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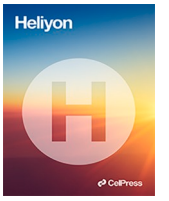

Review article

A bibliometric and thematic analysis of the trends in the research on *ginkgo biloba* extract from 1985 to 2022

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ABSTRACT

Background: *Ginkgo biloba* extract (GBE), a complementary and alternative medicine, has been widely used for disorders such as brain infarction, dementia, and coronary heart disease, in recent decades. Given its widespread clinical use, GBE has always been a vital research topic. However, there are no bibliometric analyses on this topic; furthermore, published reviews of GBE focus only on a specific research field or lack scientific and systematic evaluation. This study combined bibliometrics with thematic reviews by visual analysis to identify the current status of GBE research and to better identify research hotspots and trends in the past 40 years to understand future developments in basic and clinical research.

Methods: Articles and reviews on GBE were retrieved by topic from the Web of Science Core Collection from inception to 2022.12.01. Countries, institutions, authors, journals, references, and keywords in the field were visually analyzed using CiteSpace, Scimago Graphica, and VOSviewer software; then, these visualization results for references and keywords were clarified in detail by thematic reviews in subdivisions of the fields.

Results: In total, 2015 publications were included. The GBE-related literature has high volumes of publications and citations. The majority of literature is from China, and the USA cooperates most closely with other countries. In GBE research, Christen Yves is the most cited author, Phytotherapy Research is the most prolific journal, and the Journal of Ethnopharmacology is the most co-cited journal. Through a comprehensive analysis of keywords, references, and reviews, the quality of the meta-analysis of randomized controlled clinical trials of GBE in treating dementia was evaluated by the Risk of Bias in Systematic Reviews scale (ROBIS). Current research on GBE focuses on its pharmacological mechanisms, and neuroprotective application in diseases such as Alzheimer's disease, and glaucoma. Randomized controlled trials are the current research hotspot.

Conclusion: Research on GBE is flourishing; using bibliometric and thematic analysis, we identified its hotspots and trends. The pharmacological mechanisms and clinical applications of GBE are the focus of present and likely future research.

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1. Introduction

Ginkgo biloba extract (GBE) has been one of the most successful and influential natural product drugs with multiple effective pharmacological ingredients since the 1960s [1,2]. It is extensively used for treating dementia, ischemic stroke, detoxification, female reproduction, atherosclerosis, diabetic retinopathy, delirium, and tinnitus [3–8]. Furthermore, GBE has become one of the best-selling drugs in the world due to its extensive therapeutic application, rapid onset of action, reliable efficacy, low toxicity, and ease of obtaining [9–14]. Although GBE is the most popular and classical herbal medicine, it is still highly controversial for its neuroprotective function, which mainly prevents dementia [15] and adverse side effects such as spontaneous bleeding, allergenic reaction, and herb-drug interaction [10,11,16–21]. However, its use doesn't show a decreasing trend but remains high [3,22]. There was even a growing trend in use during the coronavirus COVID-19 pandemic due to GBE could be beneficial for coronavirus COVID-19 infections [23]. Although serial reviews of GBE have been published, they all focus on a specific research direction or lack quantitative analysis [3,7,9–11,18,19,22,23].

Bibliometrics is a method for statistical and quantitative analysis of scientific publications in a specific subject and journal. Which enables knowledge structure mapping, presents development, and predicts trends in a given field [24–26]. It is an emerging method widely used in various medical fields [27–29]. Herein, we applied a bibliometric approach to quantitative analyze the publications on GBE from 1985 to 2022. However, bibliometrics mainly implements quantitative terms analysis in publications, which cannot wholly replace the systematic review. In the context of what was mentioned above, combining quantitative with systematic analytical studies of the publications related to GBE is tremendously significant. In order to better grasp the worldwide research progress, the present situation, hot spots, and trends of GBE and to give guidance and investigation direction for consequent application of GBE, this study hired bibliometric analysis and theme reviews of GBE.

