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A Bibliometric Analysis to Preclinical Studies of *Tinospora Crispa* (L.) Hook. F. & Thomson as An Antidiabetic

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ABSTRACT

The number of diabetes mellitus (DM) cases has increased, and *Tinospora crispa* (L.) Hook. f. & Thomson is recognized for treating DM. Despite publications on *T. crispa* as an antidiabetic, there were no bibliometric reports on this topic. Thus, this study aimed to conduct bibliometric studies of existing articles on the preclinical trials of *T. crispa* in DM management. We used Scopus to obtain a bibliographic database of primary research related to the topic. There were 24 selected publications between 1989 and 2019. We analyzed data with VOSviewer 1.6.16. Malaysia, John Radcliffe Hospital (United Kingdom), *Journal of Ethnopharmacology*, Hamdan Noor, and Stephen J.H. Ashcroft (John Radcliffe Hospital, United Kingdom) were the most impactful country, institution, source, and author, respectively. This plant is promising for treating DM, meanwhile, there were case studies of harmful effects on the gastrointestinal tract and liver. The majority and diverse fields of this topic were phytochemistry and pharmacology. Our findings strengthen research collaboration and identify research gaps required for herbal medicine applications.

Keywords: *Tinospora crispa* (L.) Hook. f. & Thomson, diabetes mellitus, bibliometric, Scopus, VOSviewer

INTRODUCTION

Unhealthy lifestyles, including fast food, sleeplessness, stress, inadequate physical exercise, and smoking, rapidly promote noncommunicable diseases, including diabetes mellitus (DM) (Habib *et al*., 2020; Khaltaev & Axelrod, 2021). High glucose levels mark DM due to β-cell destruction or insulin resistance (Cerf, 2013; Chen *et al*., 2017). Chronic manifestations of these disorders can stimulate microvascular and macrovascular complications (Rangel *et al*., 2019; Yang *et al*., 2019). The DM incidence has constantly increased over time, with 463 million patients in 2019, and it is estimated to grow to 578 million and 700 million by 2030 and 2045, respectively. Besides the high prevalence, DM becomes a health burden, decreasing the quality of life, causing death, and affecting economic costs (Attaallah *et al*., 2021). We can apply natural products to prevent and/or treat the disease (Rohman *et al*., 2020).

Recently, numerous medicinal plants have been used to treat DM (Arifah *et al*., 2022). *Tinospora crispa* (L.) Hook. f. & Thomson is a plant that can help control hyperglycemia (Abu *et al*., 2015). The species is a member of Menispermaceae and is widespread across South East Asia and Africa (Ahmad *et al*., 2016). The plant empirically controls DM, jaundice, malaria, fever, hypertension, internal inflammation, and rheumatism (Ahmad *et al*., 2016). Indonesian people (especially Javanese ethnic) use decoction of dried stems of *T. crispa* twice a day to treat DM (Utaminingrum *et al*., 2020). Preclinical studies of *T. crispa* on DM have elucidated the mechanisms of action of antidiabetics, such as glucose absorption inhibitors (α-glucosidase and α-amylase) (Hamid *et al*., 2015),

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insulinotropic (M. Hamid *et al*., 2008), sterol regulatory-element-binding protein suppressors (Xu *et al*., 2017), and other mechanisms. Thus, two case studies reported that *T. crispa* showed harmful effects on the gastrointestinal tract, liver and biliary organs, and general problems (Langrand *et al*., 2014; Saokaew *et al*., 2011).

Many scientific publications on *T. crispa* as an antidiabetic are original and review studies. For example, two review articles reported that *T. crispa* was used by the community in Thailand and Indonesia as DM therapy (Andrade *et al*., 2020; Arifah *et al*., 2022). However, there have been no bibliometric approaches to this issue. Thus, a bibliometric study of *T. crispa* in DM was conducted to carry out further research progress. Bibliometric analysis is a field that incorporates managerial aspects (assessments of literature to evaluate the authors, institutions, and sources) and theoretical aspects (assessments of literature to analyze the knowledge within topic areas) (Bamel *et al*., 2020; Yeung, Heinrich, *et al*., 2018). The outcomes of bibliometric studies on managerial aspects provide considerations for new policies, help funding agencies and policymakers prioritize financing, and increase research collaborations (Elisha & Viljoen, 2021). Furthermore, bibliometric studies of theoretical aspects help comprehend publication trends and future trends in specific fields (Bamel *et al*., 2020). Thus, this study proposed a novel approach to quantitative studies of the antidiabetic properties of *T. crispa*, correlates previous studies on the topic, and suggests future research.

