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Anti-diabetic properties of traditional herbal concoction containing *Eleutherine palmifolia* (L.) Merr., *Momordica charantia* L., and *Syzygium polyanthum* (Wight.): a bibliometric analysis

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Abstract

Eleutherine palmifolia, Momordica charantia, and *Syzygium polyanthum* are herbal plants, traditionally used as natural remedies for diabetes. There have been numerous articles published on the anti-diabetic efficacy of these plants; yet, no bibliometric study on the subject is available. In this study, the published papers on the utilization of *E. palmifolia, M. charantia*, and *S. polyanthum* as anti-diabetic agents were examined using bibliometric approach, focusing on countries, organizations, authors, and keywords. The phytochemicals, pharmacological properties, and mechanism of action of each herbal plant associated with diabetes were also discussed in detail. The data were searched through the SCOPUS database and bibliometric analysis was performed using VOSviewer software. The World Flora Online (WFO) was used to confirm the identity of the plant species. A total of 1008 articles were retrieved with *M. charantia* (977 articles) showing the highest number of publishing articles compared to *E. palmifolia* (9 articles), and *S. polyanthum* (22 articles). Upon further review of these plants, the findings showed that each plant has active ingredients that can prevent as well as control the complications of diabetes. Eleutherol, eleuthenone, eleutherinoside A, kuguacin, momordicin, vicine, squalene, myricitrin and epigallocatechin gallate (EGCG) were among the phytochemicals responsible for the effect. The possible underlying mechanisms of action were attributed to lowering blood glucose, increasing insulin production, inhibiting intestinal glucose absorption, and enhancing glucose uptake by the muscles. Based on the review, it is evidenced that the individual plants demonstrated a promising anti-diabetic activity, thus, it is recommended to conduct further studies using a polyherbal mixture, combining these three extracts and analyzing using in vitro and in vivo models.

Keywords Herbal medicine, VOSviewer, Type 2 diabetes, SCOPUS, Metabolic disease

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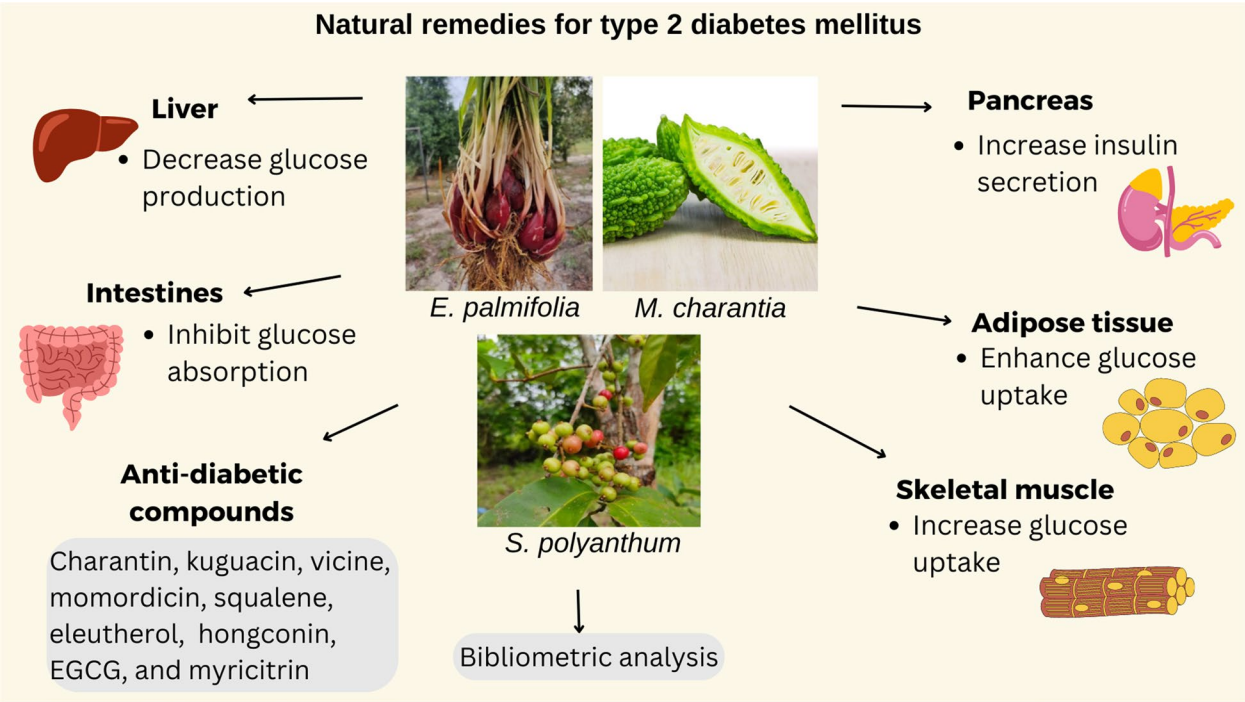
Graphical Abstract



Introduction

Diabetes mellitus (DM), one of the most common chronic diseases, is linked to high rates of morbidity and mortality. It is characterized by a hyperglycemic state and insulin deficiency, resistance, or both. There are three types of diabetes including type 1, type 2, and gestational diabetes. Type 2 DM is the most common type of DM and it accounts for 90–95% of diabetic cases (American Diabetes Association 2009). It affects 537 million adults aged 20 to 79, according to the International Diabetes Federation (IDF). This number is expected to increase to 643 million by 2030 and 783 million by 2045 (Ampofo & Boateng 2020). Diabetes can cause long term complications including nephropathy, neuropathy, and retinopathy as well as macrovascular issues like heart failure, atherosclerosis, and peripheral vascular disease if it is not controlled (Ahmed et al. 2020).

Type 2 DM is caused by the failure of pancreas to produce enough insulin or when the insulin is utilized inefficiently. The body do not respond normally to insulin, which is called insulin resistance and therefore it could not bring the glucose into the cells (Joseph & Raj 2010). This causes the body to rely on the alternative sources from the tissues, muscles and organs. Medications such as metformin, insulin, and mimetics are prescribed to control blood sugar levels and improve insulin sensitivity (Colberg et al. 2016; Yakubu et al. 2020). However, the consumption of these medications may cause adverse effects, including dyspepsia, nausea, and diarrhea in the early stage (Thulé 2012). Metformin also should be avoided by those who have impaired renal function, heart failure, liver disease, or other serious medical conditions (Hahr & Molitch 2015). This findings prompted scientists and medical experts to look for deeper insights into this chronic illness, with a focus on natural remedies as an appealing strategy to prevent and cure diabetes.

In this study, *E. palmifolia, M. charantia,* and *S. polyanthum* were chosen because ethnobotanical findings indicated that these particular herbs were effective in treating diabetes among local people (Febrinda et al. 2014; Saeed et al. 2018). In Indonesia, *E. palmifolia* is used by the Dayak community to treat various illnesses including diabetes (Ahmad et al. 2018). It can be taken raw or the bulb can be boiled to make a decoction. Meanwhile, among the Caribbean people, *M. charantia* is administered as medication as a leaf decoction and fruit juice in treating diabetes. In Turkish folk medicine, the

oil extracted from ripened fruit is combined with honey and warmed olive oil (Peter et al. 2019). *S. polyanthum*'s leaves are also traditionally used to cure diabetes in many region of Indonesia (Kusuma et al. 2011). According to an ethnobotanical survey, *S. polyanthum* was the most often utilized herb among diabetic patients in North Sumatera, Indonesia (57.1%) (Widyawati et al. 2015a).

The healing properties of these plants are probably due to their bioactive compounds such as phenolics, glycosides, alkaloids, terpenoids, flavonoids, and carotenoids (Kayarohanam & Kavimani 2015; Zohary & Hopf 2000). Scientific studies have proven the efficacy of these herbs in preventing and treating diabetes (Rahim et al. 2018; Widyawati et al. 2019; Yin et al. 2014). Preclinical trials for *E. palmifolia, M. charantia,* and *S. polyanthum* also provided abundance of data for their anti-diabetic effects (Febrinda et al. 2014; Lelono & Tachibana 2013; Sandikapura et al. 2018). They were found to inhibit α-glucosidase and α-amylase, modulate glucose uptake, increase insulin level, increase pancreatic β-cell proliferation and regulate oxidative stress (Arifah et al. 2021).

The discovery of herbal plants with various anti-diabetic mechanisms has prompted researchers to develop polyherbal mixtures to treat diabetes. According to Perumal et al. (2022), polyherbal combinations have better anti-diabetic effects than single extracts. Several reviews including systematic and meta-analysis studies have been conducted on *E. palmifolia, M. charantia* and *S. polyanthum* individually, but, there is lacking of bibliometric analysis focusing on the combination of *E. palmifolia, M. charantia* and *S. polyanthum* as an anti-diabetic agent. Based on the expanding number of publications and demonstrated anti-diabetic compounds of these plants, *E. palmifolia, M. charantia,* and *S. polyanthum* are worthy plant candidates for tracking the collective knowledge of global research activities in this field, reviewing their prospective combined effect on anti-diabetic properties, and identifying a fresh perspective on the future direction of these plants as a potential polyherbal mixture in anti-diabetic research.

Methods

Search strategy

The data for this review were extracted from the SCOPUS database on 3rd October 2022 using the following search terms, "*Eleutherine palmifolia* AND anti-diabetic OR diabetes", "*Momordica charantia* AND anti-diabetic OR diabetes" and "*Syzygium polyanthum* AND anti-diabetic OR diabetes". SCOPUS was chosen in this study because it covers a wide range of journals and more comprehensive than other databases (Falagas et al. 2008). Web of Science was not included because 99% of the journals indexed in this database are already indexed in SCOPUS (Singh et al. 2021). Meanwhile, Google scholar was not considered for the study because it does not provide detailed information demanded by network analysis, like the bibliometric approach.

The PRISMA flowchart is described in Fig. 1. Full texts that met the eligibility criteria from the inclusion and exclusion requirements were analyzed based on the title, abstract, and introduction. The inclusion criteria included original articles and English language. We excluded the literature research based on the review article, conference paper, book chapter, survey and report. The species names were confirmed using The World Flora Online (WFO) (Arifah et al. 2022). The chemical structures of the compounds were drawn using ChemSketch software (ACD/labs, Canada).

Data analysis

The data analysis was performed based on the methods by Arifah et al. (2022). The selected articles were retrieved and sorted systematically using Microsoft Excel in the comma-separated value (CSV) format. To perform bibliometric analysis, all data were imported into visualization of similarities (VOS) viewer v.1.6.18 (Leiden University, The Netherlands). The following parameters for co-authorship analysis was assessed such as contributing countries, authors, and organizations and a full counting method was chosen as a part of analysis. Then, author keyword co-occurrence analysis was done and the network and overlay visualizations were generated. Thesaurus tool was also applied to merge the keywords with similar meanings.

