanoparticles, and Zn-Fe3O_4 nanoparticles). *In vitro* studies using cell lines (RIN-m cells, 3T3-L1 cells, 1.1B4 cells, WRL-68 cells, L6 cells, and Caco-2 cells) and non-cell lines (DPP-IV, α-glucosidase, pancreatic lipase, lipoprotein lipase, lipase, and glucokinase assays). *In vivo* models using a genetic animal model (db/db mice), diabetogenic agents (alloxan, STZ, and STZ-nicotinamide), nutritional agents (high-fat diet), and a combination of a high-fat diet and STZ. Antidiabetic mechanisms of this period were related to antioxidants, anti-inflammation, glucokinase pathway regulation, inhibition of glucose absorption, the Nrf2 pathway, DPP-IV pathway, and Akt/NF-κB pathway, stimulation insulin production through the pancreatic and duodenal homeobox 1 (PDX-1) pathway, and enhanced glucose uptake, and intestinal barrier function, and microbial composition.

After 2020, five published papers discussed *A. paniculata* as an antidiabetic. A combination of an ethanolic extract with other plants, andrographolide, and nanoformulations (self-nano-emulsifying, neodymium oxide nanoparticle, and Ytterbium oxide nanoparticle) was tested in this period. *In vitro* studies on the α-amylase assay, primary hippocampal cultures, and 3T3-L1 cells were used. Also, STZ-induced diabetic rats were used in this period. Several molecular mechanisms were reported, including inhibiting glucose absorption, enhancing glucose uptake, promoting glucose metabolism, and regulating renal function.

This section reveals the chronological progression of the research on *A. paniculata* in preclinical trials of DM. This exploration began with preliminary studies of various extracts as material tests to determine their ability to decrease glucose levels. Then, the single phytochemical compound fraction was modified to increase the antidiabetic effect, such as andrographolide derivative, and innovations of its formulations. Besides that, this exploration focused on the ability to decrease glucose levels and well-studied molecular mechanisms.

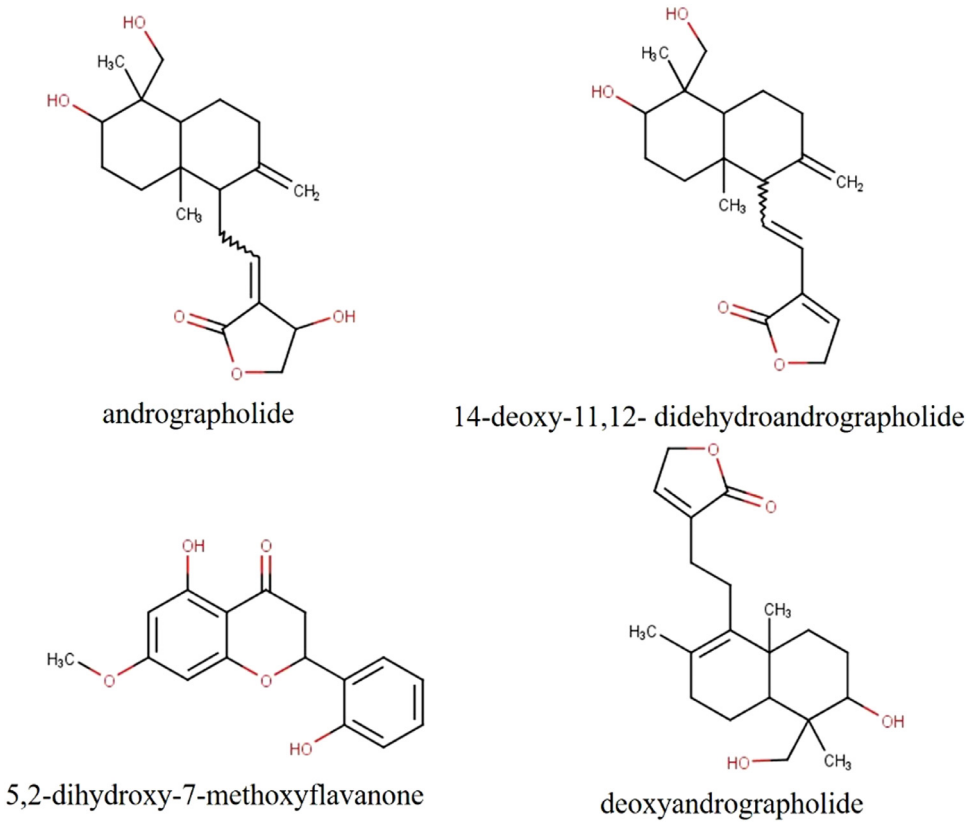

Fig. 3. Some phytochemical compounds of *A. paniculata*.

Table 1
The most productive countries.

No.	Country	Total publication	Total citation	Average citation per publication
1	India	29	328	11.31
2	Indonesia	20	209	10.45
3	Malaysia	20	448	22.40
4	China	12	336	28.00
5	Taiwan	5	256	51.20
6	Japan	4	136	34.00
7	United States	3	232	77.33

Table 3
The most productive publishers.

No.	Publisher	Total publication	Total citation	Average citation per publication
1	Journal of Ethnopharmacology	4	250	62.50
2	Pharmaceutical Biology	3	53	17.67
3	International Food Research Journal	3	26	8.67
4	Asian Journal of Pharmaceutical and Clinical Research	3	22	7.33

3.2. Analysis of contributing countries

Of 97 selected published papers, 22 countries explored the antidiabetic activity of *A. paniculata*. The most productive countries were dominated by the Asia continent, as shown in Table 1. India led the total of publications. Meanwhile, the United States had the highest average number of citations per publication (AC) among the top seven countries. Furthermore, countries not listed in the top seven countries had only one or two publications.

3.3. Analysis of contributing institutions

The performance of institutions in the 97 selected papers, indicated that 121 institutions contributed to the research preclinical trials of *A. paniculata* as antidiabetic. The most productive institution was Universitas Gadjah Mada (Indonesia). Meanwhile, the highest AC among the top nine institutions was National Cheng Kung University (China). Table 2 showed that the contributing institutions have a minimal 3 number of papers about the topic. Thus, the study spread to the most contributing institutions in the Asia continent.

3.4. Analysis of contributing publishers

The most productive was Elsevier/ the *Journal of Ethnopharmacology* (the total number of publications = 4; the total number of citations/=250; AC = 62.5). The publishers' total was 75 publishers, while publishers with a minimal of three documents were only four publishers (Table 3). Information about the publishers that produce on preclinical trials of *A. paniculata* as an antidiabetic will help scholars pursue a particular publisher and submit their report of research related to this topic in those publishers.

3.5. Analysis of authors and their bibliographical coupling network

The most productive authors in a discipline will help to identify the scholars who have made a major contribution to the exploration and development of a research field. Furthermore, knowing about the scientists in a particular field also helps determine who could help make policy decisions and resolve institutional issues in a particular field (Bamel et al., 2020). From 97 selected documents, 376 authors contributed to the preclinical trial research of *A. paniculata* as an antidiabetic. The most productive authors had a minimum of four documents (Table 4). Table 4 shows that Agung Endro Nugroho (nine documents) has the highest number of publications, followed by Suwijiyo Pramono (eight documents), Rammohan Subramanian (four documents), Zaijun Zhang (four documents), and Sudarsono (four documents).

The most productive authors are affiliated with universities in Indonesia (Universitas Gadjah Mada), Malaysia (Universiti Sains Malaysia), and China (Jinan University). This is related to the wide distribution of *A. paniculata* across Asia, such as India, Sri Lanka, Cambodia, Indonesia, Laos, Malaysia, Thailand, and Vietnam (Kumar et al., 2021). The author's name, institution, and country of origin will help other scientists to benchmark this topic and encourage research collaboration.