MATERIALS AND METHODS

Data source

The materials on *T. crispa* as an antidiabetic were obtained using the Scopus database. The dataset covers broad scientific papers, is comprehensive, and is compatible with bibliometric analysis (Bamel *et al*., 2020; Bankar & Lihitkar, 2019; Khitous *et al*., 2020). On October 27, 2021, we used the following keywords to search the Scopus database: "*Tinospora crispa*" AND diabet* OR "diabetes mellitus" OR dm OR insulin OR glucose (Figure 1). We used these keywords in the title, abstract, or keywords of scientific articles. The full text that fulfilled the inclusion and exclusion requirement was assessed. The inclusion criteria were as follows: Scopus database literature, primary research (original articles or conference papers), English only, and relevant topics to *T. crispa* as an antidiabetic in preclinical levels. The exclusion criteria were irrelevant terms such as the previous article (Arifah *et al*., 2021), insufficient and biased information, non-accessible, and duplication (Arifah *et al*., 2021). This study also examined toxicological issues. We used the following keywords in the Scopus database: "*Tinospora crispa*" AND toxicity OR toxicology OR "adverse effect" OR "side effect." The inclusion and exclusion requirements were the same as in the previous article (Arifah *et al*., 2021). Some detected chemical structures were sketched using the MarvinSketch program.

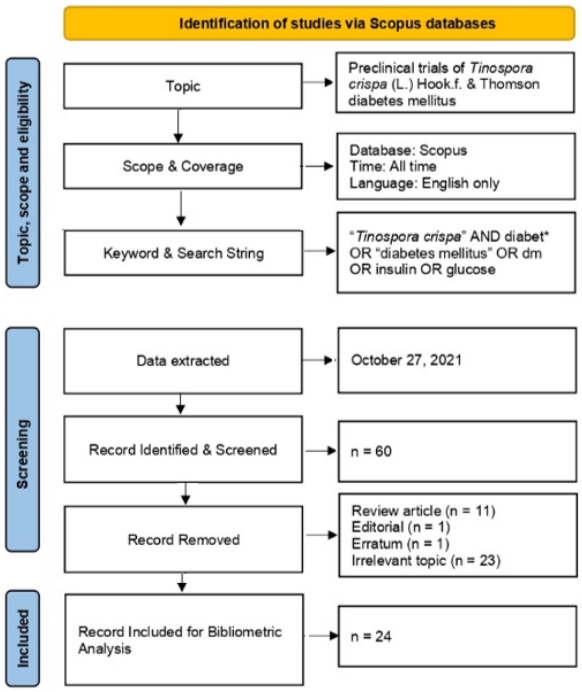

Figure 1. Search process methodology

Data extraction and analysis

Figure 1 depicts the data extraction and analysis process. For bibliometric analysis, the eligible documents were saved as ".CSV" and transferred to VOSviewer 1.6.16 (van Eck & Waltman, 2020). This program evaluated publication trends, impactful countries, institutions, sources, authors and bibliographical coupling networks, documents and co-citation networks, keyword co-occurrence network, and overlay (Arifah *et al*., 2021). The bubble map visualization represents a term or phrase (Ramamoorthi *et al*., 2021). Moreover, the bubble size and distance between bubbles demonstrated the word frequency and co-occurrence frequency, respectively (Yeung *et al*.,2018; 2020).