Term map

For the term map, the number of publications or frequency shown by the size of the circular nodes in the illustrated map, the distance between nodes represented the degree of interaction, and the link between nodes signified interactions such as collaboration or co-occurrence. The total link strength of a node was determined as the sum of its link strengths over all other nodes (Arifah et al. 2022).

Results

Ethnobotanical description and distribution of the plants

E. palmifolia (Iridaceae family) is also known as Dayak onion, originated from the Kalimantan in Indonesia. Dayak onion have several scientific names such as *E. bulbosa, E. americana, E. elicata,* and *E. latifolia. E. palmifolia* was suggested as an official scientific name by Kew and Missouri Botanic Garden (Couto et al. 2016). The diameter of the bulb is ranging from 20 to 50 mm (Fig. 2). The bulb is oval and consists of many layers

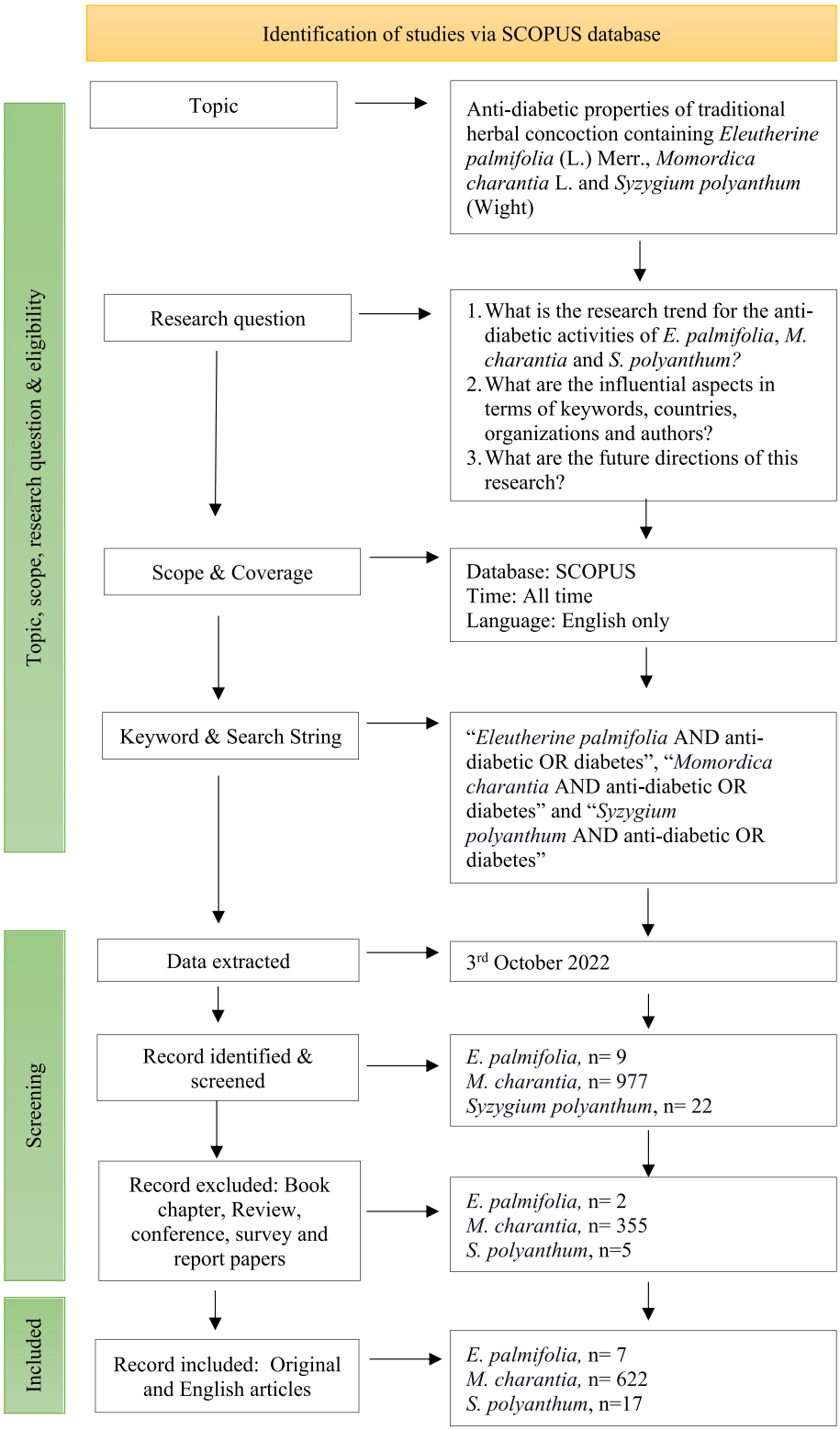


Fig. 1 PRISMA flow diagram of the search strategy

Fig. 2 The bulb of the *E. palmifolia* (own photo)

Fig. 3 The fruit of *M. charantia* (own photo)

like a regular onion with a striking deep reddish color (Wiendi et al. 2012).

M. charantia, also known as karela, bitter gourd, or bitter melon, is a fruit from Cucurbitaceae family. It originated from East India, but it is now widely planted and consumed in tropical, subtropical, and temperate climates. The fruit is bright green, with a pointy surface, a cone shape, and a bitter taste (Fig. 3) (Palamthodi & Lele 2014).

S. polyanthum (Myrtaceae family) is referred to as daun salam and serai kayu, in Malaysia whereas in Indonesia, the plant is known as ubat serai, meselengan, manting, Indonesia laurel, or Indonesian bay leaf (Widyawati et al. 2015a). *S. polyanthum* is widely found in the hillsides and forests of South-East Asian countries such as Malaysia, Thailand, Indonesia, and Singapore. The plant can grow to be up to 25 m tall. The leaf shape is elliptical and pointy (Fig. 4) (Roskov et al. 2013).

Publication trends

Overall data searches for *E. palmifolia, M. charantia,* and *S. polyanthum* were done with no time limitation including all areas of studies. The output in the Fig. 5 showed that the number of documents publishing about *E. palmifolia* was constantly low in the beginning, but fluctuated from 2009 to 2015. The number consistently increased from 2017 until 2020 before going down in 2021. For *M. charantia,* the documents published were higher compared to *E. palmifolia* and *S. polyanthum*. The number of publication started to increase from 2005 to 2021 but the trend reduced after 2022. *S. polyanthum* on the other hand, it could be seen that number the of the document was higher than *E. palmifolia* but lower than *M. charantia.* The number of documents increased from 2016 to 2021 before dropping in 2022.

Bibliometric analysis of *E. palmifolia*

Only papers that were published in English were included in the results. Non-original articles and reviews were not considered. Among nine papers obtained, only seven articles were retrieved for VOSviewer analysis. There was a total of 38 authors with eight clusters produced

Fig. 4 The leaves and fruit of *S. polyanthum* (own photo)

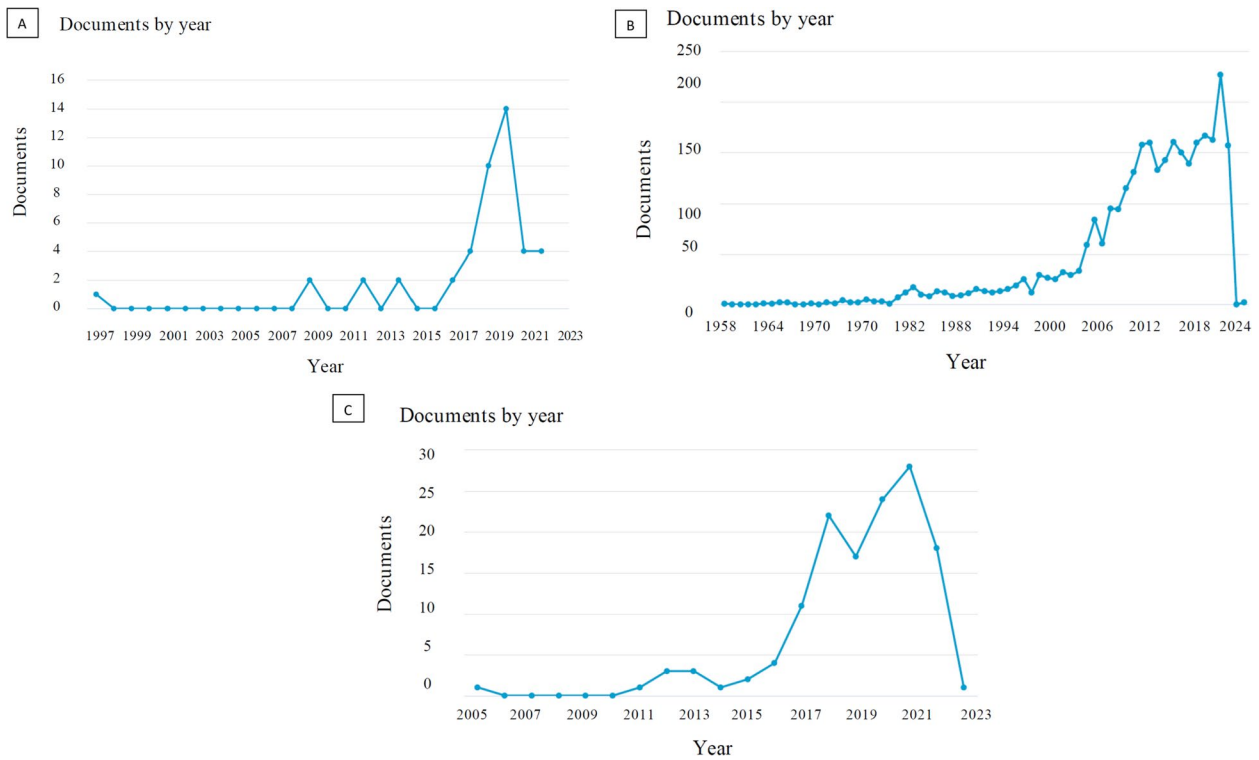


Fig. 5 Publication trends of *E. palmifolia* (**A**), *M. charantia* (**B**), and *S. polyanthum* (**C**) articles

(Supplementary 1, Fig. 1). Table 1 shows the top 10 authors that published one article each author with Bin Sayeed M.S. obtained the highest citation. When analyzing the paper by the organization, there was a total of 26 organizations grouped into eight clusters (Supplementary 1, Fig. 2). Each organization published only one paper and the Department of Clinical Pharmacy and Pharmacology, University of Dhaka produced the highest citation (Table 2). For the analysis of the country, Indonesia published the highest number of articles, followed by Bangladesh and Japan (Table 3). As in as in Supplementary 1 (Fig. 3), the distribution of countries was grouped into three clusters.