In our study, we also developed a bibliographical coupling network to analyze the authors. This analysis indicates that two authors cite the same article(s) in articles that both authors have published (Ma, 2012). A high value in bibliographical coupling strength demonstrates a similar topic between the analyzed documents (Chang et al., 2015). We used the fractional counting method to develop a bibliographical coupling network because it offers a more useful perspective than full counting and avoids misinterpretations (Perianes-Rodriguez et al., 2016; van Eck and Waltman, 2014). Fractional counting revealed that each publication has the same overall weight that means the publication is equal to one (Bamel et al., 2020). Then, we used the thesaurus tool to implement a data cleansing function to merge the names of different authors, but it meant the same authors.

The results of the bibliographical coupling based on the authors of our study are presented in Fig. 4. We put a criterion of a two document minimum per author, which resulted in 44 authors out of 375 authors. When we put a criterion of a one document minimum, 375 authors met the threshold; however, only 346 authors had the largest set of connected items. With a criterion of a minimum of three documents, 11 authors met the criteria, but it was too low for developing a meaningful co-citation network. So, we used two minimum numbers of documents as the criteria to show the total link strength of the network is 1621.26 with 624 links.

The size of the bibliographical coupling network based on authors indicates the strength of the author coupling within the cluster,

Table 2
The most productive institutions.

No.	Name of institution	Country	Total publication	Total citation	Average citation per publication
1	Universitas Gadjah Mada	Indonesia	13	166	12.77
2	Universiti Sains Malaysia	Malaysia	6	273	45.50
3	Universiti Putra Malaysia	Malaysia	6	56	9.33
4	National Cheng Kung University	Taiwan	3	210	70.00
5	Jinan University	China	3	115	38.33
6	Andhra University	India	3	57	19.00
7	Universiti Teknologi Malaysia	Malaysia	3	24	8.00
8	Universiti Malaysia Trengganu	Malaysia	3	2	1.50
9	University of Indonesia	Indonesia	3	2	1.50

Table 4
The most productive authors.

No.	Author name	Total publication	Total citation	Average citation per publication	Affiliation/ Country	Discipline	Description of studies
1	Nugroho, A.E.	9	153	17.00	Universitas Gadjah Mada, Indonesia	Pharmacology	- Plant material test: extract, fraction, the combination of extract/ fraction with other plants, andrographolide, self-nano-emulsifying of andrographolide - Model test: 3T3-L1 cell, α-glucosidase assay, streptozotocin (STZ), alloxan, high fructose-fat-fed - Mechanism: enhancing glucose uptake through glucose transporters (GLUT)−4 and peroxisome proliferator-activated receptor (PPAR)-γ, inhibiting the absorption of glucose through an α-glucosidase mechanism
2	Pramono, S.	8	146	18.25	Universitas Gadjah Mada, Indonesia	Pharmaceutical Biology	- Plant material test: extract, fraction, the combination of extract/ fraction with other plants, andrographolide - Model test: 3T3-L1 cell, α-glucosidase assay, STZ, high fructose-fat-fed - Mechanism: enhancing glucose uptake through GLUT-4 and PPAR-γ, inhibiting the absorption of glucose through an α-glucosidase mechanism
3	Subramanian, R.	4	257	64.25	Universiti Sains Malaysia, Malaysia	Pharmacology	- Plant material test: extract, andrographolide - Model test: α-glucosidase and α-amylase assays, fat-fed diet, and STZ - Mechanism: inhibiting the absorption of glucose through α-glucosidase and α-amylase mechanism, regulating liver functions related to type 2 diabetes
4	Zhang, Z.	4	132	33.00	Jinan University, China	New Drug Research	- Plant material test: andrographolide, andrographolide analog, andrographolide derivative - Model test: 3T3-L1 cell, RIN-m cell, alloxan - Mechanism: β cell protector, regulating insulin resistance through nuclear factor-κB resistance
5	Sudarsono	4	12	3.00	Universitas Gadjah Mada	Pharmaceutical Biology	- Plant material test: the combination of extract/ fraction with other plants - Model test: alloxan, STZ - Mechanism: -

GLUT, glucose transporter; PPAR, peroxisome proliferator-activated receptor; STZ, streptozotocin.

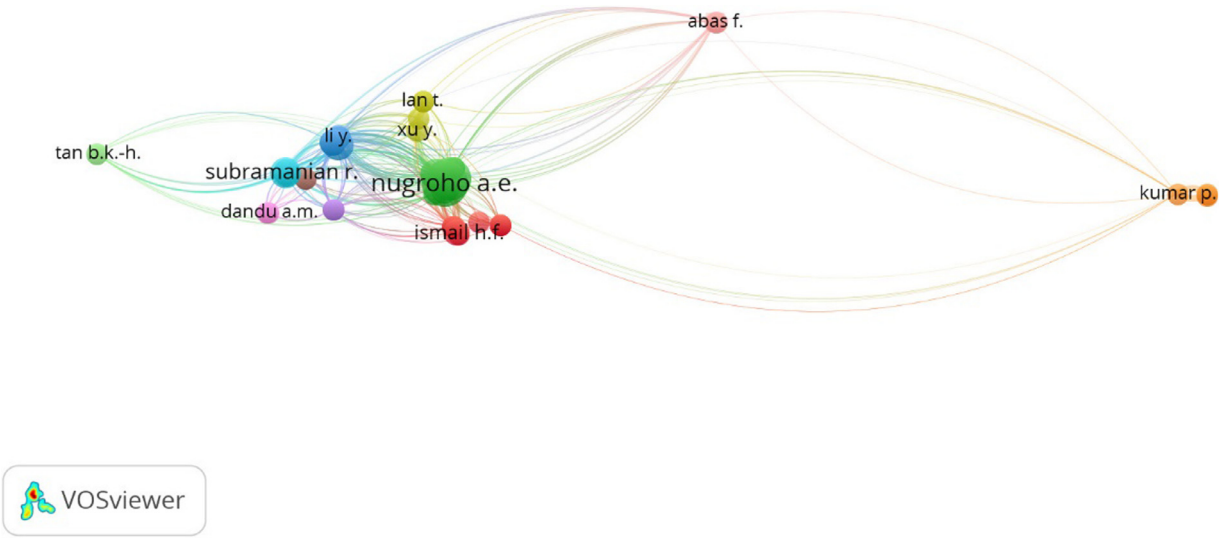

Fig. 4. Bibliographic coupling network (author based).

meaning that their reference list has the highest similarity within the cluster. The clusters are named using the author's name with the largest node in the cluster. The description of our bibliographical coupling network analysis is described in Table 5 and reveals 11 clusters. Clusters 1, 2, and 4 are close to each other and were led by Hassan Fahmi Ismail and Agung Endro Nugroho for clusters 1 and 2, whereas cluster 4 was led by Tian Lan and Yang Xu. These clusters occurred from 2011 to 2021 and mainly discussed antidiabetic explorations or mechanisms of action of *A. paniculata* extract, andrographolide, combined with other plant extracts or phytochemical compounds, or a nanoformulation of andrographolide through *in vitro* and *in vivo* studies.

Thus, clusters 3, 5, 6, 8, and 9 were close in position on this network, led by Yongmei Li, Rammohan Subramanian, no one, and Anilkumar M. Dandu, respectively. These clusters were published in 2003–2004, 2006–2009, 2011–2012, and 2015–2016. These clusters presented data about the antidiabetic activity or its mechanisms of action of *A. paniculata*, andrographolide, andrographolide derivative, andrographolide analog through *in vitro* and *in vivo* studies. Furthermore, 3 clusters were far apart, *i.e.*, clusters 7, 10, and 11, led by Padma Kumar, Faridah Abas, and Benny Kwong-Huat Tan, respectively. These clusters were published in 2000, 2013, 2016–2017, and 2021 which discussed the exploration of antidiabetic activity, other related pharmacological activities, or mechanisms of action of *A. paniculata* extract or a nanoformulation of the extract through *in vitro* and *in vivo* studies.