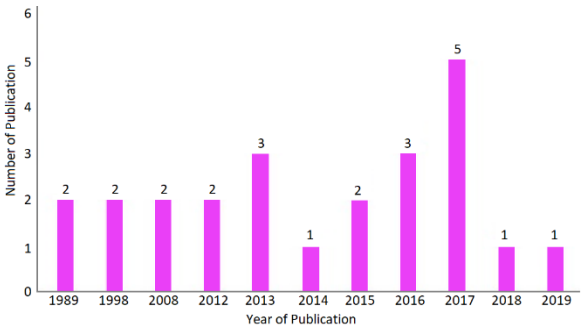

Figure 2. Trends in T. *crispa* publication in diabetes preclinical studies

RESULTS AND DISCUSSION

Publication trends

The articles were published from 1989 to 2019, including 18 sources and 90 authors from 24 selected articles. The oldest paper was published in the *Journal of Ethnopharmacology* in 1989 about water extracts of *T. crispa* stems on alloxan-diabetic rats (Figure 2). Moreover, 2017 has seen the highest number of publications, with five published articles. Before 2000, published articles revealed experiments of water extract of stems using HIT-T15 cells and alloxan as diabetic models to elucidate the mechanisms related to insulinotropic (Supplementary File Table I). From 2005 to 2010, research evidence demonstrated the mechanisms of methanolic and water extracts of stems to enhance insulinotropic and glucose uptake through *in vitro* studies using BRIN-BD11 and L6 myoblast cells. Furthermore, eight articles published from 2011 through 2015 discussed water and methanolic extracts of stems as well as some phytochemical compounds (borapetoside A, borapetoside C, and borapetol B, Figure 3) using several diabetic models, involving *in vitro* models using C2C12 cells, Hep3B cells, HepG2 cells, rat pancreatic islets, protein tyrosine phosphatase 1B (PTP-1B) test, α-amylase assay, and α-glucosidase test and *in vivo* models using streptozotocin (STZ), high-fat diet (HFD), HFD and fructose, and Goto-Kakizaki rats. As a result, many antidiabetic mechanisms were elucidated, such as suppressing hepatic gluconeogenesis, PTP-1B activity, absorption of glucose in the intestine; enhancing insulin stimulation, insulin signaling, insulin release, and glucose uptake; and ameliorating insulin resistance. From 2016 to 2020, 10 published articles tested herbal formulations, water, methanolic, ethanolic, chloroform, and petroleum ether extracts of stems, as well as some phytochemicals (borapetoside C, borapetoside E, cordifolioside A, tinocrisposide, and magnoflorine, Figure 3), using several diabetic models. *In silico* models applied the docking method; thus, *in vitro* models used cell lines (IR-HepG2 cells and 3T3-L1 cells) and non-cell lines (dipeptidyl peptidase-IV *(*DPP-IV) assay). *In vivo* models used diabetogenic (alloxan, STZ, and STZ-nicotinamide) or diet (HFD) inductions. Several antidiabetic mechanisms of this time involve enhancing the adipocyte-free fatty acid, glucose uptake, and insulin sensitivity; inhibiting DPP-IV and sterol regulatory-element binding protein pathways, ameliorating traumatic ulcer healing, and interacting with most proteins related to DM pathogenesis. Meanwhile, several papers did not examine antidiabetic mechanisms.

The timeline above shows *T. crispa* research in DM preclinical trials. The research started with stem water extracts to manage glucose and insulinotropic effects. Thus, other extracts and phytochemicals were tested for antidiabetic actions. However, no studies have reported the formulation and drug delivery of *T. crispa* as an antidiabetic.

Analysis of impactful countries

Twenty-four articles from eight nations examined antidiabetic preclinical studies of *T. crispa*. Asia controlled the majority of countries that contributed (Supplementary File Table II). Malaysia was the most impactful country based on the number of publications, whereas the UK had the most citations per publication.

Analysis of prominent institutions

Institutional contributions in the 24 articles demonstrated that 31 institutions participated in preclinical *T. crispa* antidiabetic investigations (Supplementary File Table III). John Radcliffe Hospital (UK) was the most prominent institution, whereas National Taiwan University (Taiwan) had the highest average citation per publication among the top 10. The majority of contributing institutions were located in Asia.

Analysis of contributing sources

The information regarding antidiabetic preclinical studies of *T. crispa* can assist scholars in finding a promising publisher and submitting their works. There were 18 sources, but only six with two papers (Supplementary File Table IV). The *Journal of Ethnopharmacology* published the most with two publications, 95 citations, and an average citation per publication of 47.50.