Next, the data were analyzed based on the keyword. A total of 31 keywords were identified and the top 3 keywords with the most occurrences were "Dayak onion," "traditional medicine", and "alkaloids," (Table 4). The term map in Fig. 6 indicates seven clusters, where cluster 1 (red node) consisted of six items. "Antioxidants", "Dayak onion" and "diabetes" were among the keywords

Table 1 The most prominent authors

Author	Document	Affiliation/Country	Citation	Total link strength
Bin Sayeed M.S	1	University of Dhaka, Bangladesh	52	4
Mia M.M.K	1	University of Dhaka, Bangladesh	52	4
Mostafa A	1	University of Dhaka, Bangladesh	52	4
Kadir M.F	1	University of Dhaka, Bangladesh	52	4
Setu N.I	1	University of Dhaka, Bangladesh	52	4
Kondo R	1	Kyushu University, Japan	31	4
Kusuma I.W	1	Kyushu University, Japan	31	4
Arung E.T	1	Kyushu University, Japan	31	4
Christy E.O	1	Kyushu University, Japan	31	4
Astawan M	1	Bogor Agricultural University, Indonesia	16	4

Table 2 The most influential organizations

Organization/Countries	Documents	Citations	Total Link Strength
University of Dhaka, Bangladesh	1	52	4
University of Asia Pacific, Bangladesh	1	52	4
Bangladesh National Herbarium, Bangladesh	1	52	4
Palangkaraya University, Indonesia	1	31	2
Kyushu University, Japan	1	31	2
Mulawarman University, Indonesia	1	31	2
Bogor Agricultural University, Indonesia	1	16	3
The Center of Applied Technology of Health, Indonesia	1	16	3
Universiti Putra Malaysia, Malaysia	1	7	2
New York City College of Technology, USA	1	5	4

Table 3 The most productive countries

Country	Documents	Citations	Total Link Strength
Indonesia	5	51	1
Bangladesh	2	57	1
Japan	1	31	1
Malaysia	1	7	0
United States	1	5	1

Table 4 The most common author keywords

Keywords	Occurrences	Total Link Strength
Dayak onion	3	13
Traditional medicine	2	10
Alkaloids	1	5
Antioxidants	1	5
B16 melanoma cell	1	5
Central Kalimantan	1	5
Diabetes	1	5
DPPH	1	5
Eleutherine palmifolia	1	5
Extract	1	5

included in this cluster. Whereas, cluster 2 (green node) included five keywords such as "alkaloids", "IR", "extract", TLC, and "UV". Cluster 3 (blue node) consisted of five items and among the keywords were "Bangladesh", "chemical constituents", "ethnopharmacological survey" and so on. Cluster 4 was coded by yellow color and consisted of four items such as "cam", "mandai", "ethnomedicine" and "medicinal plants". Cluster 5 was shown by the purple color. This node consisted of four items such as "merr", "diabetes", and "*Eleutherine palmifolia*". Cluster 6 (turquoise color) was indicated by the presence of four items such as "Dayak onion", "hypoglycemic", "red betel leaf" and "streptozotocin". Cluster 7 contained three items which consisted of "cholesterol", "Dayak onion tea" and "type 2 diabetes mellitus".

The keywords were also color-coded by VOSviewer based on the publication year, and the yellow color indicated that they were published in more recent years (Fig. 7). The keywords of recently published articles were "Dayak onion tea" "type 2 diabetes mellitus," and "cholesterol," whereas the top 3 keywords of the oldest articles (purple) were "B16 melanoma", "central Kalimantan" and "DPPH". From 2010 until 2016, the research focused in the area of Central Kalimantan and Bangladesh. The papers discussed about the ethnopharmacological and verification of *E. palmifolia* chemical compounds in traditional medicine as a source of anti-diabetic, antioxidant, anticancer and tyrosinase inhibitor. In the recent years (2017–2020), supporting evidences were provided from in vitro and in vivo experiment of the extract using streptozotocin to elucidate the mechanism of Dayak onion in type 2 diabetes mellitus.

Bibliometric analysis of *M. charantia*

For *M. charantia,* 977 articles were obtained and after the exclusion of the document type, and language, only 622 papers were retrieved for VOSviewer analysis. Distribution by the author showed 15 authors produced five or more articles with Zafar M. publishing the most paper with seven articles, followed by Ahmad M. and Ahmed I (Table 5). The authors are classified into 10 clusters as shown in Supplementary 2, Fig. 1. In terms of organization, six research organizations published three papers, and Suzuka University of Medical Science, Japan received the highest citation compared to other organizations (Table 6). Based on overlay visualization (Supplementary 2, Fig. 2), the organizations were grouped into six clusters

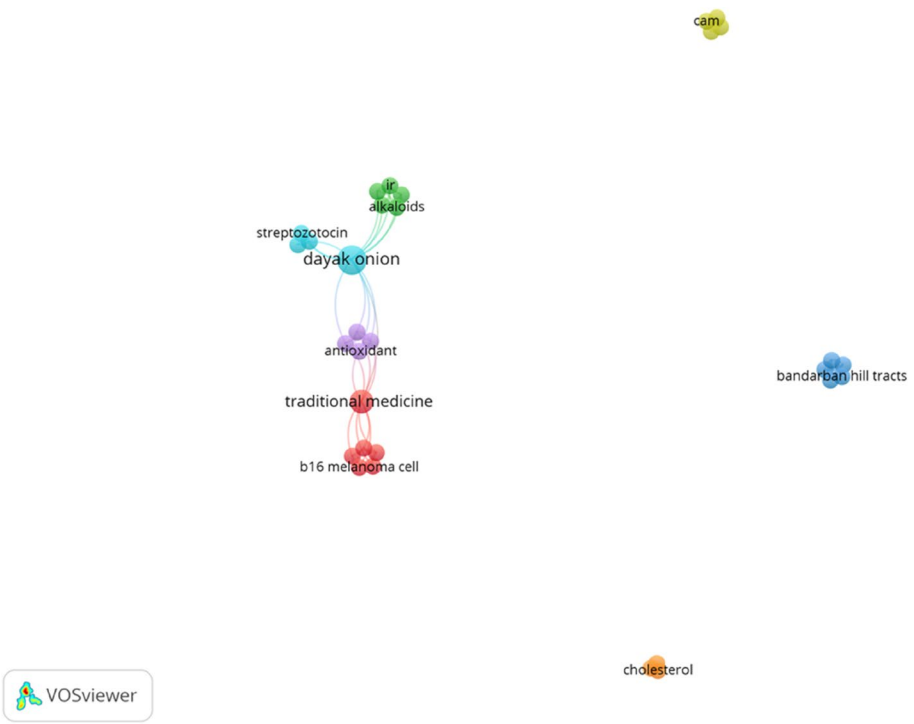


Fig. 6 Keyword co-occurrence network of *E. palmifolia*

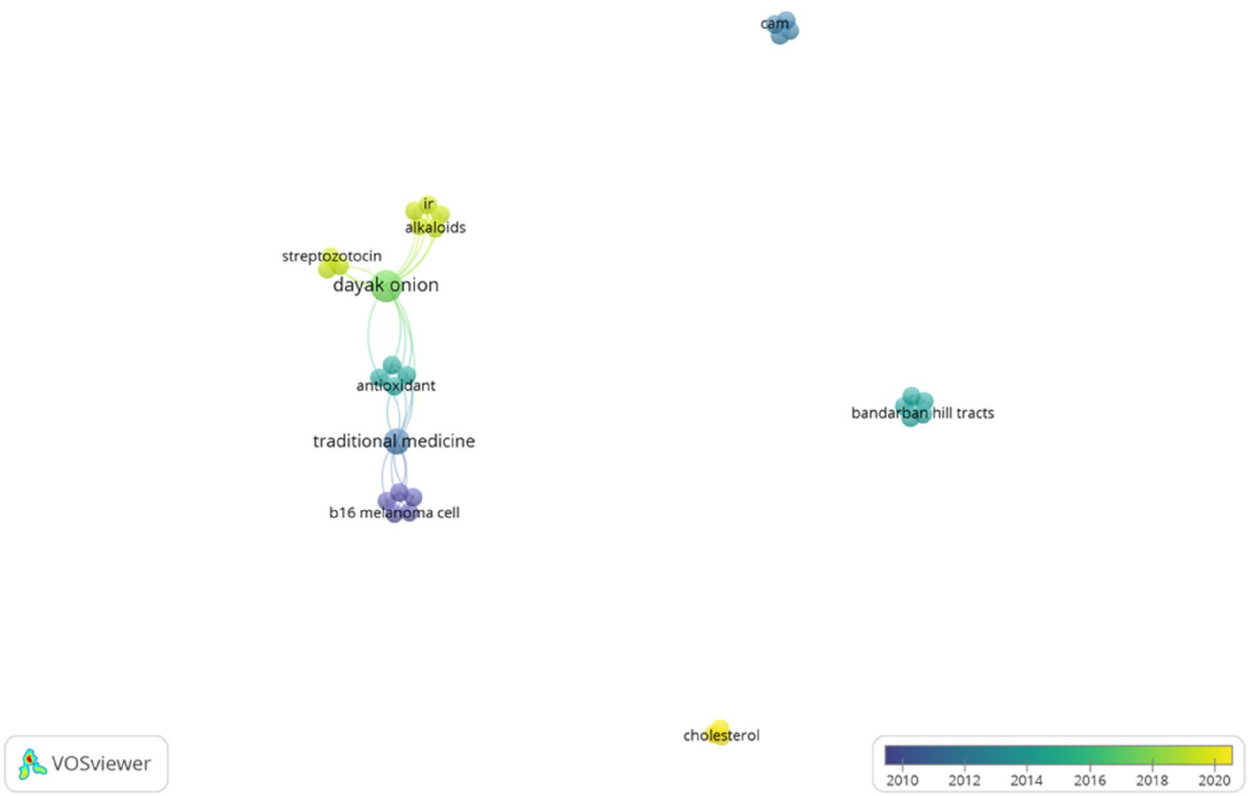


Fig. 7 Keyword co-occurrence map of *E. palmifolia* based on the average publication year

Table 5 The most prominent authors

Author	Affiliation/Countries	Documents	Citations	Total Link Strength
Zafar M	University of Gujrat, Pakistan	7	107	5
Ahmad M	University College of Conventional Medicine, Pakistan	6	103	5
Ahmed I	Manchester Metropolitan University, UK	6	712	0
Grover J.K	All India Institute of Medical Science, India	6	2323	0
Cheng H.L	National Pingtung University of Science and Technology, Taiwan	5	212	0
Ho T.Y	China Medical University, Taiwan	5	86	10
Hsiang C.Y	China Medical University, Taiwan	5	86	10
Jayaprakasha G.K	Texas A&M University, USA	5	75	5
Kumar D	King George's Medical University, India	5	11	0
Kumar G.S	International Medical University, Malaysia	5	192	4

Table 6 The most influential organizations

Organization/Countries	Documents	Citations	Total Link Strength
Suzuka University of Medical Science, Japan	3	194	0
Universiti Kebangsaan Malaysia, Malaysia	3	131	0
Chungnam National University, South Korea	3	84	0
University of Mauritius, Mauritius	3	69	0
Quaid-I-Azam University, Pakistan	3	63	0
Texas A&M University, USA	3	36	0

Table 7 The most productive countries

Country	Document	Citations	Total link strength
India	215	7933	18
China	63	1721	14
United States	48	1412	20
Pakistan	37	700	10
Malaysia	30	604	2
Nigeria	26	474	9
Japan	25	1176	10
United Kingdom	25	1107	14
Taiwan	23	671	5
South Korea	19	308	14

Table 8 The most common author keywords

Keyword	Occurrences	Total Link Strength
Momordica charantia	201	742
Diabetes mellitus	182	647
Bitter gourd	76	318
Medical plants	46	144
Anti-diabetic	37	144
Streptozotocin	28	129
Insulin resistance	21	90
Hypoglycemic	21	86
Antioxidants	19	85
Hyperglycemic	19	81

with yellow color, indicating that they were published in more recent years. A total of 29 countries published five or more papers with India publishing the highest document (215), followed by China (63) and the United States (48) (Table 7). Based on the average publication year (Supplementary 2, Fig. 3), Egypt, Saudi Arabia, and Iran were among the countries which published the recent articles.