3.6. Analysis of the most influential papers and their co-citation network

The most influential papers were assessed based on the total citations of each document. The analysis revealed the top 10 papers with more than 50 citations (Table 6). The highest citation was gained by Subramanian's team in 2008 with the title of "*in vitro* α-glucosidase and α-amylase enzyme inhibitory effects of *A. paniculata* extract and andrographolide." The top 10 most influential papers discussed the activities of extracts, combinations with other plants, andrographolide, andrographolide analogs, and formulation modifications in antidiabetics with several mechanisms, such as α-glucosidase and α-amylase inhibitors, antioxidants, and anti-inflammatories.

Co-citation network analysis is used to analyze and manage the structure of knowledge and basics of topics in scientific fields (Shiau et al., 2017). A co-citation network is constructed when two documents are cited by third documents, which are termed as "co-cited" (Bamel et al., 2020; Shiau et al., 2017). Two documents are a strong correlation if both are intermittently cited by other documents (Bamel et al., 2020; Shiau et al., 2017). Co-citation network measures have semantic similarity among documents based on citation relationships that show the structure and periodic progression of a research topic (Bamel et al., 2020; Shiau et al., 2017). A research gap addressed in this study was to identify the relationships between influential scholars and theirs works by constructing a co-citation network (Bamel et al., 2020). This network also provided spatial positions of the most cited documents in the network visualization diagram (Bamel et al., 2020).

We used fractional counting for the same reasons as the bibliographic coupling network (Perianes-Rodriguez et al., 2016; van Eck and Waltman, 2014). Before we selected documents in the Vosviewer to make a co-citation network of the most influential papers, the thesaurus was used to merge different documents indicating the same documents. We established a minimum criterion of two minimum citations. Of 3070 cited references, 40 documents met the threshold. When we set the criterion of three minimum citations, 13 documents met the criteria of three minimum citations, which was too low in developing a meaningful co-citation network. With a criterion of one minimum citation, 3070 documents met the threshold. When we created a co-citation network of 3070 documents, the program only selected 1000 documents but excluded some items that were not connected in the network visualization. This criterion created a network consisting of 296 items which built the largest set of related items. Thus, to create a meaningful and interpretable network, the criterion of two minimum citations was used, even though only 34 items built the largest set of related items.

The result of co-citation analysis is shown in Fig. 5 and described in Table 7. Meanwhile, six items were included in cluster 7, which consisted of two papers entitled "Tetrazolium dyes as tools in cell biology: new insights into their cellular reduction," and "Development and *in vitro* characterization of galactosylated low molecular weight chitosan nanoparticles bearing doxorubicin," cluster 8 with the paper entitled "Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays," cluster 9 with the paper entitled "Green synthesis of ionic liquid assisted ytterbium oxide nanoparticles by Couroupita guianensis leaves extract for biological applications", cluster 10 with a paper entitled "Effects of Averrhoa bilimbi leaf extract on blood glucose and lipids in STZ-diabetic rats," and cluster 11 with the paper entitled "*In vitro*

Table 5
Highlights of bibliographic coupling network analysis based on authors.

Cluster	Authors	Focus	Publication timelines
Cluster 1 (Red Nodes)	Arbianti, R., Hashim, Z., Imansari, F., Ismail, H.F., Majid, F.A.A., Sahlan, M., Sukandar, E.Y., Wong, T.S., Zainol, S.N.	Antidiabetic activity or its mechanisms of polyherbal which consisted of *A. paniculata*, nanoformulation of its extract and combination of andrographolide with gallic acid using several diabetic models, involving streptozotocin (STZ), obese diabetic mice, α-glucosidase assay, dipeptidyl peptidase-IV assay and cell lines (3T3-L1, WRL-68, and 1.1B4)	2016–2020
Cluster 2 (Dark Green Nodes)	Andrie, M., Ariastuti, R., Fitrawan, L.O.M., Lukitaningsih, E., Nugroho, A.E., Pramono, S., Sudarsono., Taher, M.	Antidiabetic activity or its mechanisms of the combination of extract of *A. paniculata* with andrographolide or other plants extracts, *i.e., Centella asiatica, Azadirachta indica, Caesalpinia sappan, Morinda citrifolia*, moreover nanoformulation of andrographolide using several diabetic models, involving STZ, alloxan, high fructose fat-feed, and 3T3-L1 cells	2011–2015, 2017–2021
Cluster 3 (Dark Blue Nodes)	Li, Y., Sun, Y., Wang, Y., Xu, L., Yan, H., Yu, P., Zhang, G., Zhang, Z.	Antidiabetic activity or its mechanisms of andrographolide, andrographolide derivative, or andrographolide analog using several diabetic models, involving high-fat diet and STZ, alloxan, RIN-m cells, and 3T3-L1 cells	2009, 2011, 2015–2016
Cluster 4 (Yellow Nodes)	Lan, T., Wang, L., Wu, T., Xu, Y.	Antidiabetic activity or its mechanisms of andrographolide using several diabetic models, involving high-fat diet and STZ, non-obese diabetic mice, db/db mice, mesangial cells, and Caco-2 cells	2013, 2016, 2020
Cluster 5 (Purple Nodes)	Annapurna, A., Nageswara Rao, S., Radhika, P.	Antidiabetic activity and other related activities of extract of *A. paniculata* using STZ and nicotinamide-STZ	2012
Cluster 6 (Light Blue Nodes)	Asmawi, M.Z., Sadikun, A., Subramanian, R.	Antidiabetic activity or its mechanisms of action of *A. paniculata* extract and/-or andrographolide using several diabetic models, involving type 2 diabetic animals, α-amylase assay, and α-glucosidase assay	2006–2008
Cluster 7 (Orange Nodes)	Kumar, P., Muthulakshmi, V., Sundrarajan, M.	Extract or nano-formulation of extract of *A. paniculata* as α-amylase inhibitor	2013, 2021
Cluster 8 (Dark Brown Nodes)	Cheng, J.-T., Yu, B.-C.	Antidiabetic activity or its mechanisms of andrographolide using several diabetic models, involving STZ, type 1 diabetic, and myoblast C2C12 cells	2003–2004, 2008
Cluster 9 (Pink Nodes)	Dandu, A.M., Inamdar, N.M.	Antidiabetic and antioxidant of extract of *A. paniculata* using STZ as a diabetic model	2008–2009
Cluster 10 (Light Brown Nodes)	Abas, F., Ismail, A.	Antidiabetic and related activities of extract of *A. paniculata*	2016–2017
Cluster 11 (Light Green Nodes)	Tan, B.K.-H., Zhang, X.-F.	Antidiabetic and antioxidant of extract of *A. paniculata* using STZ as a diabetic model	2000

STZ, streptozotocin.
Source: Scopus data (n = 97).

alpha-glucosidase and alpha-amylase enzyme inhibitory effects of *A. paniculata* extract and andrographolide".

The size of the circle and the distance between the two circles represented the number of citations and the level of similarity between them, respectively (Bamel et al., 2020). The results of co-citation network analysis showed six different clusters expressed by six different colors, *i.e.*, red, green, dark blue, yellow, purple, and light blue, where each color represents a research topic. As seen in Fig. 5, cluster 1 revealed red-colored nodes in the middle of the network. It is the largest cluster and consists of seven publications. This cluster focused on the global prevalence of diabetes (Wild et al., 2004), underlying physiological regulation of diabetes through the pancreas (McClenaghan, 2007), mechanisms of diabetogenic agents (Szkudelski, 2001), and phytochemical isolation (Rao et al., 2004). This cluster focused on (Yu et al., 2003) the antihyperglycemic activity of andrographolide in STZ-diabetic rats. Cluster 1 consisted of publications from the 1950s to 2007.