2. Methods and research design

2.1. Data sources and documents collection

Data were fetched from the SCI-EXPANDED database of the Web of Science Core Collection, then downloaded intraday on 22 December 2022. The search formula was set to topic = ("*Ginkgo biloba* extract"), and documents ranging from 1 January 1985 to 01 December 2022, were retrieved. A total of 2015 articles were retrieved, and 167 irrelevant articles, including meeting abstract, proceeding paper, editorial material, early accesses, letter, book chapters, new item, corrections, and publication with expression of concern were excluded. A total of 1848 articles were derived in the form of all records and references; the following is saved in a plain text file format (Fig. 1).

2.2. Bibliometric softwares and data analysis

All data were acquisitive from the Web of Science Core Collection and introduced into VOSviewer, Scimago Graphica, and CiteSpace for visual analysis. VOSviewer is a sociometric network analysis free software developed in 2009 at Leiden University [30]. The goal of VOSviewer is to illustrate bibliometric networks, set up visual network maps, facilitate a comprehensive grasp of the structure and development of scientific research [31]. CiteSpace is another visualization software, as an effective tactic for analyzing big data,

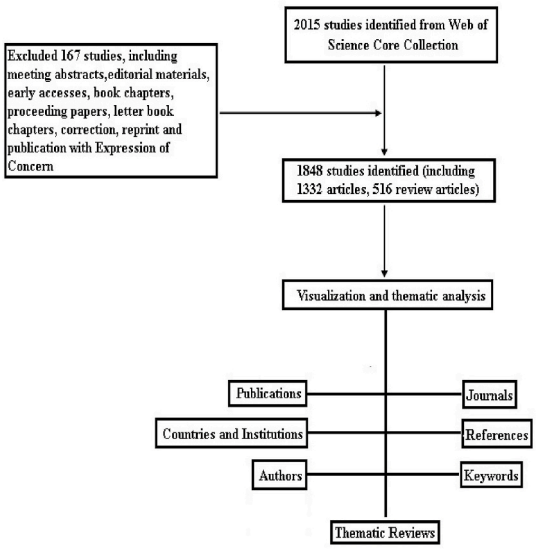

Fig. 1. Resarch flow of literature selection.

can visually show research hotspots and evolutionary processes and predict development trends in various domains [32–34].

Before downloading data was imported into the software for analysis, all of the mentioned software was initialized. Synonyms were merged into the same word, and meaningless keywords were removed. Besides, a region of a country belonged to that country, and different titles of the same person/country/institution were combined. Microsoft Office Excel and CiteSpace 6.1.R2 software are used to analyze trends in the annual number of published articles and the number of citations and visualize references and timelines. Keywords were derived by VOSviewer and divided into three stages for analyzing GBE's tendency and research hotspots. Data from VOSviewer were transformed into Graph Modeling Language (GML) format and then loaded into Scimago Graphica software to visually explore countries, institutions, and authors. In the circle shape generated by Scimago Graphica software every node represents an author, and the node's size shows the literature's citation. Then, the lines indicate cooperation between authors; the darker line shows closer cooperation. In addition, Web of Science obtained the journal impact factor (IF) and Journal Citation Reports (JCR) category quartile in 2022. The milestone reviews of GBE were listed as a roadmap to the direction of GBE research development. The quality of meta-analysis for randomized controlled trials (RCTs) of GBE in clinical application has been assessed by Risk of Bias in Systematic Reviews scale (ROBIS).

3. Results

3.1. Annual outputs and citation trends

According to the bibliographic retrieval strategy, a total of 2015 papers were incorporated into the bibliometric analysis. The number of literature published in each period reminds trends in the investigation in this domain. As exhibited in Fig. 2, the number of articles and citations of GBE articles from 1999 to 2022 remained high, especially in the last five years, indicating that the study of GBE has been valued in the past decades.

3.2. Countries/regions

789 institutions published a total of 1848 articles in 80 countries/regions. In Table 1, the overwhelming majority of publications come from China (623, 33.71 %). Surprisingly, the USA has the largest total link strength (TLS = 153), indicating that the USA co-operates most closely with other countries. The following are Germany (TLS = 108) and Australia (TLS = 71); different degrees of cooperation have also been constituted with other countries. The research institutions with the most number of publications and citations, respectively, are the China Academy of Chinese Medical Sciences (28, 584) and the Chinese University of Hong Kong (27, 850). Most of the top 10 institutions belonged to China, followed by Japan and Egypt. This discovery suggests that these countries/institutions may have played a pivotal role in GBE research. In Fig. 3A, the lines between nodes represent cooperation between countries/institutions. The USA and China show the closest cooperation; denser red lines color and a deeper shade of blue color correspond with closer cooperation. The China Academy of Chinese Medical Sciences has the largest total link strength (TLS = 32), indicating that the China Academy of Chinese Medical Sciences cooperates most closely with other institutions (Fig. 3B).