A total of 123 keywords were generated that related to the authors with at least three occurrences. "*Momordica charantia*", "bitter gourd" and "diabetes mellitus" were the top 3 keywords with the most occurrences (Table 8). These keywords were also classified as the highest occurrence frequency based on the largest size of the node as illustrated Fig. 8. This term map indicates that the keyword network had 12 clusters. Cluster 1 (red node) was the largest and consisted of 20 items such as "inflammation", "molecular docking", "obesity", and others. Cluster 2 which was green in color, contained 15 items related to "flavonoids", "lipid profile", "antioxidants" and

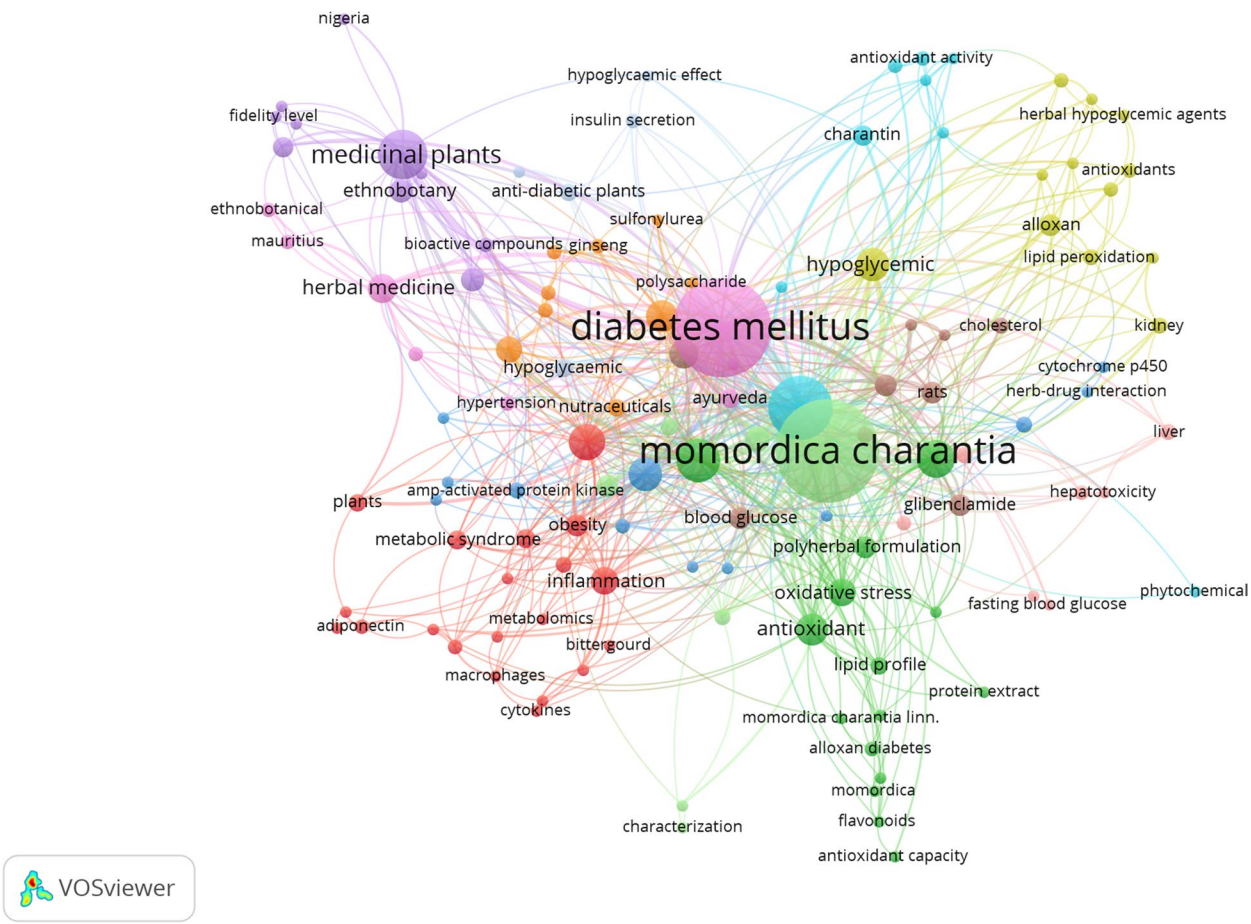


Fig. 8 Keyword co-occurrence network of *M. charantia*

so on. Cluster 3 (blue node) included 12 keywords and the main items in these nodes included "nitric oxide", "triterpene", "metformin" and others. Cluster 4 (yellow node) consisted of 12 items such as "alloxan", "kidney", "hypoglycemic" and so on. Cluster 5 (purple node) had 10 items as well and the keywords were "traditional knowledge", "ethnobotany", "medicinal plants" and others. Cluster 6 which was light blue, indicated by the keywords such as "charantin" and "encapsulation". Next, cluster 7 (orange node) consisted of nine items such as "ginseng" and "polysaccharide". Cluster 8 was indicated by the keywords such as "blood glucose" and "insulin". This cluster was shown by a light pink node and comprised of nine items. Clusters 9 and 10 were shown by magenta and light brown nodes, respectively and these clusters consisted of the keywords such as "functional food", "Ayurveda", "hepatotoxicity" and "liver". While, clusters 11 and 12 were comprised of the terms such as "saponin", "a-amylase", "b-glucosidase" and "ethnobotanical survey".

The keywords were also color-coded according to the year of publication, with yellow denoting more recent publication (Fig. 9). The top keywords of recently published articles were "flavonoid", "molecular docking" and "macrophages" whereas the top keywords of the oldest articles were "antioxidants", "lipid peroxidation" and "alloxan". In the earlier years (2010–2014), it was observed that the structures of phytoconstituents were elucidated by chemical and spectroscopic methods. In vitro experiments were also done based on the keywords such as lipid peroxidation, lipid profile, antioxidants and inflammation. Also, in vivo diabetogenic agents such as alloxan and streptozotocin were also used in elucidating the mechanisms of anti-diabetic activity through inhibiting glucose absorption, lowering blood glucose and preventing oxidative stress in induced-diabetic rats. In recent years, many published papers shifted to studying the molecular mechanisms based on the keywords such as molecular docking. Clinical trial using a double-blind design, combining *M. charantia* extract with other herbal plants was also noted. Efficacy and

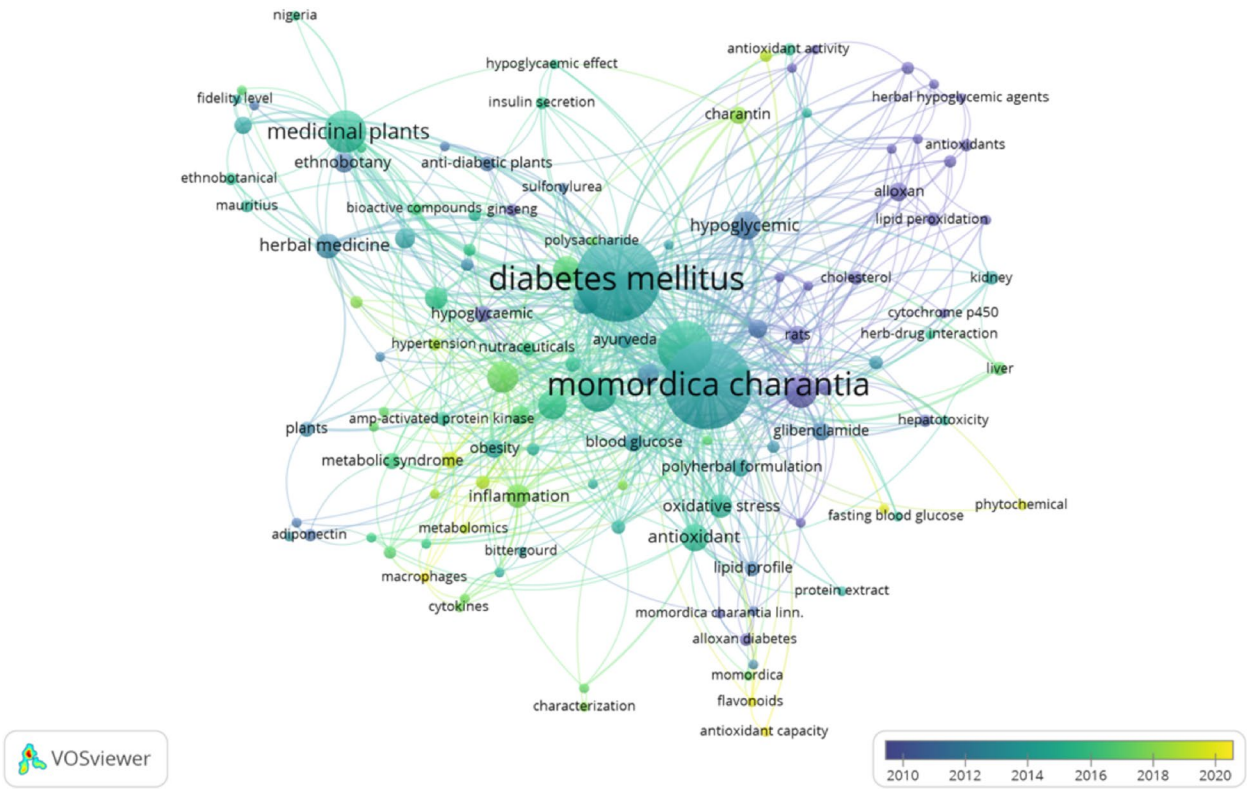


Fig. 9 Keyword co-occurrence map of *M. charantia* based on the average publication year

safety of the polyherbal capsule containing *M. charantia* was also conducted as adjuvant therapy in subjects with type 2 DM.