Cluster 2 (green-colored nodes on the bottom of the network) consisted of six publications from the1980s to 2002. The main focus of this cluster was the pathogenetic mechanisms of diabetes

Table 6
The most influential papers.

No.	Author	Title	Publisher	Total citation
1	Subramanian et al. (2008a)	*In vitro* α-glucosidase and α-amylase enzyme inhibitory effects of *A. paniculata* extract and andrographolide	Acta Biochimica Polonica	223
2	Zhang et al. (2000)	Antihyperglycaemic and antioxidant properties of *A. paniculata* in normal and diabetic rats	Clinical and Experimental Pharmacology and Physiology	210
3	Yu et al. (2003)	Antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats	Planta Medica	152
4	Zhang et al. (2000)	Antidiabetic property of ethanolic extract of *A. paniculata* in streptozotocin-diabetic rats	Acta Pharmacologica Sinica	96
5	Reyes et al. (2006)	Antidiabetic potentials of *Momordica charantia* and *A. paniculata* and their effects on estrous cyclicity of alloxan-induced diabetic rats	Journal of Ethnopharmacology	95
6	Husen et al. (2004)	Screening for antihyperglycemic activity in several local herbs of Malaysia	Journal of Ethnopharmacology	93
7	Zhang et al. (2009)	Hypoglycemic and beta cell protective effects of andrographolide analog for diabetes treatment	Journal of translational medicine	82
8	Nugroho et al. (2012)	Antidiabetic and antihyperlipidemic effect of *A. paniculata* and andrographolide in high-fructose-fat-fed rats	Indian Journal of Pharmacology	65
9	Ji et al. (2016)	Andrographolide ameliorates diabetic nephropathy by attenuating hyperglycemia-mediated renal oxidative stress and inflammation via Akt/ nuclear factor-κB pathway	Molecular and Cellular Endocrinology	55
10	Rajakumar et al. (2018)	Green approach for synthesis of zinc oxide nanoparticles from *A. paniculata* leaf extract and evaluation of their antioxidant, antidiabetic, and anti-inflammatory activities	Bioprocess and Biosystems Engineering	52

Table 7
Highlights of co-citation network clusters based on cited references.

Cluster	Authors	Title	Year	The theme of the cluster	Future research suggestions
Cluster 1 (Red Nodes)	Burgos, R.A., Caballero, E.E., Sánchez, N.S., Schroeder, R.A., Wikman, G.K., Hancke, J.L.	Testicular toxicity assessment of *A. paniculata* dried extract in rats	1997	Revealing the urgency of diabetes topic, underlying physiological regulation of diabetes, mechanisms of diabetogenic agent, isolation phytochemical and preliminary screening of the antidiabetic effect	Extension research topic about molecular pathophysiological of diabetes, the molecular mechanism of a diabetogenic agent, isolation of *A. paniculata* compounds, the molecular mechanism of *A. paniculata* against diabetes
	Chakravarti, R.N., Chakravarti, D.	Andrographolide, the active constituent of *A. paniculata*	1951		
	Mcclenaghan, N.H.	Physiological regulation of the pancreatic beta-cell: functional insights for understanding and therapy of diabetes	2007		
	Rao, Y.K., Vimalamma, G., Rao, C.V., Tzeng, Y.M.	Flavonoids and andrographolides from *A. paniculata*	2004		
	Szkudelski, T.	The mechanism of alloxan and streptozotocin action in β cells of the rat pancreas	2001		
	Wild, S., Roglic, G., Green, A., Sicree, R., King, H.	Global prevalence of diabetes: estimates for the year 2000 and projections for 2030	2004		
	Yu, B.C., Hung, C.R., Chen, W.C., Cheng, J. T.	Antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats	2003		
Cluster 2 (Green Nodes)	Berger, J., Biswas, C., Vicario, P.P., Strout, H.V., Saperstein, R., Pilch, P.F.	Decreased expression of the insulin-responsive glucose transporter in diabetes and fasting	1989	Underlying of the pathogenesis of diabetes, exploration of antidiabetic activity and related activity of uncomplicated mechanism	Extension research topic about molecular pathophysiological of diabetes, the molecular mechanism of *A. paniculata* against diabetes
	Cheng, J.T., Liu, I.M., Chi, T.C., Tzeng, T.F., Lu, F.H., Chang, C.J.	Plasma glucose-lowering effect of tramadol in streptozotocin-induced diabetic rats	2001		
	Panossian, A., Hovhannisyan, A., Mamikonyan, G., Abrahamian, H., Hambardzumyan, E., Gabrielian, E., Goukasova, G., Wikman, G., Wagner, H.	Pharmacokinetic and oral bioavailability of Andrographolide from *A. paniculata* fixed combination Kan Jang in rats and human	2000		
	Shen, Y.C., Chen, C.F., Chiou, W.F.	Andrographolide prevents oxygen radical production by human neutrophils: possible mechanism(s) involved in its antiinflammatory effect	2002		
	Trivedi, N.P., Rawal, U.M.	Hepatoprotective and antioxidant property of *A. paniculata* in BHC induced liver damage in mice	2001		
	Zhang, X.F., Tan, B.K.	Antihyperglycaemic and antioxidant properties of *A. paniculata* in normal and diabetic rats	2000		
Cluster 3 (Dark Blue Nodes)	Aruna, K., Koul, I.B., Banerjee, S.K., Gupta, B.D.	Antihepatotoxic effects of major diterpenoid constituents of *A. paniculata*	1993	Measurement technique of biochemical parameter, exploration of antidiabetic activity and related activity of uncomplicated mechanism	Extension research topic about the advanced technique to measure the biochemical parameter, the molecular mechanism of *A. paniculata* against diabetes
	Bonner-Weir, S., Trent, D.F., Honey, R.N., Weir, G.C.	Responses of neonatal rat islets to streptozotocin: limited β-cell regeneration and hyperglycemia	1981		
	Lakhanpal, P., Rai, D.K.	Quercetin: a versatile flavonoid	2007		
	Lowry, O.H., Rosebrough, N.J., Farr, A.L., Randall, R.J.	Protein measurement with the Folin phenol reagent	1951		
	Nugroho, A.E., Andrie, M., Warditiani, N. K., Siswanto, E., Pramono, S., Lukitaningsih, E.	Antidiabetic and antihiperlipidemic effect of *A. paniculata* and andrographolide in high-fructose-fat-fed rats	2012		
	Subramanian, R., Asmawi, M.Z., Sadikun, A.	*In vitro* alpha-glucosidase and alpha-amylase enzyme inhibitory effects of *A. paniculata* extract and andrographolide	2008		
Cluster 4 (Yellow Nodes)	Shao, Z.J., Zheng, X.W., Feng, T., Huang, J., Chen, J., Wu, Y.Y. Zhou, L.M., Tu, W.W., Li, H.	Andrographolide exerted its antimicrobial effects by upregulation of human β-defensin-2 induced through p38 mitogen-activated protein kinase and nuclear factor-κB pathway in human lung epithelial cells	2012	Revealing the urgency of diabetes topic, exploration of antidiabetic activity and molecular mechanism	Extension research topic about the molecular mechanism of *A. paniculata* against diabetes
	Shaw, J.E., Sicree, R.A., Zimmet, P.Z.	Global estimates of the prevalence of diabetes for 2010 and 2030	2010		
	West, I.C.	Radicals and oxidative stress in diabetes	2000		
	Yu, B.C., Chang, C.K., Su, C.F., Cheng, J.T.	Mediation of beta-endorphin in andrographolide-induced plasma glucose-lowering action in type I diabetes-like animals	2008		
	Zhang, Z., Jiang, J., Yu, P., Zeng, X., Larrick, J.W., Wang, Y.	Hypoglycemic and beta cell protective effects of andrographolide analogue for diabetes treatment	2009		
	Zimmet, P., Alberti, K.G., Shaw, J.	Global and societal implications of the diabetes epidemic	2001		
Cluster 5 (Purple Nodes)	Chan, S.J., Wong, W.S., Wong, P.T., Bian, J. S.	Neuroprotective effects of andrographolide in a rat model of permanent cerebral ischemia	2010	Mechanisms of a diabetogenic agent, measurement technique of biochemical parameter	Extension research topic about the molecular mechanism of a diabetogenic agent, advanced
	Kakkar, P., Das, B., Viswanathan, P.N.	A modified spectrophotometric assay of superoxide dismutase	1984 1998		