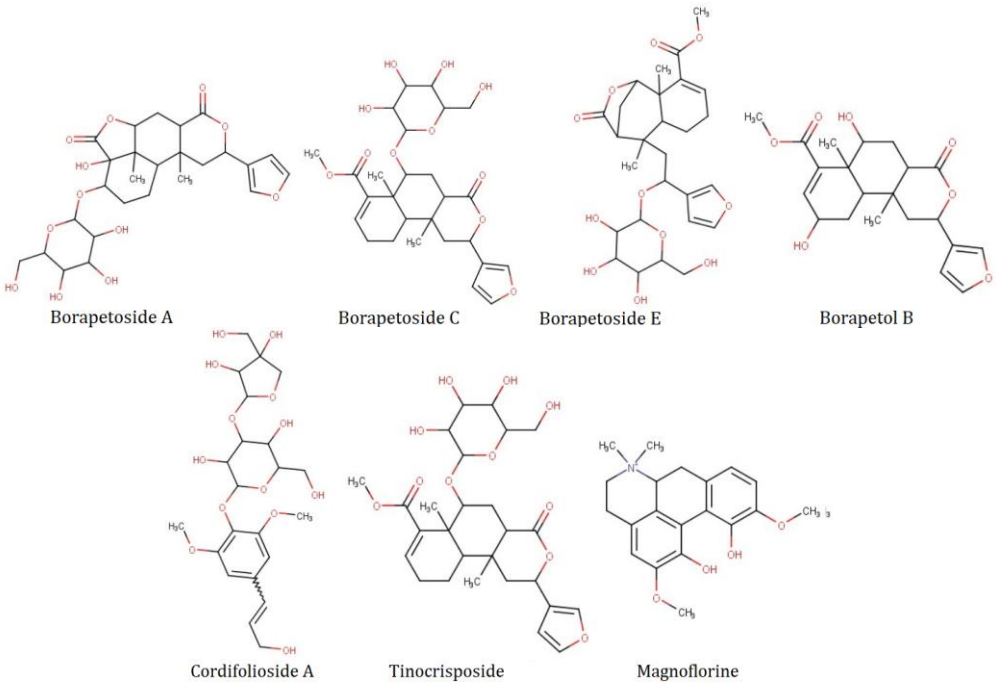

Figure 3. Structures of some phytochemicals of *T. crispa*

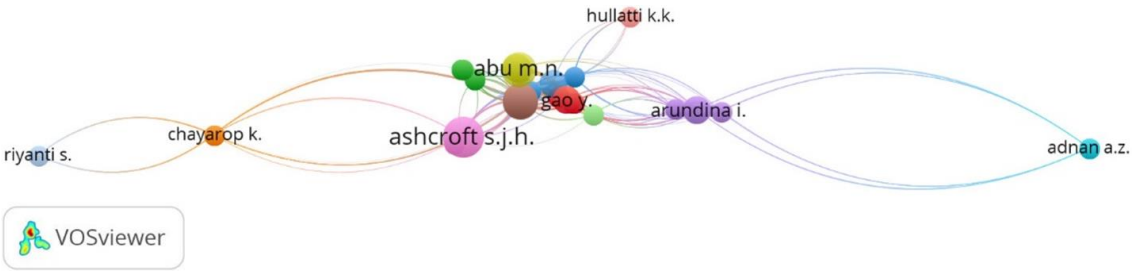

Figure 4. Author-based bibliographic coupling network

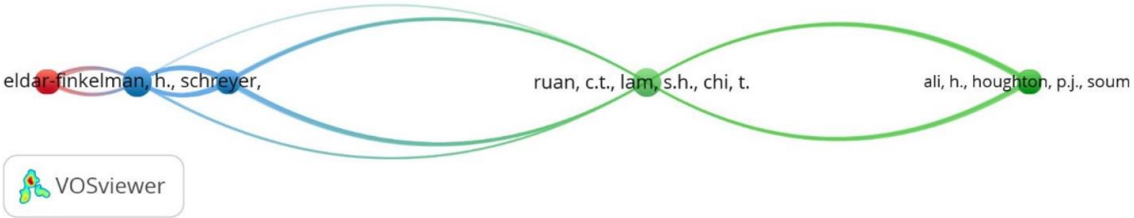

Figure 5. Co-citation network of cited references

Analysis of authors and bibliographical coupling network

Author analysis in a particular field identifies scholars who have made substantial contributions to a research area and describes collaboration patterns and the concept of collaboration among scholars (Bamel *et al*., 2020; Qin *et al*., 2022; Tan *et al*., 2021). Ninety authors researched preclinical antidiabetic activities of *T. crispa* based on a bibliometric analysis of 24 selected documents. The most influential authors had three documents as threshold (Supplementary File Table V). Hamdan Noor and Stephen J.H. Ashcroft (four documents) have the most publications (Table S5); both are linked with British institutions (John Radcliffe Hospital).