Bibliometric analysis of *S. polyanthum*

There were a total of 22 articles relating to diabetes research. After excluding the review and non-English papers, 17 articles were retrieved. The study generated three clusters consisting of 12 authors, and each with at least two published publications (Supplementary 3, Fig. 1). The author, Widyawati, T. from Indonesia produced the highest document with the highest citation, followed by Asmawi M. Z. and Ahmad M (Table 9). Here, we can observe that the major of prominent authors were from Malaysia. Whereas, for organization, a total of 47 organizations were included and classified into 16 clusters (Supplementary 3, Fig. 2). As shown in Table 10, all top organizations published only one article with

Table 9 The most prominent authors

Author	Affiliation	Documents	Citations	Total Link Strength
Widyawati T	University of Sumatera Utara, Indonesia	3	46	6
Asmawi M.Z	Universiti Sains Malaysia, Malaysia	2	46	6
Ahmad M	Universiti Sains Malaysia, Malaysia	2	46	6
Yusoff N.A	Universiti Sains Malaysia, Malaysia	2	46	6
AbdulRahman M.D	Universiti Sultan Zainal Abidin, Malaysia	2	15	8
Ali A.M	Universiti Sultan Zainal Abidin, Malaysia	2	15	8
Fatihah H.N.N	Universiti Sultan Zainal Abidin, Malaysia	2	15	8
Khandaker M.M	Universiti Sultan Zainal Abidin, Malaysia	2	15	8
Mat N	Universiti Sultan Zainal Abidin, Malaysia	2	15	8
Ismail H.F	Universiti Malaysia Terengganu, Malaysia	2	11	4

Table 10 The most influential organizations

Organization/Countries	Document	Citation	Total Link Strength
University of Indonesia, Indonesia	1	71	0
University of Sumatera Utara, Indonesia	1	46	2
Universiti Sains Malaysia, Malaysia	1	46	2
Airlangga University, Indonesia	1	30	3
Widya Mandala Catholic University Surabaya, Indonesia	1	30	3
Indonesian Traditional Medicine Polyclinic, Indonesia	1	30	3
International Islamic University Malaysia, Malaysia	1	29	1
University of Toyama, Japan	1	28	0

Table 11 The most productive countries

Country	Documents	Citations	Total Link Strength
Indonesia	11	166	2
Malaysia	7	101	4
Nigeria	2	15	2

Table 12 Most common author keywords

Keyword	Occurrences	Total Link Strength
Syzygium polyanthum	7	22
Anti-diabetic	4	14
Diabetes mellitus	4	12
α-glucosidase	3	9
Inhibitor	2	9
Extract	2	8
Antihyperglycemic	2	7
Indonesian bay leaves	2	7
Medicinal plants	2	6
Biomarker	1	5

University of Indonesia produced the highest citation. Next, the data were distributed based on the country and it generated three clusters (Supplementary 3, Fig. 3). There were only three countries that published two or more papers and Indonesia published the most papers, followed by Malaysia and Nigeria (Table 11).

A total of 58 keywords occurred in the present study. As shown in Table 12, the top 3 keywords with the most occurrences were "*Syzygium polyanthum*," "anti-diabetic", and "diabetes mellitus". These keywords were also analyzed based on a term map as illustrated Fig. 10. This term map shows that the keyword network is divided into 11 clusters. Cluster 1 (red node) consisted of eight items ("radical scavenging", "phytochemical analysis", "medicinal use" and so on), and cluster 2 (green node) was formed by seven items ("extract", "formulation", "herb" and others). Cluster 3 (blue node), cluster 4 (yellow node), and cluster 5 (purple) shared the same number of items which were six keywords such as "morphology", "anatomy", "herbal mixture", "myricitrin", "cytochrome p450", "LC–MS/MS" and "polyherbal". Whereas, both cluster 6 (light blue node) and cluster 7 (orange color) consisted of five items. The keywords such as "ethnopharmacology", "Indonesia", "medicinal plant" and "inhibitor" were included in these clusters. Cluster 8, cluster 9, and cluster 10 also shared the same number of items which were four keywords ("advanced glycation end", "methanol extract", "leaf", "squalene" and others). Finally, cluster 11 was comprised of only three items which were "metformin", "clinical study" and "type 2 diabetes mellitus".

The keywords were also color-coded according to the publication year, with yellow color indicating a recent publication (Fig. 11). The top keywords of recently published articles were "anti-diabetic," and "extract," whereas the top keywords of the oldest articles were "α-glucosidase" and "diabetic mellitus". In 2017 to 2019, there was a limited number of papers that published on the anti-diabetic activity of *S. polyanthum,* but it was noted that several authors studied the phytochemical screening through GC–MS and elucidated the mechanisms of antihyperglycemic effect in streptozotocin-induced diabetic rats. In recent years, the researchers shifted to the analysis of anti-diabetic compounds using molecular docking approach.

Discussion

Bibliometric analysis

The key findings of this study demonstrated the utilization of *E. palmifolia, M. charantia* and *S. polyanthum* in anti-diabetic research based on bibliometric analysis by considering publication trends, contributed countries, prominent authors, productive organizations and author keywords. A total of 1008 articles were retrieved with *M.*

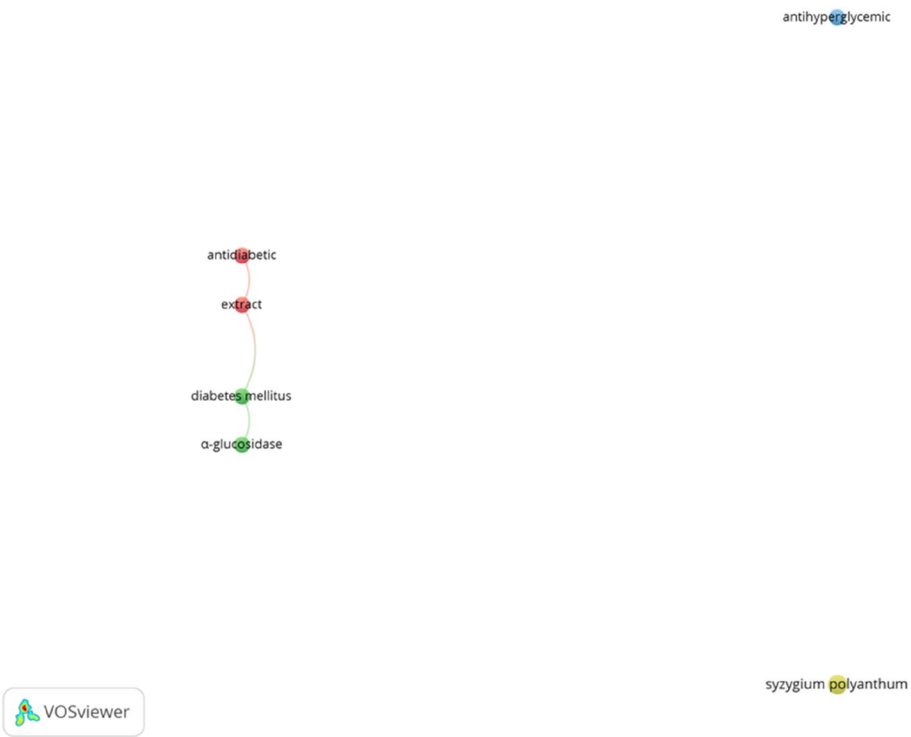


Fig. 10 Keyword co-occurrence map of *S. polyanthum*

charantia showing the highest number (977 papers) of publishing articles compared to *E. palmifolia,* and *S. polyanthum*. We continued with VOSviewer analysis even though only nine and 22 publications on *E. palmifolia* and *S. polyanthum*, respectively, were retrieved from the SCOPUS database because we intended to identify the knowledge gaps and generate fresh ideas for future studies on these plants in diabetic research.

In terms of managerial aspect, the productive countries, organizations, and authors were analyzed to help other scholars building a research network and collaboration. Due to their prominence in both complementary and alternative medicine, several countries Bangladesh, Indonesia, China, India, and Japan have more publications than others. It is unexpected that these countries have an abundance of papers on this particular research. Based on the bibliometric analysis, University of Dhaka (*E. palmifolia*), Suzuka University of Medical Science (*M. charantia*), and University of Indonesia (*S. polyanthum*) showed that the most productive organizations. Bin Sayeed, M.S. (*E. palmifolia*), Zafar M. (*M. charantia*) and Widyawati, T. (*S. polyanthum*) were the most prominent author on their research topics. Bin Sayeed, M.S. is from Bangladesh and his research focused on the ethnopharmacological studies of *E. palmifolia* in diabetic management. Zafar M. specialized in preclinical trials of anti-diabetic from *M. charantia*. Whereas, Widyawati, T. has conducted preclinical and clinical trials of *S. polyanthum* for diabetic patients. This information is intended to inspire collaborative research between productive authors, institutions, and countries in order to combine these three herbs as a new potential concoction in diabetes treatment.

Other than managerial aspect, scientific topics were discussed as well. We were able to find trends in diabetic research that were currently in progress by looking through all of the keywords and cluster classification, and we anticipate that it can be used as a reference to define the path of future studies. In earlier years, the research was merely focusing on the preliminary screening of the plant extract as an anti-cancer, anti-microbial, anti-inflammatory, and antioxidant agent. However, it was observed that the trends for *M. charantia* have changed in the recently published papers. The keywords such as "rat", "streptozotocin" and "alloxan" showing that the focus of diabetic research using these herbs is evolving from simply investigating its biological activities to testing the extract in animals to establish its efficacy and safety for drug development. In recent years as well, the research is also moving to isolation of the key compounds of the plant that is responsible for the anti-diabetic effect such as "charantin" and "alkaloids".