(*continued on next page*)

Table 7 (*Continued*)

Cluster	Authors	Title	Year	The theme of the cluster	Future research suggestions
	Masiello, P., Broca, C., Gross, R., Roye, M., Manteghetti, M., Hillaire-Buys, D. Novelli, M., Ribes, G.	Experimental non-insulin-dependent diabetes mellitus: development of a new model in adult rats administered streptozotocin and nicotinamide			technique to measure the biochemical parameter
	Ohkawa, H., Ohishi, N., Yagi, K.	Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction	1979		
	Trinder, P.	Determination of blood glucose using an oxidase–peroxidase system with a non-carcinogenic chromogen	1969		
Cluster 6 (Light Blue Nodes)	Akowuah, G.A., Zhari, I., Norhayati, I., Mariam, A.	High-performance liquid chromatography and high-performance thin-layer chromatography densitometric determination of andrographolides and antioxidant potential of *A. paniculata*	2006	Exploration of antidiabetic activity and related activity of uncomplicated mechanism, analytical method to determine phytochemical compounds	Extension research topic about the molecular mechanism of *A. paniculata* against diabetes, development advanced analytical methods to measure phytochemical compounds
	Singha, P.K., Roy, S., Dey, S.	Protective activity of andrographolide and arabinogalactan proteins from *A. paniculata* against ethanol-induced toxicity in mice	2007		
	Ye, F., Shen, Z., Xie, M.	Alpha-glucosidase inhibition from a Chinese medical herb (*Ramulus mori*) in normal and diabetic rats and mice	2002		
	Zhang, X.F., Tan, B.K.	Anti-diabetic property of ethanolic extract of *A. paniculata* in streptozotocin-diabetic rats	2000		

Source: Scopus data ($n = 97$).

(Berger et al., 1989) and the exploration of antidiabetic activity of *A. paniculata* and related activity of uncomplicated mechanisms (Shen et al., 2002). Cluster 3 (dark blue nodes) consisted of six publications from the 1950s to 2012. The main focus of cluster 3 was measurement techniques of biochemical parameters (Lowry et al., 1951) and exploration of antidiabetic activity and related activity of uncomplicated mechanisms related to glucose uptake, α-amylase, and α-glucosidase (Nugroho et al., 2012; Subramanian et al., 2008a).

Cluster 4 (yellow nodes) consisted of six publications from the 2000s to 2012. The main focus of cluster 4 was the global prevalence of diabetes (Shaw et al., 2010) and the exploration of antidiabetic activity and its molecular mechanisms (Yu et al., 2008; Zhang et al., 2009). Cluster 5 (purple nodes) consisted of five publications from the 1960s to 2010. The main focus of cluster 5 was the exploration of mechanisms of diabetogenic agents (Masiello et al., 1998) and measurement techniques of biochemical parameters (Kakkar et al., 1984; Ohkawa et al., 1979). Cluster 6 (light blue nodes) consisted of four publications from 2000 to 2007. The main focus of cluster 6 was the analytical method to determine phytochemical compounds of *A. paniculata* (Akowuah et al., 2006) and exploration of antidiabetic activity and related activity of uncomplicated mechanisms (Zhang and Tan, 2000a).

3.7. Keyword co-occurrence network and overlay

The keyword co-occurrence network and overlay can be applied to determine terms with great interest and the most influence. They might provide insights into the main research topics of the field with a quick, objective, and reproducible approach (Bamel et al., 2020; Grames et al., 2019). For generating the objective of this network analysis, keywords and their co-occurrences in various publications are extracted from the title, abstract, and keywords (authors provided keywords and indexed keywords) (Bamel et al., 2020; Grames et al., 2019). The potential keywords and the edges of network co-occurrences are represented by each node in this network visualization (Grames et al., 2019).

We used fractional counting to construct a keyword co-occurrence network because the network level can normalize the relative weights of links and present more realistic results. This approach explains the structures in the network (Vargas-Quesada et al., 2017). This analysis shows three options of a unit of analysis, *i.e.*, author keywords, indexed keywords, and all keywords (both author and indexed keywords). Thus, we used all keywords. Author keywords and indexed keywords provide author aboutness (contents presented via terms in natural language) and content interpretations, respectively (Vargas-Quesada et al., 2017). Previous reports demonstrated that author keywords are effective to investigate the knowledge structure of fields in bibliometric analysis; however, they might be biased because some scientists could use certain keywords to increase the visibility of their papers (Bonaccorsi, 2008; Vargas-Quesada et al., 2017; Zhang et al., 2016). Furthermore, indexed keywords are very comprehensive to visualize the content of articles (Vargas-Quesada et al., 2017; Zhang et al., 2016). Hence, we used the combination of author keywords and indexed keywords (all keywords). Then, we eliminated the duplications of keywords, to optimize this approach (Vargas-Quesada et al., 2017).

This visualization revealed 1270 keywords from 97 selected documents. We needed to implement data cleaning using the thesaurus function to merge different keywords, which refer to the same keywords. When we used one keyword as the requirement for the minimum number of occurrences, 1270 keywords met the criterion. However, the program only selected 1000 keywords. So, we used two keywords as the minimum requirement. Then, 305 keywords met the threshold. Thereafter, some keywords with a general meaning (for instance, article, female, male, etc.) and irrelevant keywords