Scholars, institutions, and countries will give insights for other scholars to develop and encourage research collaboration (Arifah *et al*., 2021). Author-based bibliographical coupling was also developed. This analysis describes two authors who cited similar articles in their papers (Ma, 2012). A high bibliographical coupling strength implies similar topics in analyzed articles (Abdullah & Khan, 2021). In this analysis, we applied fractional counting because it has common misinterpretations and is preferable to full counting (Perianes-Rodriguez *et al*., 2016). Each article had the same weight; therefore, it was equal to one (Bamel *et al*., 2020). Subsequently, we used the thesaurus to blend distinct author names that were the same (Arifah *et al*., 2021). We required two documents for each author, resulting in 15 of 90 authors; however, this was insufficient for building a co-citation network (Figure 4). Ninety authors satisfied the one-document minimum, but only 82 had the most connections. So then, we specified two minimum document numbers and calculated 1450.62 as the total link strength with 1860 linkages.

The size of this network shows the author's coupling intensity inside the cluster, presenting that their reference list is similar. The author's name is used for clusters with the largest node. Table S6 shows the results of our bibliographical coupling network, which identified 12 clusters. Clusters 1, 2, 3, 4, 8, 9, and 11 were close to each other and were chaired by Abdul Manaf Ali and Angkana Herunsalee for cluster 2; thus, Yuan Gao, H.A. Hamid, Mohd Nazri Abu, Sio-Hong Lam, Stephen J.H. Ashcroft, and Ashfaq Ahmad chaired clusters 1, 3, 4, 8, 9, and 11, respectively. Moreover, clusters 5, 6, 7, 10, and 12 were wide apart and were chaired by Ira Arundina, Adek Zamrud Adnan, Kullacha Chayarop, K. K. Hullatti, and Soraya Riyanti, respectively.

Analysis of the most impactful articles and co-citation network

We used the total number of citations for each document to rank the most influential articles. The study revealed the nine most-cited articles with over 20 citations (Supplementary File Table VII). Noor's team (1998) attained the highest citation for the study entitled "Pharmacological characterization of the antihyperglycaemic properties of *T. crispa* extract." The nine most impactful articles discussed extracts, borapetoside A, borapetoside C, and borapetol B in antidiabetic activities with various mechanisms, including α-glucosidase and α-amylase inhibitors, insulinotropic, PTP-1B inhibitor, insulin signaling enhancer, insulin stimulator, and hepatic gluconeogenesis suppressor.

We performed co-citation network analysis to assess scientific knowledge and research trend extensions (Cheng *et al*., 2022). A co-citation network is created when two documents are co-cited (Bamel *et al*., 2020; Shiau *et al*., 2017). If other documents regularly cite two documents, they have a strong relationship (Bamel *et al*., 2020; Shiau *et al*., 2017). Co-citation measures the semantic similarity between two or more documents based on their citation relationships, and more co-citations indicate semantic similarity (Shiau *et al*., 2017). This study built a co-citation network to investigate influential scholars' works (Bamel *et al*., 2020). This analysis also revealed spatial information for the most-cited articles in its visualization (Bamel *et al*., 2020).

We employed fractional counting in the analysis, similar to the bibliographic coupling network. We determined a minimum of one citation of a cited reference, 606 met the threshold, and we connected only 90 items in the network. We put a criterion of two minimum citations, and 12 documents met the criterion. Thus, we used one minimum citation to analyze this network (Figure 5 (Supplementary File Table VIII). Three clusters in the network were identified, i.e., cluster 1 (blue-colored), cluster 2 (green-colored), and cluster 3 (red-colored), consisting of 31, 29, and 29 publications, respectively.