There is lacking of molecular docking study and clinical trial report for *E. palmifolia*, indicating that this aspect

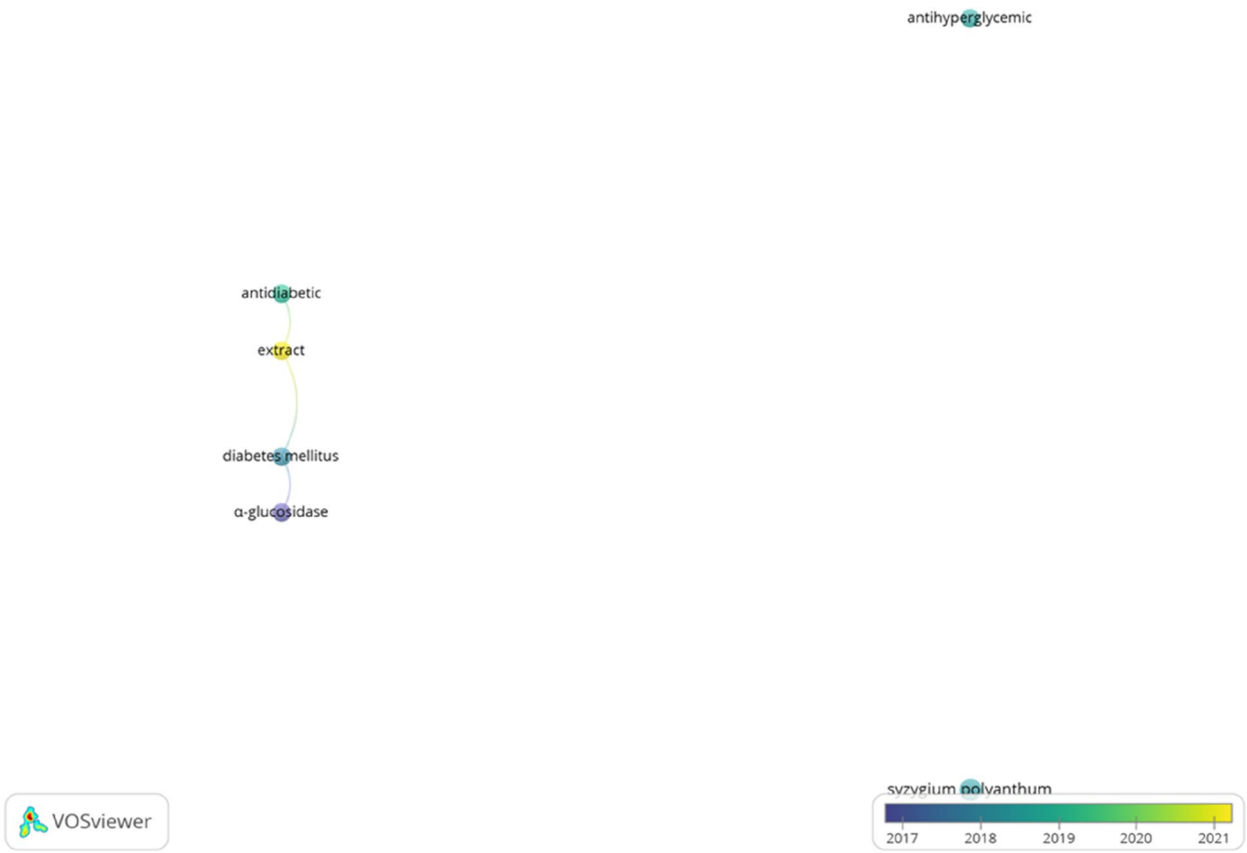


Fig. 11 Keyword co-occurrence map of *S. polyanthum* based on the average publication year

of study is still scarce. There were also several papers that published on the polyherbal formulation in treating diabetes such as *Andrographis paniculata*, *Camellia sinensis* and *Syzygium cumini*, but there was no paper that studied on the combination *E. palmifolia, M. charantia* and *S. polyanthum* as a single concoction, indicating that this specific topic has not yet been explored and therefore it demands for further research.

Phytochemical compounds related to anti-diabetic activity

The active phytochemical compounds in *E. palmifolia, M. charantia* and *S. polyanthum* and their bioactivities are summarized in Table 13. Secondary metabolites such as alkaloids, flavonoids, glycosides, and saponins were found in *E. palmifolia* that possess hypoglycemic activity, which is beneficial for the treatment of diabetes (Yaturramadhan et al. 2019). The main compounds of the plant were naphthalene, naphthol, and anthraquinone. Naphthoquinones such as elecanacine, eleutherine, and eleutherinone were also reported to be found in the bulb (Dai et al. 2013). Other isolated active compounds such as hongconin, eleutherol A, B, and C, eleuthinone B, and C were demonstrated to possess therapeutic effects against hyperglycemia (Kamarudin et al. 2021).

The biological activity of *M. charantia*, bitter melon depends on its major chemical constituents, including cucurbitane-type triterpenoids, cucurbitane-type triterpeneglycosides, flavonoids, phenolic acids, amino acids, essential oils, sterols, fatty acids, lectins, and saponin (goyasaponins I, II and III, kuguacin, momordicin, karaviloside, momordin, momordicoside, and karavilagenin) (Saeed et al. 2018). The most common chemical compounds are cucurbitane-type triterpenoids (momordicines I and II and triterpene glycosides: momordicosides). These compounds are responsible for the bitterness of *M. charantia* fruit.

The compounds that are used to treat hypoglycemia are a combination of steroidal saponins called charantins, insulin-like peptides, and alkaloids (Raman & Lau 1996). Wang et al. (2010) discovered that p-insulin from *M. charantia* significantly lowered blood sugar levels in diabetes patients following subcutaneous injection in a human clinical trial. Additionally, charantin, which work similarly to peptides and certain alkaloids to efficiently lower blood

Table 13 Anti-diabetic compounds found in *E. palmifolia*, *M. charantia* and *S. polyanthum*

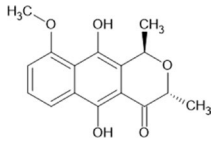
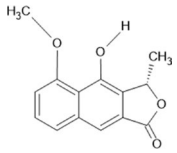
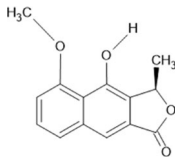
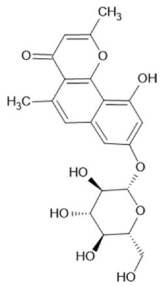
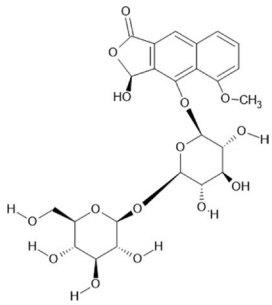
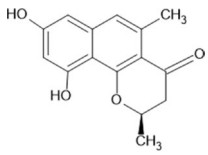
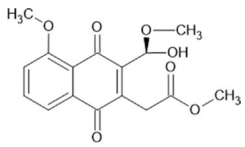
Compound	Class of compound	Chemical structure	Bioactivity	Reference
E. palmifolia				
Hongconin	Naphthalene		Protected the injury of HUVECs activity induced by high glucose level	Xu et al. (2006)
Isoeleutherol	Naphthalene		Inhibited the activity of β-glucosidase	Hara et al. (1997)
Eleutherol	Naphthalene		Inhibited the activity of β-glucosidase	Ieyama et al. (2011)
Eleutherinoside A	Naphthalene		Inhibited the activity of β-glucosidase	Ieyama et al. (2011)
Eleuthoside B	Naphthalene		Inhibited the activity of β-glucosidase	Ieyama et al. (2011)
Dihydroeleutherin	Naphthoquinone		Protected the injury of HUVECs activity induced by high glucose level	Hanh et al. (2018)
Eleuthinone	Naphthoquinone		Protected the injury of HUVECs activity induced by high glucose level	Chen et al. (2018)

Table 13 (continued)

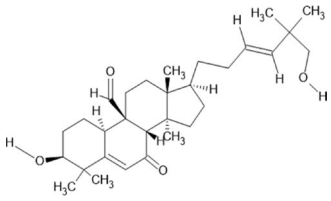
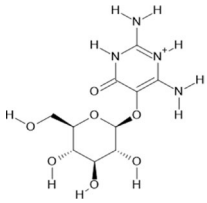
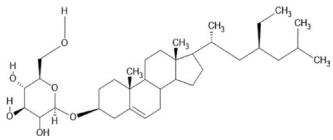
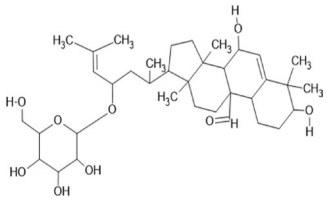
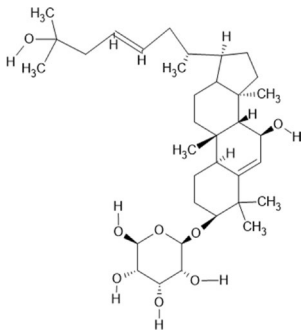
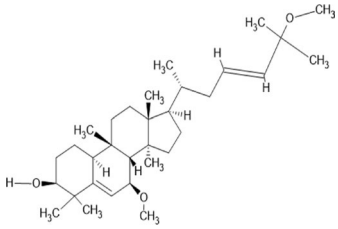
Compound	Class of compound	Chemical structure	Bioactivity	Reference
M. charantia				
Kuguacin	Cucurbitane-type triterpenoids		Promoted insulin secretion activity	Saeed et al. (2018)
Vicine	Glycol alkaloid		Lowered the glucose concentration	Raman and Lau (1996)
Charantin	Steroid saponin		Promoted the growth of beta-cells and enhanced insulin production	Wang et al. (2010)
Momordicine II	Cucurbitacin glycoside		Increased the insulin secretion	Keller et al. (2011)
Karaviloside	Cucurbitane-type triterpenoids		Activated the AMPK pathway by mediating glucose uptake and fatty acid oxidation	Saeed et al. (2018)
Karavilagenin	Cucurbitane-type triterpenoids		Inhibited PTPN2, an enzyme associated with insulin resistance	Lee et al. (2021)

Table 13 (continued)

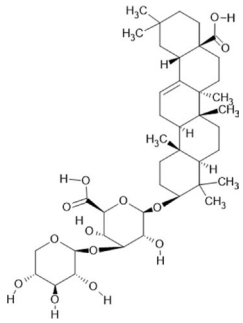
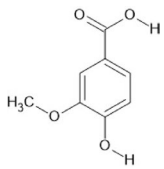
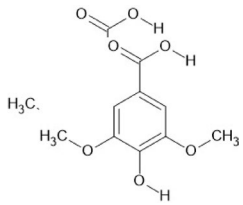
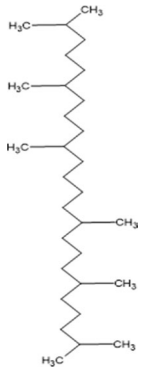
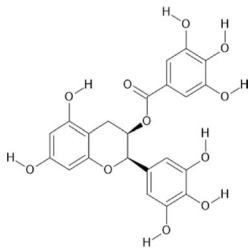
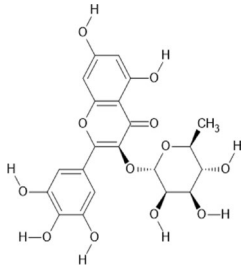
Compound	Class of compound	Chemical structure	Bioactivity	Reference
Momordin	Triterpene saponin		Reduced the glucose level	Perumal et al. (2022)
S. polyanthum				
4-hydroxy-3-methoxy-benzoic acid	Benzoic acid derivatives		Inhibited α-glucosidase	Lelono and Tachibana (2013)
4-hydroxy-3, 5-dimethoxy-benzoic acid	Benzoic acid derivatives		Inhibited α-glucosidase	Lelono and Tachibana (2013)
Squalene	Terpenoid aliphatic		Lowered the blood glucose Increased the glucose uptake in the muscle tissue	Widyawati et al. (2022) Widyawati et al. (2015a)
Myricitrin	Flavonoid		Inhibited α-glucosidase	Syabana et al. (2022)

Table 13 (continued)

Compound	Class of compound	Chemical structure	Bioactivity	Reference
EGCG	Catechin		Inhibited α-glucosidase	Syabana et al. (2022)

sugar levels by boosting insulin secretion and promoting the growth of the β-cell. The other significant compound identified from bitter melon is vicine, a glycol alkaloid. Intraperitoneal injection of this pyrimidine nucleoside has been found to induce hypoglycemia in non-diabetic fasting rats (Haixia et al. 2004). Fruit of *M. charantia* has demonstrated the most effective hypoglycemic property because these compounds are concentrated in fruits.