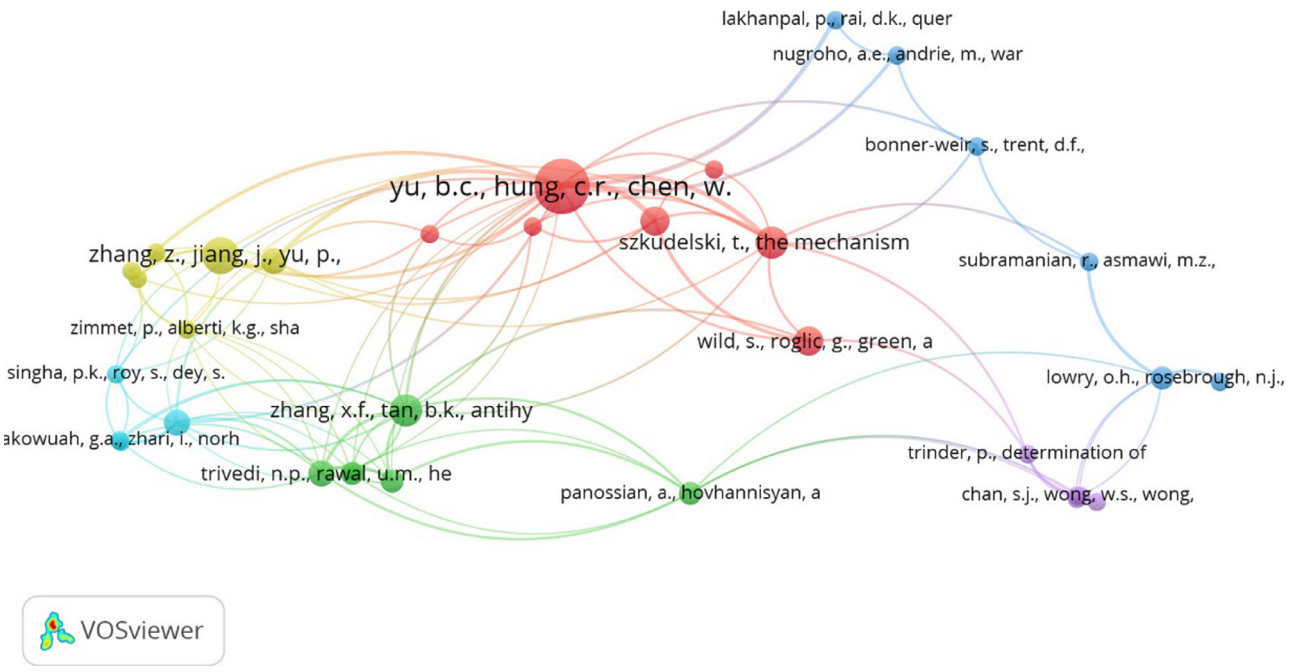

Fig. 5. Co-citation network of cited references.

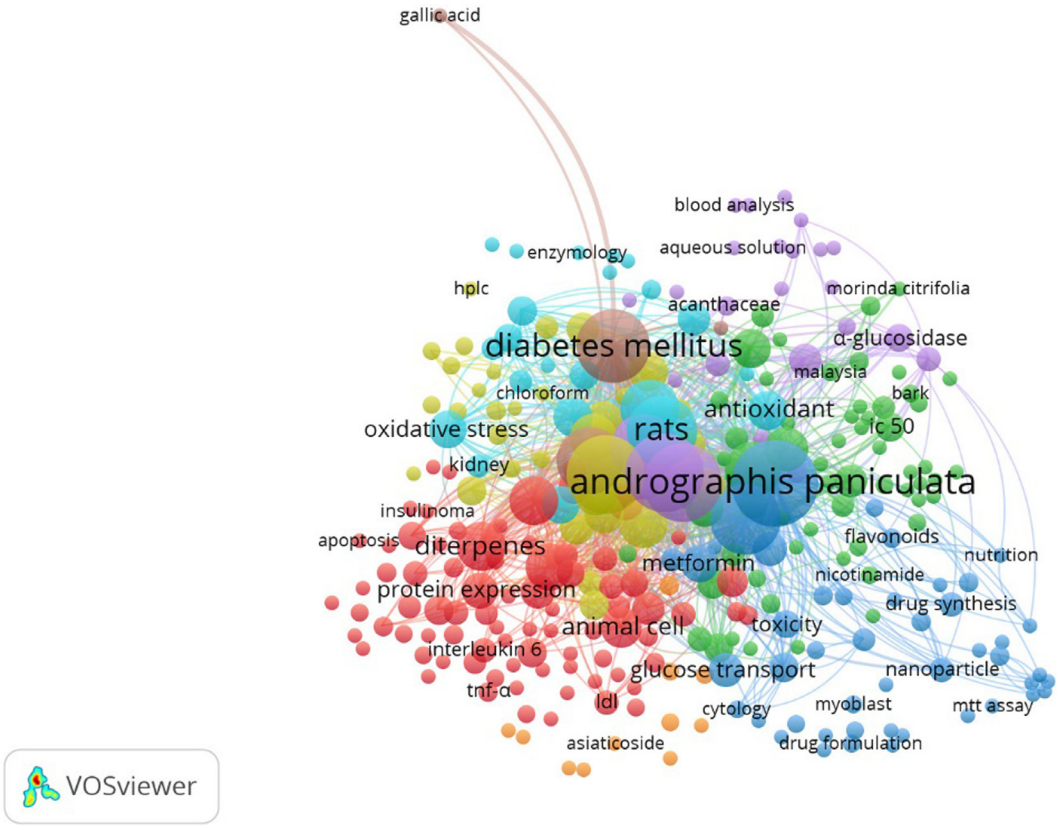

Fig. 6. Keyword co-occurrence network.

were rejected. This reduced the total number of keywords included in the co-occurrence network visualization to 282 items.

The result of the keyword co-occurrence network is presented in Fig. 6. The distance between nodes demonstrates relatedness information about keywords. Meanwhile, nodes' size reveals the frequency of occurrence of keywords (Bamel et al., 2020). Moreover, an overlap of nodes shows the number of times these keywords occur together in the network (Bamel et al., 2020). This visualization indicated that the keyword co-occurrence network has eight clusters, as described in Table 8. All of these clusters were closed positions in the

Table 8
Highlights of keyword co-occurrence network analysis based on all keywords.