Keyword co-occurrence network and overlay

We can use the keyword co-occurrence network and overlay to find research topics with much attention and give immediate, objective, and repeatable insights into the main research fields (Bamel *et al*., 2020; Grames *et al*., 2019). The nodes in the visualization represented prospective keywords and network co-occurrence edges (Grames *et al*., 2019). We applied fractional counting was applied because it normalizes link weights, creates more realistic findings, and reveals network structure (Vargas-Quesada *et al*., 2017). This analysis includes three possibilities for a unit of analysis: author keywords, indexed keywords, and all keywords; thus, we chose all keywords. Author keywords describe author aboutness with natural language phrases, whereas indexed keywords interpret the contents (Vargas-Quesada *et al*., 2017). In bibliometric research, author keywords are efficient for analyzing the knowledge

landscape of domains; nevertheless, they may be biased because certain scientists may employ specific keywords to boost the exposure of their works (Vargas-Quesada *et al*., 2017; Zhang *et al*., 2016). Moreover, indexed keywords are exhaustive visualizations of document contents and help visualize article content (Vargas-Quesada *et al*., 2017). Therefore, our construction was based on all keywords (author and indexed keywords); then, we excluded the repetitions of keywords with the thesaurus tool (Arifah *et al*., 2021).

This network visualization showed 361 keywords from 24 articles. Therefore, we used one keyword as the threshold requirement, and 361 keywords met the criterion. However, its visualization was so crowded and overlapped. Therefore, we used two keywords as the requirements, and 103 met the criteria. Thus, several keywords had a general meaning and were irrelevant (such as article, unclassified drug, controlled study, male, support non-U.S. gov't, and priority journal); thus, we included only 97.

The distance between nodes indicates how closely related terms are, and the node size indicates the frequency with which keywords appear (Bamel *et al*., 2020) (Figure 6A). Furthermore, the frequency of these keywords appearing together in the network is represented by a node overlap (Bamel *et al*., 2020). According to the visualization, this analysis comprises five clusters (Table S9). These clusters were closed network sites, except for wound healing and traumatic ulcer from cluster 5 on the network's offside.

The node size reflected the keyword's occurrence frequency (Figure 6B). Purple, purple-blue, blue-green, green, and yellow nodes were used around/before 2006, around 2008, around 2010, around 2012, and around/after 2014, respectively. Some keywords, including insulin secretion, cell line, pancreas islet, glucose transport, Ca^{2+}, and rats, occurred around 2006, whereas keywords such as human, hypoglycemia, nonhuman, and nonhuman appeared around 2008. Moreover, keywords used around 2010 involved animal tissue, animal model, and borapetol B, whereas around 2012, drug isolation, diterpenoid, methanol, fruit, bark, *Andrographis paniculata*, and *Momordica charantia* were used. Furthermore, around 2014, cholesterol, triacylglycerol, drug effect, chemistry, obesity, type 2 diabetes mellitus, insulin resistance, protein expression, protein kinase B, glucose transporter (GLUT)-2, protein phosphorylation, apoptosis, wound healing, and traumatic ulcer were used. This research timeline shows that preclinical studies of *T. crispa* as an antidiabetic have expanded, starting with blood level and exploringmolecular mechanisms.

Toxicological aspects

According to the search process of toxicological aspects, we found no data about *T. crispa* on this topic. Meanwhile, case studies regarding this plant were reported in Thailand and Vietnam. For example, a case study from Thailand demonstrated the harmful effects of *T. crispa* on the gastrointestinal tract (symptoms such as abdominal pain, constipation, and abdominal discomfort), liver and biliary organs (hepatitis), and general problems (chest tightness) (Saokaew *et al*., 2011). Moreover, a case study from Vietnam revealed that *T. crispa* was implicated in developing of hepatitis in a 49-year-old man (Langrand *et al*., 2014).

The current study contributes to the research topic raised by exemplifying the theoretical and methodological based on a timeline that we can apply in various contexts. The study revealed publication trends, the most contributing countries, the most contributing institutions, the most publishers, and the most influential papers. This study also examines how the researchers built on the knowledge of each other via a bibliographical coupling network based on authors and co-citation network of the most influential paper and how knowledge expanded in a timeline using keyword co-occurrence network and overlay.

This study discusses two approaches, such managerial and scientific aspects. The number of publications fluctuated between 1989 and 2019; 2017 was the highest of publications. Other managerial aspects of bibliometric analysis assessing the productive countries, institutions, publishers, and authors will help other researchers initiate a research network and collaboration. Several countries have more than three publications, such as Malaysia, the United Kingdom, Taiwan, and Indonesia. Thus, Malaysia had the highest number of publications (six papers). John Radcliffe Hospital was the most productive institution. No publishers have the highest number of publications.