3.3. Citation authors and co-cited authors

In Fig. 4A, all citation authors cluster into nine clusters that bend into a circle shape. The top ten citation authors all have been cited more than 9000 times. The maximum size of a node in the circle is Christen Yves, cited most frequently (2257) and had the largest total link strength (TLS = 1065).

In Fig. 4B, each node delegates a co-cited author, and the dimension of the node is proportional to the digital citations. The lines between nodes stand for cooperation between co-cited authors. As can be drawn from Fig. 4B, the co-cited authors were distributed in

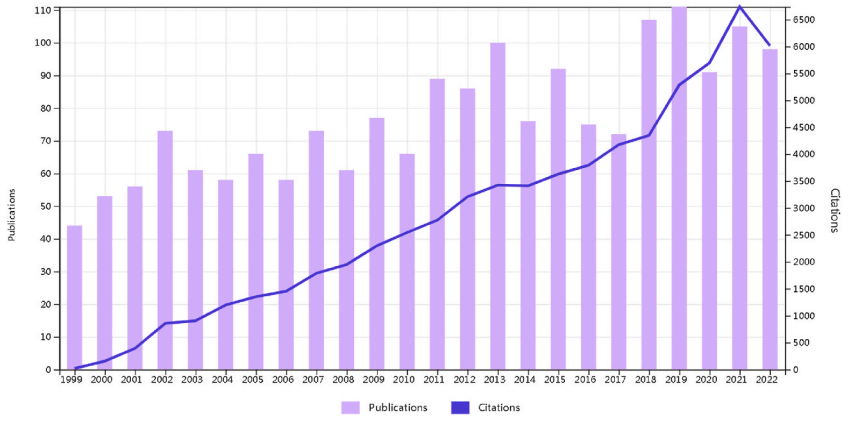

Fig. 2. Annual output and citation times of publications with GBE from 1999 to 2022.

Table 1
Distribution of publications according to country/region and institution.

Rank	Country	Count (%)	Citations	TLS	Institution (country)	Count	Citations	TLS
1	USA	296 (16.02%)	17308	153	China Academy of Chinese Medical Sciences (China)	28	584	32
2	China	623 (33.71%)	13940	130	Capital Medical University (China)	18	297	29
3	Germany	161 (8.71%)	7244	108	National Yang-Ming University (Taiwan)	20	824	29
4	Australia	56 (3.03%)	2585	71	China Medical University (China)	21	741	27
5	France	71 (3.84%)	5672	56	National Institute of Health Nutrition Japan (Japan)	23	696	27
6	England	86 (4.65%)	9161	54	Chinese Academy of Sciences (China)	15	518	25
7	Italy	70 (3.79%)	4381	54	Mukogawa Women 'S University (Japan)	21	661	25
8	Saudi arabia	38 (2.06%)	743	41	Beijing University of Chinese Medicine (China)	21	525	24
9	India	61 (3.30%)	1986	40	Chinese University of Hong Kong (Hong Kong)	27	850	23
10	Spain	37 (2.00%)	3698	38	Alexandria University (Egypt)	14	343	20

four clusters, showing different levels of cooperation between clusters. Gurley BJ had the most significant total link strength, as the highlight and displayed in the VOSviewer (TLS = 12810) (Fig. 4C). A total of 8092 authors published articles on GBE. In Table 2, Drieu. K had the highest number of published papers (22), followed by Shinozuka Kazuma (19) and Yin Xiaoming (19).