Clusters	Keywords	Thematic interpretation
Cluster 1 (Red Nodes/ 80 items)	Adiponectin, adipose tissue, alanine aminotransferase, alkaline phosphatase, animal cell, animal tissue, anti-inflammatory agent, apoptosis, aspartate aminotransferase, biochemical analysis, blood urea nitrogen, C57BL mice, cell damage, cell membrane, cell nucleus, cell proliferation, cell viability, cholesterol, creatinine, cytokine, diabetic nephropathy, diterpenes, drug dose comparison, drug mechanism, enzyme activation, fibronectin, gamma glutamyl transferase, gene expression, glomerulus, GLUT-2, HDL, high-fat diet, homeostatis model assessment, i kappa b alpha, immunoblotting, immunofluorescence, immunoglobulin enhancer binding protein, *in vivo* study, inflammation, insulin receptor substrate 1, insulin resistance, insulin sensitivity, insulin signaling, insulin tolerance test, insulinoma, interleukin 1beta, interleukin 6, kidney mass, lactate dehydrogenase, ldl, leptin, lipid blood level, lipid diet, mesangial cells, messenger rna, mice, NF-κB, pancreas, pancreas neoplasms, pathology, pathophysiology, phosphatidylinositol 3 kinase, physiology, protein blood level, protein expression, protein kinase b, protein localization, protein phosphorylation, reactive oxygen metabolite, reactive oxygen species, RT-PCR, signal transduction, Sprague Dawley rats, synaptotagmin i, TNF-α, transcription factor NRF2, transforming growth factor beta, triacylglycerol, tumor necrosis factor	This cluster revealed about various parameter which tested in antidiabetic experiment and other related diseases, several pharmacological experiments in antidiabetic test and described other supporting scientific fields
Cluster 2 (Green Nodes/ 61 Items)	3T3 cell line, 3T3-L1 cell line, *Acanthus ebracteatus*, adipocyte, adipogenesis, albumin, ayurveda, bark, black pepper extract, *Caesalpinia sappan*, clove, concentration response, drug cytotoxicity, drug determination, drug screening, *Eurycoma longifolia*, fractionation, fruit, glucose 6 phosphatase, glycogen, *Harrisonia perforata, Homalomena aromatica*, human, human cell, *Hydnophytum formicarum*, IC_{50}, India, Indonesia, Indonesian medicinal plant, insulin release, *Lagerstroemia speciosa*, lipid metabolism, lipid storage, lipogenesis, Malaysia, medicinal plant, methanol, molecular docking, molecular structure, *Momordica charantia, Morinda citrofolia*, nicotinamide, niddm, peroxisome proliferator-activated receptor gamma, plant extract, plant leaf, plant root, plant stem, pomegranate extract, *Rhinacanthus nasutus*, rosiglitazone, *Salacia chinensis, Smilax glabra, Syzygium aromaticum*, T2DM, *Terminalia bellirica, Tinospora crispa,* tolbutamide, traditional medicine, triglycerides, *Urceola minutiflora*, water	This cluster showed about the combination with other plants, plant part used, type of solvent, various parameters which tested in antidiabetic experiment, other supporting technical aspects in antidiabetic experiments, such as fractionation, drug screening, etc. and countries which develop this research topic
Cluster 3 (Dark Blue Nodes/ 46 Items)	14 deoxy 11, 12 didehydroandrographolide, *Andrographis paniculata*, antidiabetic, anti-inflammatory, *Azadirachta indica*, binding energy, biomedical applications, blood, cell culture, chemical analysis, cytology, cytotoxicity, drug delivery system, drug formulation, drug synthesis, *Escherichia coli*, extraction, flavonoids, glucose tolerance, glucose transport, glucose uptake, green synthesis, *in vitro* study, ionic liquids, leaf extracts, medical applications, metformin, molecular docking, MTT assay, myoblast, myotube, nanoencapsulation, nanoparticle, nitric oxide, nutrition, obesity, *Ocimum tenuiflorum, Orthosiphon stamineus*, particle size, phenols, plant, polycaprolactone, scanning electron microscopy, skeletal muscle, skeletal muscle cell, solvent, sustained drug release, toxicity	This cluster demonstrated the combination of other plants, phytochemical compounds, description of other supporting scientific fields, and formulation aspects
Cluster 4 (Yellow Nodes/ 32 Items)	Alloxan, animal model, blood, cell damage, chemically induced disorder, chemistry, chloroform, disease model, dose response relationship, drug structure, experimental diabetes mellitus, gamma interferon, gene expression regulation, genetics, glibenclamide, glucose tolerance test, GLUT-4, HPLC, hypoglycemia, hypoglycemic agents, IDDM, immunohistochemistry, insulin, insulin release, insulin-secreting cells, isolation and purification, metabolism, oral drug administration, pancreas islet, pancreas islet beta cell, soleus muscle, T1DM	This cluster presented several pharmacological experiments in antidiabetic tests and other supporting technical aspects in antidiabetic experiments, such as isolation and purification, glucose tolerance test, and others
Cluster 5 (Purple Nodes/ 26 Items)	*Acanthaceae*, acarbose, aqueous solution, area under the curve, blood analysis, blood glucose, blood sampling, diabetes control, diet restriction, drug effect, drug isolation, enzyme inhibition, enzyme inhibitors, *Gymnema sylvestre*, nonhuman, peak blood glucose, phytochemistry, phytotherapy, plant preparations, post-prandial hyperglycemia, single drug dose, starch, sucrose, *Syzygium cumini* extract, α-amylase, α-glucosidase	This cluster described the combination with other plants, the various parameter which tested in antidiabetic experiment and several pharmacological experiments in antidiabetic test
Cluster 6 (Light Blue Nodes/ 22 Items)	Antioxidant, body weight, brain function, catalase, enzyme activity, enzymology, glutathione, glutathione peroxidase, hyperglycemia, kidney, lipid peroxidation, liver, malonaldehyde, niacinamide, nootropic agent, oxidative stress, quantitative analysis, rats, streptozotocin, superoxide dismutase, weight gain, Wistar rats	This cluster demonstrated about various parameter which tested in antidiabetic experiment and other related diseases
Cluster 7 (Orange Nodes/ 11 Items)	Asiaticoside, cell differentiation, *Centella asiatica*, dexamethasone, drug potentiation, drug synergism, fructose, histopathology, hyperlipidemia, postprandial state, preadipocyte	This cluster showed the combination with other plant and phytochemical and described other supporting scientific fields
Cluster 8 (Brown Nodes/ 4 Items)	Andrographolide, diabetes mellitus, gallic acid, glucose metabolism	This cluster revealed the combination with other phytochemicals and target of action

Source: Scopus data (n = 97).

network, except gallic acid from cluster 8 in the offside of this network. This indicated the relatedness of information in the research topic of the preclinical trial of *A. paniculata.*

Fig. 7 shows the keyword co-occurrence with a timeframe. The size of the nodes reveals the frequency of appearance of a keyword. The color of the nodes reveals the average publication year of the keyword where purple, purple-blue, blue-green, green, and yellow used around/ before 2010, around 2012, around 2014, around 2016 and around/ after 2018, respectively (Bamel et al., 2020). Several keywords, like *Acanthaceae*, blood analysis, kidney, and aqueous solution appeared around 2010, whereas keywords in 2012 to 2014 included antioxidant, oxidative stress, bark, diterpenes, and animal cell. Furthermore, keywords used between 2014 and 2016 included protein expression, glucose transport, TNF-α, and α-glucosidase, whereas around 2018, keywords involving drug formulation, nanoparticle, dimethylthiazol-diphenyltetrazolium bromide, or MTT assay appeared. This research timeline revealed that, preclinical trial research with *A. paniculata* as an antidiabetic was expanded, beginning with testing its hypoglycemic ability and other relevant activities (such as an antioxidant). The molecular mechanisms of other extracts, phytochemicals, or their combinations were also tested. Thus, this testing led to formulation development.

3.8. Toxicological studies

Toxicological studies of *A. paniculata* have two approaches of toxicity tests, *i.e.*, general and specific toxicities. General toxicities, included acute and sub-chronic toxicity modes. Acute toxicity model

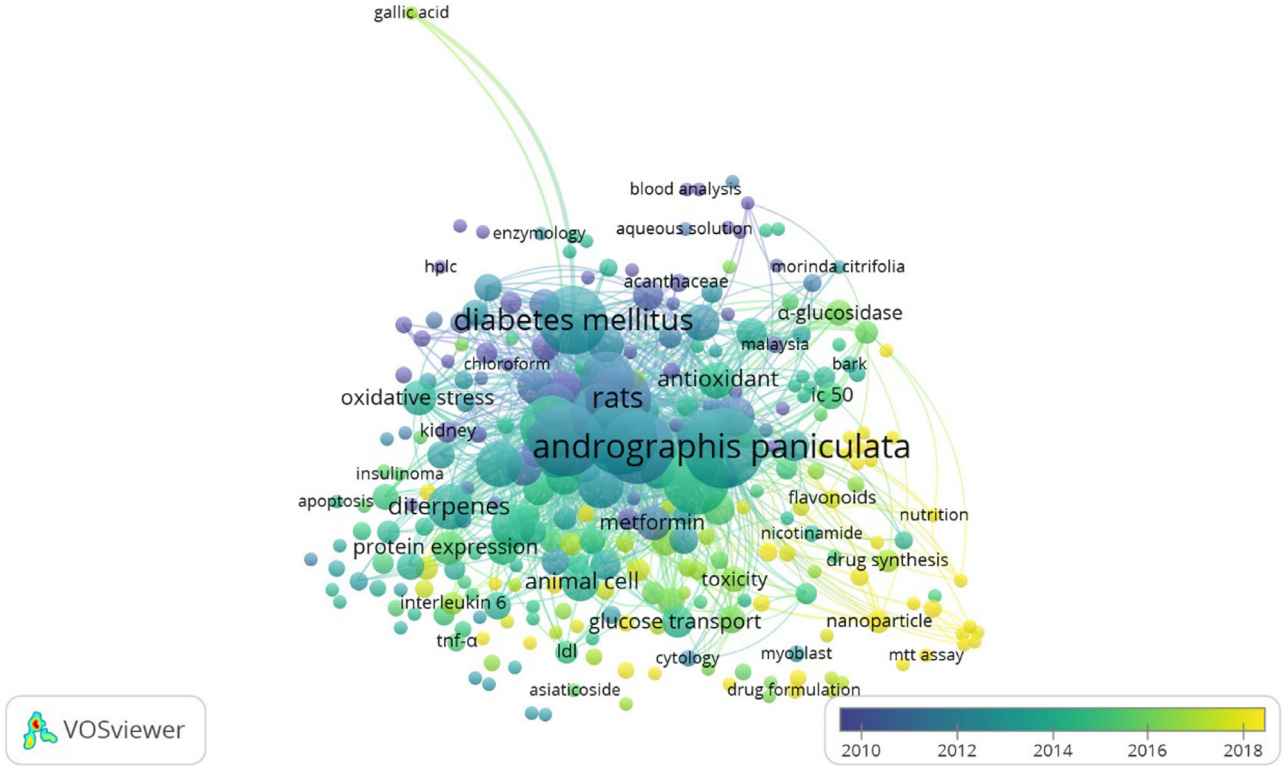

Fig. 7. Keyword co-occurrence overlay with a time frame.