Meanwhile Journal of Ethnopharmacology had the highest number of publication and average citation per publication. This journal dedicates to the topic of the exploration of natural products in health issues.

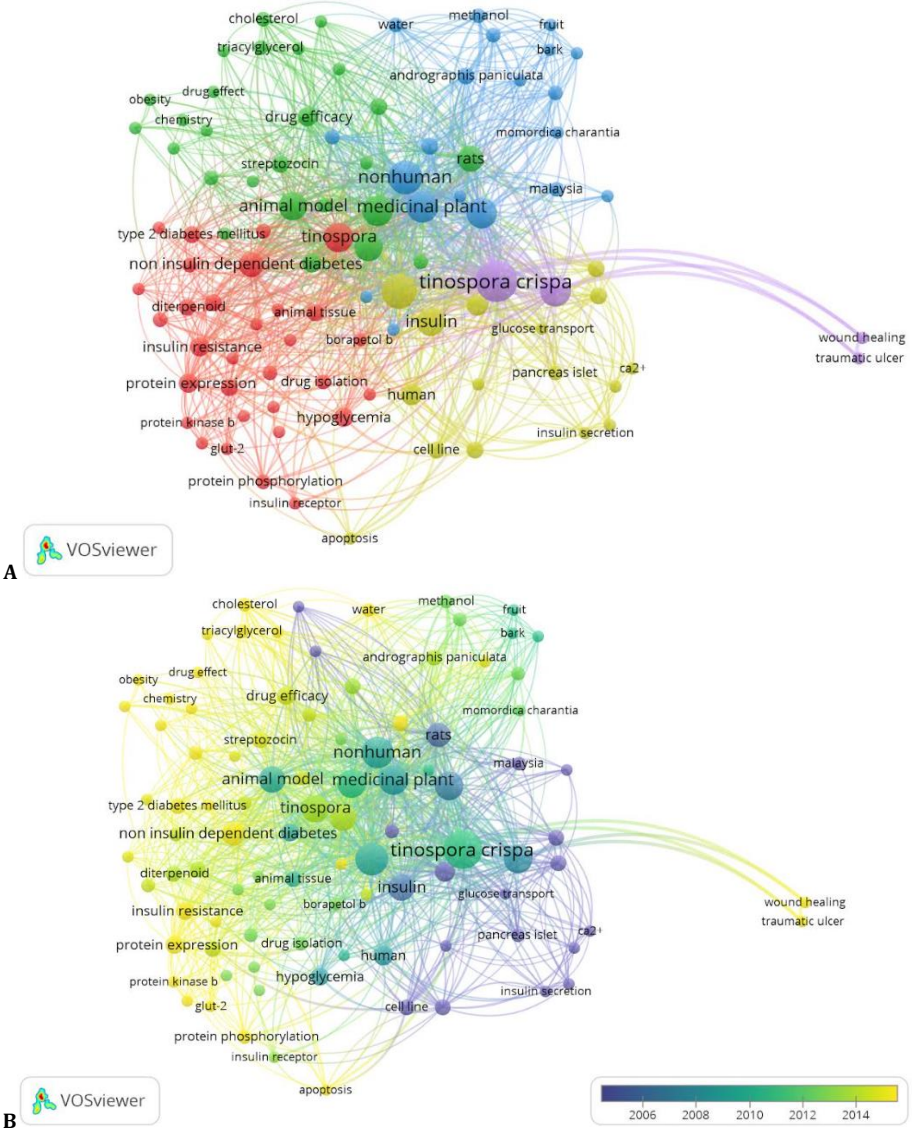

Figure 6. (A) keyword co-occurrence network, (B) keyword co-occurrence overlay with a timeline

Hamdan Noor and Stephen J.H. Ashcroft (John Radcliffe Hospital, United Kingdom) were the most productive authors on preclinical trials of antidiabetic from *T. crispa*. They have focused on the preliminary screening of water extracts of stems and mechanisms of action by stimulating insulin release through Ca^{2+} modulation (Noor *et al*., 1989; Noor & Ashcroft, 1989, 1998a, 1998b). This data should promote research collaboration among authors, institutions, and countries.