3.4. Journals and co-cited academic journals

The journals that had published articles on GBE performed a visual analysis using the VOSviewer software. Moreover, we found that the 1848 articles related to GBE were published in 761 scholarly journals. Table 3 presents that the top three journals, by yield, are Phytotherapy research (47, 1.55 %), Frontiers in pharmacology (31, 1.55 %), and Phytomedicine (26, 1.50 %). GBE-related literature mainly focused on: dementia, phytomedicine, and pharmacology. Additionally, in Table 3, most of the journals remain with Q1/Q2. The co-cited frequencies in a journal can reflect the impact of the journal in a particular territory of study. Among all of the co-cited journals, the top 10 journals were cited over 1000 times. Journal of Ethnopharmacology (1771) was the most frequently co-cited journal, followed by Journal of Biological Chemistry (1436), Proceedings of The National Academy of Sciences of The United States of America (1401), and Phytotherapy Research (1363). According to the 2022 JCR, most of the co-cited academic journals among the top-ranked journals belong to Q1/Q2. A dual map overlay of journals shows the distribution of relationships between journals. In Fig. 5, the left clusters represent where the retrieved records are published, whereas the right clusters indicate where they are cited [35]. The colored paths between the two sides figure out the cited relationships. There are four main citation paths, including one green and three orange paths. The three orange paths indicate that studies published in Molecular/Biology/Immunology journals are cited in studies in Health/Nursing/Medicine journals, Molecular/Biology/Genetics journals, and Environmental/Toxicology/Nutrition journals. And the green path indicates that studies published in Medicine/Medical clinical journals are generally cited by Molecular/Biology/Genetics journals.

3.5. Co-cited references and reference bursts

The timeline visualization presents a temporal overview of nodes, links, and clusters. As illustrated in Fig. 6, the references selected in this study were mainly clustered in 15 categories: glaucoma, herb medicine, complex I, dementia, drug interaction, ischemic stroke, brain health, interaction, retinal ganglion cells, Alzheimer's disease, gastric cancer, drug transporter, acetycholinesterase, flavonoid and cytochrome P450. The research hotspots and fields of concern differ in different periods. Cytochrome P450, drug interaction, acetycholinesterase, and flavonoid were earlier areas of concern. Over time, the research on Alzheimer's disease, retinal ganglion cells, gastric cancer, and glaucoma of GBE clinical application has gradually become prominent. Two or more articles are cited by one or more papers at the same time; then, these two articles are in a co-citation relationship. Among the retrieved co-cited references, Table 4 shows the top 10 co-cited references and the references with citation bursts, of which the top three for both co-cited reference counts and references with citation bursts are LeBars PL [36] (73, 36.31), Vellas B [37] (43, 23.67), and Oken BS [10] (40, 17.68). Moreover, the different references exhibit different bursts in different periods. As can be seen in Fig. 7, the bursts of Oken BS [10], DeFeudis FV [38], Luo Y [39], Maclennan KM [40], Abdel-Kader R [41], Weinmann S [42], and Tan MS [43] references have the most prolonged duration, as much as 7 years, reflecting the current research focus to some extent and showing an important consultative value. Analysis of Fig. 7 shows that the top 20 cited publications were all included in the references with the most robust citation bursts. This literature can be considered the most valuable and influential research in the field. First, the most highly cited study published in the JAMA showed that GBE could improve the cognitive performance and the social functioning of demented patients for half a year to one year without any adverse events [36]. However, long-term use of GBE cannot prevent Alzheimer's Disease in elderly individuals with normal cognition [37], then serial follow-up studies confirmed the research conclusions of Le Bars et al. [38,44,45,42,43]. Second, as shown in Fig. 7, an article published in J Alzheimers Dis in 2015 has the most prolonged duration (2015–2022), which will be a higher number of citations as time goes by. GBE can stabilize or slow decline in cognition, function, and behavior in cognitive impairment and dementia patients [43]. These further confirmed the conclusion of Le Bars et al. [36]. Several articles on the mechanism of GBE neuroprotective were published successively. The report showed the potential effectiveness of GBE via inhibiting Abeta-induced toxicity aggregation, decreasing tissue levels of reactive oxygen species, and inhibiting membrane lipid peroxidation in neurodegenerative diseases [10,46,45,47,39,40]. From this, we can speculate on the direction of GBE in basic research and clinical application.