of ethanolic extracts of leaves (300, 2000, and 5000 mg/kg BW) used male and female Swiss mice which revealed no mortality and no observed signs of toxicity (Worasuttayangkurn et al., 2019). Additionally, ethanolic extracts of herbs (20, 200, and 1000 mg/kg BW) used male Sprague-Dawley rats in sub-chronic testicular toxicity model which showed no toxicity of testicular organs (Burgos et al., 1997). Specific toxicity models also determined through mutagenic and genotoxic test. Ames tests of methanolic extracts of leaves (16 to 5000 μg/ml) showed that the samples were no mutagenic (Chandrasekaran et al., 2009). Furthermore, genotoxic tests through chromosome aberration and micronucleus tests of methanolic extracts of leaves (8.8 to 345 μg/ml) proved non genotoxic (Chandrasekaran et al., 2009).

4. Discussion

The present study has a role in the topic raised by elucidating a theoretical and methodological timeframe that can be used in broad contexts. Specifically, the key findings of this study demonstrate the epistemological discourse of using bibliometric analysis by considering publication trends, the most contributed countries, the most productive authors, and the most influential papers. Also, it considers how the researchers built on the knowledge of each other through a bibliographical coupling network based on authors and co-citation network of the most influential papers, and how knowledge expanded in a time period using keyword co-occurrence network and overlay.

Besides discussing the scientific aspects, this study also incorporates managerial issues. Publication trends revealed many fluctuations between 1994 and 2021; 2021 had the highest number of publications. This study applied bibliometric analysis to managerial issues by analyzing the productive countries, institutions, publishers, and authors. This analysis will help other scholars build a research network and collaboration. Some countries have more than 10 publications, including India, Indonesia, Malaysia, and China. These countries are well known in traditional and alternative medicine. So, it was not surprising that these countries have an abundance of publications on this research topic. According to the bibliometric analysis, Universitas Gadjah Mada showed that the most productive institution. Furthermore, Journal of Ethnopharmacology was the most productive publisher. This journal focuses on the topic about biological and pharmacological activities of natural products. Agung Endro Nugroho (Professor of Molecular Pharmacology, Universitas Gadjah Mada, Indonesia) was the most productive author on preclinical trials of antidiabetic from *A. paniculata*. Agung Endro Nugroho has focused on the affectivity test of *A. paniculata* extract or compounds and its combination with other plants, even nanoformulations, to determine antidiabetic activity and molecular mechanisms. This information is expected to encourage research collaboration between productive authors, institutions, and countries.

Detailed scientific aspects of this topic can be accessed from a section of publication trends, the bibliographical coupling network based on authors, co-citation network of the most influential papers, and keyword co-occurrence network and overlay demonstrated expansion research on *A. paniculata* as an antidiabetic. Preliminary research began with the hypoglycemic effect of water extract on glucose-induced rabbits (Borhanuddin et al., 1994). Material plants of *A. paniculata* have been tested, such as extracts, fractionated isolates, phytochemical derivatives, and modifications of the formulation.

Every year, the preclinical trial research of *A. paniculata* on DM increases in the number and development of this topic area, such as investigating molecular mechanisms through antioxidant mechanisms (Zhang and Tan, 2000a), increasing glucose metabolism (Zhang and Tan, 2000b), enhancing glucose uptake (Yu et al., 2003), inhibiting glucose absorption at the intestine (Subramanian et al., 2008a), inhibiting hepatic gluconeogenesis (Yu et al., 2008), repairing endothelial dysfunction (Dandu and Inamdar, 2008), inhibiting glycolytic and gluconeogenic (Subramanian et al., 2008b), promoting lipogenic (Subramanian et al., 2008b), inhibiting NF-κB pathway (Zhang et al., 2009), inhibiting apoptosis related to diabetic

nephropathy (Lee et al., 2010), antioxidant related to brain function (Radhika et al., 2012), inhibiting the PTP-1B pathway (Saifudin et al., 2013), maintaining Th1/Th2/Th17 homeostasis (Zhang et al., 2013), inhibiting the AP-1 pathway (Lan et al., 2013), inhibiting angiogenesis and inflammation related to diabetic retinopathy (Yu et al., 2015), inhibiting oxidative damage (Li et al., 2015), inhibiting DPP-IV activity (Riyanti et al., 2016), enhancing intestinal barrier function and enhancing microbial composition (Su et al., 2020), inhibiting indoleamine 2, 3-dioxygenase related to the retina (Kumar et al., 2020), stimulating insulin production through the PDX-1 pathway (Zhang et al., 2020), and regulating the glucokinase pathway (Ab Rahman et al., 2020). However, some previous studies overlapped with other published papers. Here, functions of bibliometric analysis are needed to analyze research gaps.

Further research on *A. paniculata* within traditional and alternative medicine fields would contribute substantially to the therapeutic guidelines in healthcare. Several supporting aspects have been published, *i.e.*, analytical chemistry of phytochemicals (Akowuah et al., 2006), chemical fingerprinting (Srivastava et al., 2004), toxicity assessment (Worasuttayangkurn et al., 2019) and stability under accelerated conditions (Plubrukarn et al., 2006). A clinical trial of aqueous extract of *A. paniculata* and *Syzygium polyanthum* was reported in patients of type 2 DM. Research gaps of preclinical trials of *A. paniculata* on DM have opportunities to be developed in pharmacological aspects, such as detailed molecular mechanisms of its complications and clinical trials of drug formulation.

5. Limitations

The present study attempted to provide a scientific mapping of preclinical trial knowledge of *A. paniculata* as an antidiabetic using bibliometric analysis. The results of this study are to comprehend the existing research and conference articles on this topic. Our study has several limitations. The first limitation is related to the source of the database that we used in this study. We used only Scopus without other databases because Vosviewer can only read metadata from specific databases. Second, we selected articles only using the English language. Third, in the present study, the co-citation network and bibliographical coupling network are only based on articles and authors, respectively. Another unit of analysis for network construction could be used to complete our study.

6. Conclusion

A. paniculata remains a promising plant with broad benefits for human health and gains researchers' attention in exploring pharmacological fields. To the best of our knowledge, this study is the first bibliometric analysis on preclinical trials of *A. paniculata* as an antidiabetic. The study exhibited a fluctuating number of publications from 1994 to 2021 and described the general information of publications, including the most productive country (India), the most productive institution (Universitas Gadjah Mada, Indonesia), the most productive publisher (Journal of Ethnopharmacology), and the most productive author (Agung Endro Nugroho, who was affiliated with the Universitas Gadjah Mada, Indonesia). Furthermore, information from the most influential papers, co-citation network of the most influential papers, bibliographical coupling network based on authors, the keyword co-occurrence network, and overlay revealed that preliminary studies need to be conducted on the molecular mechanisms of antidiabetic action so that research topics about detailed molecular mechanisms of diabetic complications can be developed in future research.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

CRediT authorship contribution statement

Fitriana Hayyu Arifah: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Project administration. **Agung Endro Nugroho:** Conceptualization, Supervision, Funding acquisition, Writing – review & editing. **Abdul Rohman:** Supervision, Writing – review & editing. **Wawan Sujarwo:** Supervision, Writing – review & editing.

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Supplementary materials

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