Several phytochemical compounds of *S. polyanthum* were also reported. Three phenolic compounds were analyzed in *S. polyanthum* leaves which were caffeic acid, gallic acid, and 4-allyl-1,2-dihydroxybenzene (hydroxychavicol) (Har & Ismail 2012). Phytol, an acyclic diterpene alcohol, is another important compound found in the ethanolic extract of *S. polyanthum* leaves (Wahjuni & Wita 2017). Rahim et al. (2018) discovered the presence of phytol and squalene in *S. polyanthum* leaf extracts. Another work employed NMR and HPLC-metabolomics to identify myricitrin and epigallocatechin gallate (EGCG) as α-glucosidase inhibitors from *S. polyanthum* leaves, and docking analysis confirmed their inhibitory actions (Syabana et al. 2022).

Antidiabetic activity and mechanism of actions

The plants act as anti-diabetic agents by inhibiting the activity of α-glucosidase and α-amylase and therefore reducing starch digestion in the small intestine and lowering the amount of glucose absorbed to the bloodstream (Sharma et al. 2020). The amylase enzyme converts polysaccharides into dextrin, which is then digested into glucose by the α -glucosidase enzyme before entering the bloodstream via epithelial absorption (Setyawan et al. 2020). A high blood glucose level can cause multiple endothelial dysfunctions such as migration, dysregulation of endothelial proliferation, and apoptosis (Dong et al. 2017). The schematic presentation in Fig. 12 presents the mechanisms of *E. palmifolia* as the anti-diabetic agent.

In the previous study, 100 mg/kg of *E. palmifolia* aqueous bulb extract was proven to reduce the blood serum level, increase blood serum insulin level, and lower blood serum total cholesterol in diabetic rats. This finding showed that *E. palmifolia* bulb can be a functional bioactive agent for diabetic research (Febrinda et al. 2014). Another study showed that flavonoids improved the activity of the pancreatic tissue by elevating the insulin level over islet β-cells and lowering blood glucose levels (Lahrita et al. 2015). While, Ahmed et al. (1998) found that a methanolic extract of *E. palmifolia* bulb reduced glucose tolerance in Swiss albino rats. Nurcahyawati et al. (2017) also revealed that the bulb of *E. palmifolia* protected the kidneys of alloxan-induced Wistar rats. A dosage of 400 g/kg of *E. palmifolia* bulb was evidenced to protect against kidney tubule degeneration, tubular and globular necrosis, and interstitial infiltration.

Alpha glucosidase inhibitor (AGI) is an anti-diabetic agent that works by inhibiting the activity of the α-glucosidase enzyme. Amylase and synthetic α-glucosidase inhibitors like acarbose are commonly used in the remedy of type 2 DM, but they have also been associated with several adverse effects (Feng et al. 2011). To treat diabetes, AGI agents derived from natural resources must be obtained and tested further. Glucosidase action is important for a variety of biochemical mechanisms, including the breakdown of polysaccharides into monosaccharide units. As a result, suppressing the α-glucosidase enzyme can be useful in the case of hyperglycemia, as it limits the quantity of monosaccharide absorbed by the intestine (Setyawan et al. 2020). Despite the wide utilization of *E. palmifolia*in several traditional medicine, there is a scarce data from human clinical trials.

M. charantia is hypothesized to exhibit hypoglycemic effect via multiple physiological, pharmacological, and biochemical mechanisms as shown in the schematic presentation (Fig. 13). The hypoglycemic impact, stimulation of peripheral and skeletal muscle glucose utilization, inhibition of intestinal glucose absorption, inhibition of adipocyte development, suppression of key gluconeogenic enzymes, stimulation of key enzyme of hexose monophosphate (HMP) pathway, and preservation of islet cells and their functions are some of the potential mechanisms of

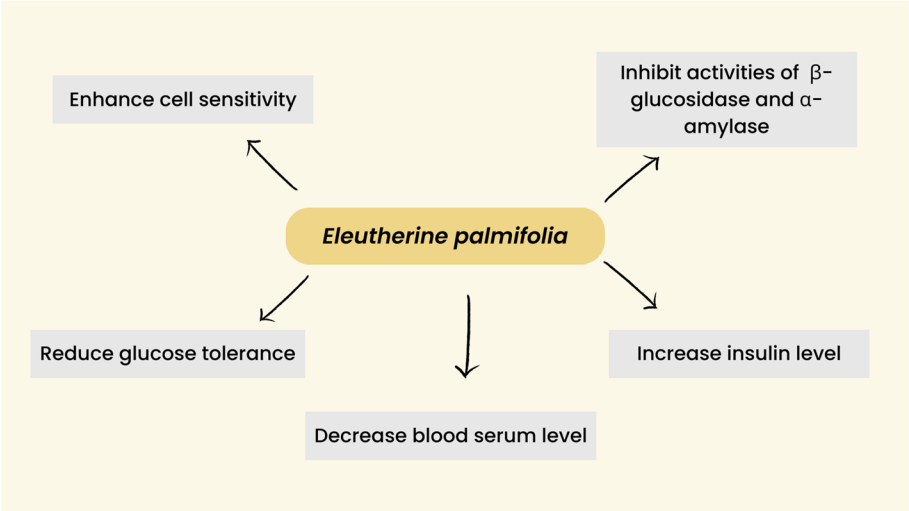


Fig. 12 The mechanism of the *E. palmifolia* as the anti-diabetic agent

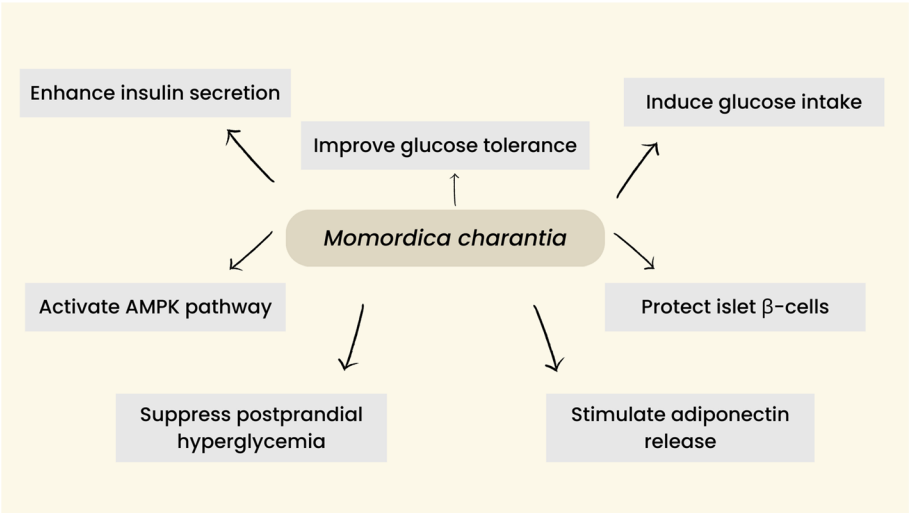


Fig. 13 The mechanism of the *M. charantia* as the anti-diabetic agent

the hypoglycemic actions of *M. charantia* and its numerous extracts and components (Wang et al. 2014).

The anti-hyperglycemic and hypoglycemic properties of various extracts and compounds from *M. charantia* have been studied in both human and animal models. In a clinical trial, the extract of *M. charantia* was administered in 95 participants (Yin et al. 2014). The extract improved heart function by reducing the degree and extent of infarctions and lowering serum cholesterol levels. As a result, bitter melon extract was proposed to be useful as a supportive therapy for type 2 diabetes and related cardiovascular illnesses. Yang et al. (2022) also performed a randomized, double-blind, placebo-controlled experiment to investigate the hypoglycemic effect of *M. charantia* fruit extracts in type 2 diabetes patients. They concluded that the extract has a hypoglycemic activity and can significantly reduce FBG and HbA1c when anti-diabetic medications are ineffective.

In the study conducted by Keller et al. (2011), saponin-rich part of *M. charantia* was found to enhance insulin production in MIN6 pancreatic cells in a concentration-dependent manner. In another investigation, following 24 h of treatment with an aqueous extract of *M. charantia,* RIN-m5F pancreatic cells survived significantly longer than untreated glucotoxic cells (Wang et al. 2014). It is hypothesized that it is attributed to an increase in glucagon-like peptide-1

release, which can aid in insulin secretion and β-cell expansion. In one study, when treated with a saponin fraction of *M. charantia* at a dose of 500 mg per kg weight, the insulin secretion level and glycogen synthesis of alloxan-induced hyperglycemic mice increased with improved glucose tolerance and decreased blood glucose (Han et al. 2008).

In another investigation, it was reported that bitter gourd water extract triggered glucagon-like peptide-1 (GLP-1) secretion in the enteroendocrine cell line STC-1 in a dose-dependent manner (Huang et al. 2013). While Ru et al. (2020) found that a polysaccharide extracted from *M. charantia* (MCPIIa) and *M. charantia* polysaccharidechromium (III) complex (MCPIIaC) have been shown to be efficient in protecting pancreatic cells and boosting insulin levels in streptozotocin (STZ) induced diabetic mice. In the study by Ahmed et al. (1998), *M. charantia* extract was found to increase the number of β-cells and therefore increased insulin secretion. Whereas, oral administration of *M. charantia* juice was proven to improve pancreatic histopathology and cell function by decreasing pancreatic malondialdehyde, increasing pancreatic glutathione levels, and boosting serum total antioxidant capacity (Mahmoud et al. 2017).