The section on publication trends, the bibliographical coupling network based on authors, the co-citation network of the most influential articles, and the keyword co-occurrence network and overlay revealed the growth of research on *T. crispa* as an antidiabetic. Preliminary research began with the ability to decrease glucose and increase insulin level of water extract of stems (4 g/l for two weeks) on the alloxan-induced diabetic rats (35-40 mg/kg BW, i.v) (Noor & Ashcroft, 1989). In addition, material plants of *T. crispa* have been tested, such as polyherbal formulations, extracts, and single phytochemical compounds.

Many molecular mechanisms of *T. crispa* as antidiabetic have been elucidated, such as stimulating insulin release (Lokman *et al*., 2013; Noor *et al*., 1989; Noor & Ashcroft, 1998b), promoting insulinotropic effect (M. Hamid *et al*., 2008; Noor & Ashcroft, 1998a), enhancing glucose uptake (Abu *et al*., 2014; Noipha *et al*., 2008), reducing hepatic gluconeogenesis (Lam *et al*., 2012; Ruan *et al*., 2013), enhancing insulin stimulation through IR/Akt/GLUT-2 pathway (Ruan *et al*., 2012, 2013), inhibiting PTP-1B activity (Saifudin *et al*., 2013), ameliorating insulin resistance (Abu *et al*., 2015), inhibiting the absorption of glucose at the intestine (H. A. Hamid *et al*., 2015), inhibiting DPP-IV activity (Riyanti *et al*., 2016), and ameliorating traumatic ulcer healing (Arundina *et al*., 2017; Roestamadji *et al*., 2017).

Some previous studies reported on the relationship between structure and antidiabetic activities. Isolated alkaloids in *T. crispa* were constructed from A-rings, B-rings, and C-rings with sp^2 hybridization; thus, these atoms form a large conjugated system for interaction with α-glucosidase and α-amylase (Hamid *et al*., 2015). Moreover, the presence of methylene dioxide in liriodenine and lysicamine has an essential role in α-glucosidase inhibition; at the same time, the two hydroxyl groups in dihydrodiscretamine and magnoflorine are beneficial for α-amylase inhibition (Hamid *et al*., 2015). Furthermore, *N*-trans-feruloyltyramine has a phenyl hydroxyl group and lacks rings A, B, and C indicating significant inhibitory activity (Hamid *et al*., 2015). Thus, other compounds in *T. crispa*., i.e., borapetosides A, B, and C, suggested that C-8 stereochemistry plays a crucial role in diabetic effects (Ruan *et al*., 2013). Borapetosides A and C were active due to 8R-chirality, while borapetoside B was inactive due to 8S-chirality (Ruan *et al*., 2013). The location of glycoside also influenced different potency, i.e., C-3 for borapetoside A but C-6 for borapetoside C, and the formation of lactone between C-4 and C-6 (Ruan *et al*., 2013).

Several earlier investigations, however, overlapped with previously published articles. In this case, bibliometric analysis functions are required to identify research gaps. In addition, other topics support *T.* crispa, which would contribute to alternative medicine in healthcare. For example, there was a clinical trial of the capsule of *T. crispa* stems. Meanwhile, the results revealed that it could not affect serum glucose and insulin levels in healthy subjects and type 2 DM patients (Klangjareonchai & Roongpisuthipong, 2012).

CONCLUSION

Tinospora crispa has health benefits, including DM. This study is the first bibliometric analysis of preclinical trials of *T. crispa* as an antidiabetic. The number of publications fluctuated from 1989 to 2019. The analysis identified the most productive country (Malaysia), institution (John Radcliffe Hospital, UK), source (*Journal of Ethnopharmacology*), and author (Hamdan Noor and Stephen J.H. Ashcroft, are affiliated with the John Radcliffe Hospital, UK). Information from the most influential publications based on influential papers, co-citation network, author-based bibliographical coupling network, keyword co-occurrence network, and overlay showed basic investigations on antidiabetic efficacy. Several suggestions for further researchers based on bibliometric studies on preclinical trials of *T. crispa* in DM are pharmacological markers, effective doses to optimize the effects on human application, and formulation technologies.

AUTHORS' CONTRIBUTIONS

Fitriana Hayyu Arifah: Conceptualization, Methodology, Formal analysis, Data Curation, Writing – Original Draft, Writing – Review & Editing, Project Administration. Agung Endro Nugroho: Supervision, Funding acquisition. Abdul Rohman: Supervision. Wawan Sujarwo: Supervision, Writing – Review & Editing. All the authors have read and approved the final manuscript.

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