The inhibitory action of protein extracts *M. charantia* on α- glucosidase and α- amylase were evaluated and the findings indicated that their inhibition rates were 66 to 69% and the IC_{50} values ranging from 0.26 to 0.29 mg, which were equivalent to acarbose (positive control) (Poovitha & Parani 2016). Other investigations also reported the inhibitory effect of *M. charantia* ethanol extract on pancreatic lipase (20.12 to 68.34%) in a dose-dependent manner with an IC_{50} value of 607.6 ± 1.3 μg/mL (Lydia et al. 2019). *M. charantia* ethanolic extracts also depicted the lowest α-glucosidase activity (57.13 ± 2.3 to 18.14 ± 1.3 U/L) in a α-glucosidase inhibition assay, proving its efficacy as an anti-diabetic agent.

Researchers also discovered that gastro-resistant insulin receptor-binding peptide from *M. charantia* improved glucose tolerance in STZ-induced diabetic mice via the insulin receptor signalling pathway (Lo et al. 2017). The peptide, 9-amino-acid-residue peptide (mcIRBP-9) activated IR signalling transduction pathway, which resulted in the phosphorylation of IR, the translocation of glucose transporter 4, and the uptake of glucose in cells. In another report, ethanolic extract of *M. charantia* was found to reduce serum glucose fructosamine, total cholesterol, triglycerides levels, insulin resistance index, and pancreatic malondialdehyde content. It also increased serum insulin, HDL-cholesterol, total antioxidant capacity levels, β-cell function percent, pancreatic reduced glutathione content, and improved histopathological changes in the pancreas (Mahmoud et al. 2017).

S. polyanthum also has a few possible mechanisms of anti-diabetic action as drawn in the schematic presentation (Fig. 14). This includes inhibiting α-glucosidase, reduction of glucose intake, and increasing muscle glucose uptake (Sutrisna et al. 2016). α-glucosidase is an enzyme that can convert huge polysaccharides into sucrose and glucose. Inhibiting this enzyme slows the time for carbohydrate assimilation and so defers digestion and diminishes the amount of glucose intake (Feng et al. 2011).

A recent study found that *S. polyanthum* leaf methanol extract significantly reduced intestinal glucose absorption and increased muscle tissue glucose absorption in vitro (Widyawati et al. 2015b). Controlling postprandial

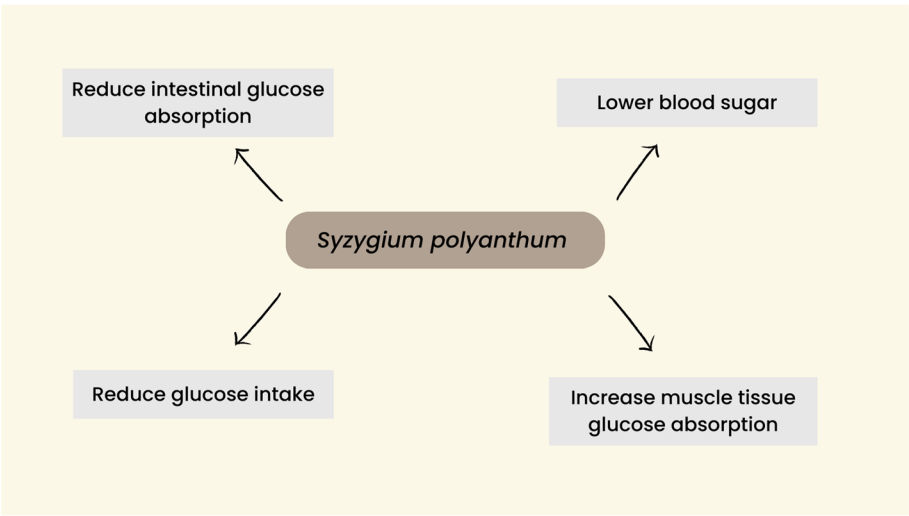


Fig. 14 The mechanism of the *S. polyanthum* as the anti-diabetic agent

plasma glucose levels is crucial in the early of diabetes mellitus treatment. One of the treatment options for postprandial hyperglycemia is the inhibition of enzymes involved in carbohydrate metabolism. According to Widyawati et al. (2015b), who employed the averted sac method, methanol extract was able to limit glucose absorption from the intestine, producing a result that was comparable to acarbose. This characteristic may have contributed to *S. polyanthum* leaf extract's antihyperglycemic efficacy.

The primary function of insulin in the skeletal muscles is to stimulate the translocation of the insulin-responsive glucose transporter, glucose transporter-4 (GLUT4), from intracellular vesicles to the cell surface; hence, it boosts amino acid intake, activates the ribosomal protein synthesis machinery, and raises the rate of glycogen synthase activity and subsequent glycogen storage while decreases the rate of glycogen breakdown (Rahman et al. 2021).

Widharna et al. (2015) found that the leaf extract of *S. polyanthum* significantly lowered the blood sugar levels in both alloxan and streptozotocin-induced diabetic rats. In the isolated abdominal muscle model of the study conducted by Widyawati et al. (2015a), similar to how metformin behaves, *S. polyanthum* leaf increased glucose absorption by the muscles both with and without the presence of insulin. In the presence of insulin, the extract increased the sensitivity of insulin to promote glucose absorption; however, in the absence of insulin, the action was likely caused by an effect on the glucose transporters that directly contributed to the uptake of glucose. This mechanism contributed to the antihyperglycemic activity of the leaves of *S. polyanthum.*

Clinical study in human to verify the anti-diabetic activity of *S. polyanthum* leaves is limited. However, a study with a small number of participants (< 10) found that administering a capsulated ethanolic extract of *S. polyanthum* for 14 days reduced fasting blood glucose levels in diabetic patients (Widyawati et al. 2019). In a different trial, Widyawati et al. (2019) found that 350 mg of the ethanol extract was safe to be consumed by healthy human volunteers during 28 days of treatment.

Toxicity and safety data

Clinical safety data for *E. palmifolia* and *S. polyanthum* are scarce. However, there are no safety concerns about the traditional use or its preparations in general. When administered in accordance with the dosages given for each preparation, the herbs are regarded as safe. Febrinda et al. (2014) carried out a study on the anti-diabetic impact of *E. palmifolia* bulb and discovered that renal function was improved with no liver damage. According to the World Health Organization (WHO) and the Organization for Economic Cooperation and Development (OECD), the extract showed no sign of toxicity even at the highest dose of 5000 kg/mg (Hanh et al. 2018).

Khan et al. (2019) found teratogenicity and cardiac toxicity in the seeds and fruit extracts of *M. charantia,* therefore the supplementation made from the fruit and seeds of *M. charantia* should be used with great caution in pregnant diabetic patients to prevent potential harm to the developing baby. Patients who have reported allergies to other Cucurbitaceae plants also should always avoid the supplements made of *M. charantia* extracts. Patients with glucose-6-phosphate dehydrogenase deficiency also should avoid from the consumption *M. charantia* because it was reported that it could develop favism, which is an acute haemolytic syndrome (Khan et al. 2019). Precautions is also advised in patients with hepatic impairment, because transaminase elevation has been documented in rats, even without histological abnormalities (Raman & Lau, 1996). Mardani et al. (2014) also reported in their study that kidney damage was observed in mice given 4 g/kg of *M. charantia* extract for more than a week.

Despite the widespread utilization of *S. polyanthum* leaves in the treatment of various diseases, there is still a scarcity of scientific data on the herb's toxicological profiles. Sumiwi et al. (2019) recently determined the subchronic toxicity of *S. polyanthum* ethanol extract throughout a 90-day treatment period. This study showed that, while the plant extract did not exhibit toxicity on the majority of parameters, female rats did develop fatty liver and necrosis. Widharna et al. (2015) previously investigated the acute toxicity of an aqueous extract of *S. polyanthum* combined with *Andrographis paniculata*. They found that a single dose of 2000 mg/kg body weight of this plant extract did not cause acute toxicity in all rats. In addition, cytotoxic tests from other studies revealed that the leaves extract is non-cytotoxic to normal mammalian cell lines (Perumal et al. 2012). Furthermore, Kusuma et al. (2011) observed that the extract of *S. polyanthum* leaves had an LC_{50} of more than 1 mg/mL, indicating that it was non-cytotoxic. These few studies are still insufficient to establish the general safety of these herbs or to build consumer confidence in their quality before they are produced as new herbal therapeutic products. Therefore, future research should look deeper into the potential toxicological effects of *E. palmifolia*, *M. charantia*, and *S. polyanthum* as a herbal mixture.

Limitation of study

The review paper like all research studies, has limitations. The first limitation is the scarcity of published papers relevant to the search keywords especially for *E. palmifolia* and *S. polyanthum*. There is also a limited

data from human clinical trials and toxicological studies of *E. palmifolia,* and *S. polyanthum*. For a thorough analysis of the therapeutic efficacy of *E. palmifolia, M. charantia,* and *S. polyanthum* as a herbal combination, more preclinical research especially in toxicology is required.

Conclusion

The research questions of this review have been addressed, allowing us to pinpoint the direction of the study, prominent authors, their affiliations, the field of study and the countries where the majority of the anti-diabetic research has been conducted. This analysis helped us in identifying the gaps in the previous studies, relating to the effect of *E. palmifolia, M. charantia,* and *S. polyanthum* as anti-diabetic agents. Eleutherol, eleuthenone, eleutherinoside A, momordicin, EGCG, charantin, vicine, squalene and myricitrin were among the compounds that exert their therapeutic effects, either working alone or in combination through various mechanisms. We also discovered that there are no existing studies that combine the extracts of *E. palmifolia, M. charantia,* and *S. polyanthum* into a single formulation to treat diabetes, thus this finding prompted a more thorough investigation of this specific topic.

Abbreviations

DM	Diabetes mellitus
WHO	World Health Organization
HPLC	High performance liquid chromatography
DPPH	2,2-Diphenyl-1-picrylhydrazyl
STZ	Streptozotocin
GLUT4	Glucose transporter-4
EGCG	Epigallocatechin gallate
FRAP	Ferric reducing ability of plasma
NMR	Nuclear magnetic resonance
IDF	International Diabetes Federation
VOS	Visualization of similarities

Supplementary Information

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Additional file 1: Supplementary 1: Fig. 1. Distribution by authors based on average publication year. **Fig. 2.** Distribution by organization based on average publication year. **Fig. 3.** Distribution by countries based on average publication year. **Supplementary 2: Fig. 1.** Distribution by authors based on average publication year. **Fig. 2.** Distribution by organizations based on average publication year. **Fig. 3.** Distribution by countries based on average publication year. **Supplement 3: Fig. 1.** Distribution by authors based on average publication year. **Fig 2.** Distribution by organizations based on average publication year. **Fig. 3.** Distribution by countries based on average publication year.

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Authors' contributions

FAAM designed the study. MASH performed the literature search and drafted of the manuscript and NHZ critically edited the manuscript. DH, AFA and HIS revised the manuscript. All authors approved the final version to be submitted.

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Declarations

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interest.

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