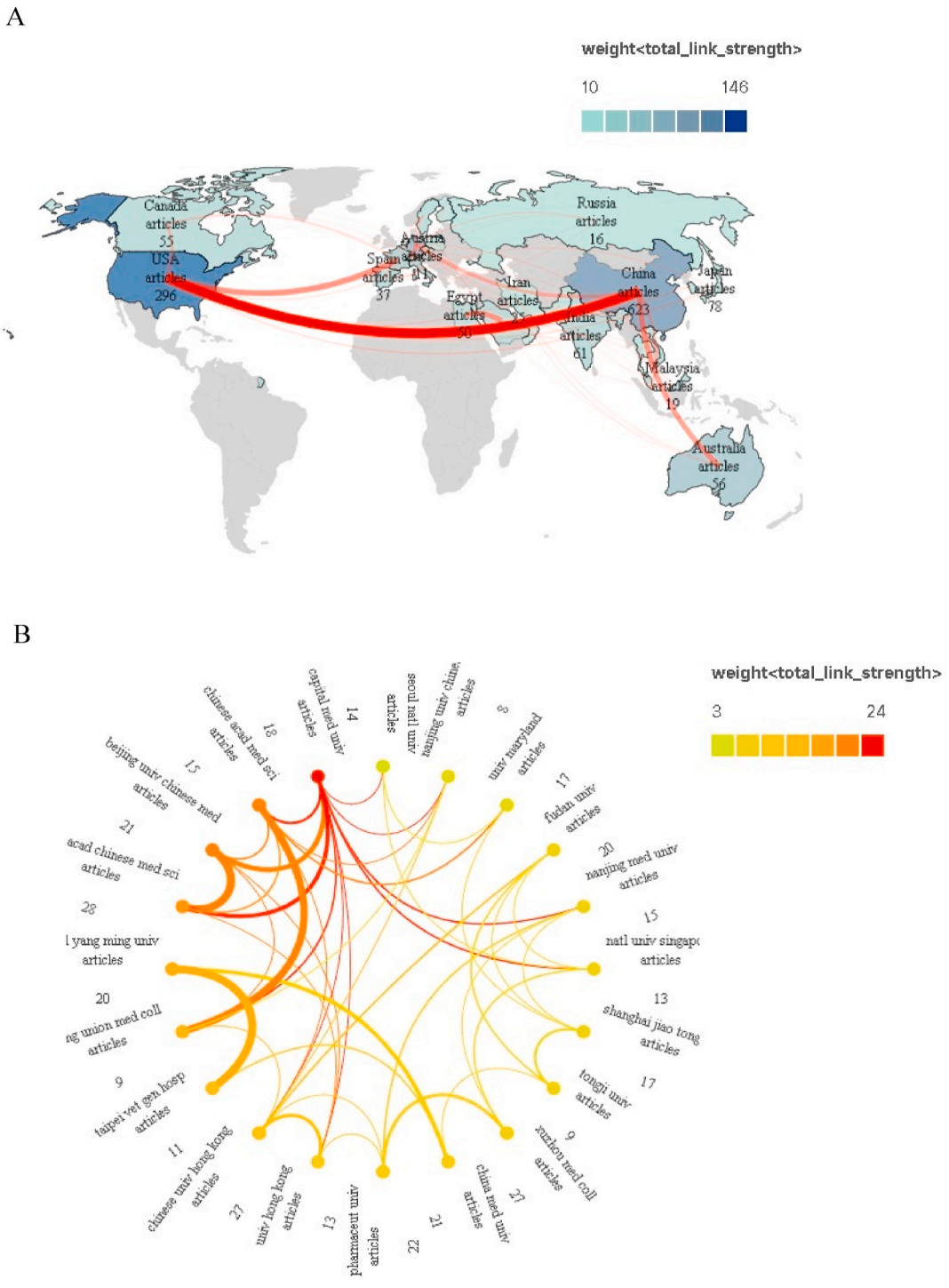

Fig. 3. A.Distribution of publications according to country region
Fig. 3B.Cooperation network among institutions. Note the thickness of the lines between countries institutions indicates the strength of cooperation.

3.6. Keywords

Keywords can supply a point of view of the research topic and the conclusion of the scientific hotspots in a particular field. In this study, keyword co-occurrence arrangement graphs were generated by VOSviewer software. Keywords of all literature that appeared more than 50 times were extracted. Then the 20 most frequently occurring keywords were listed in Table 5. Besides GBE, the high-

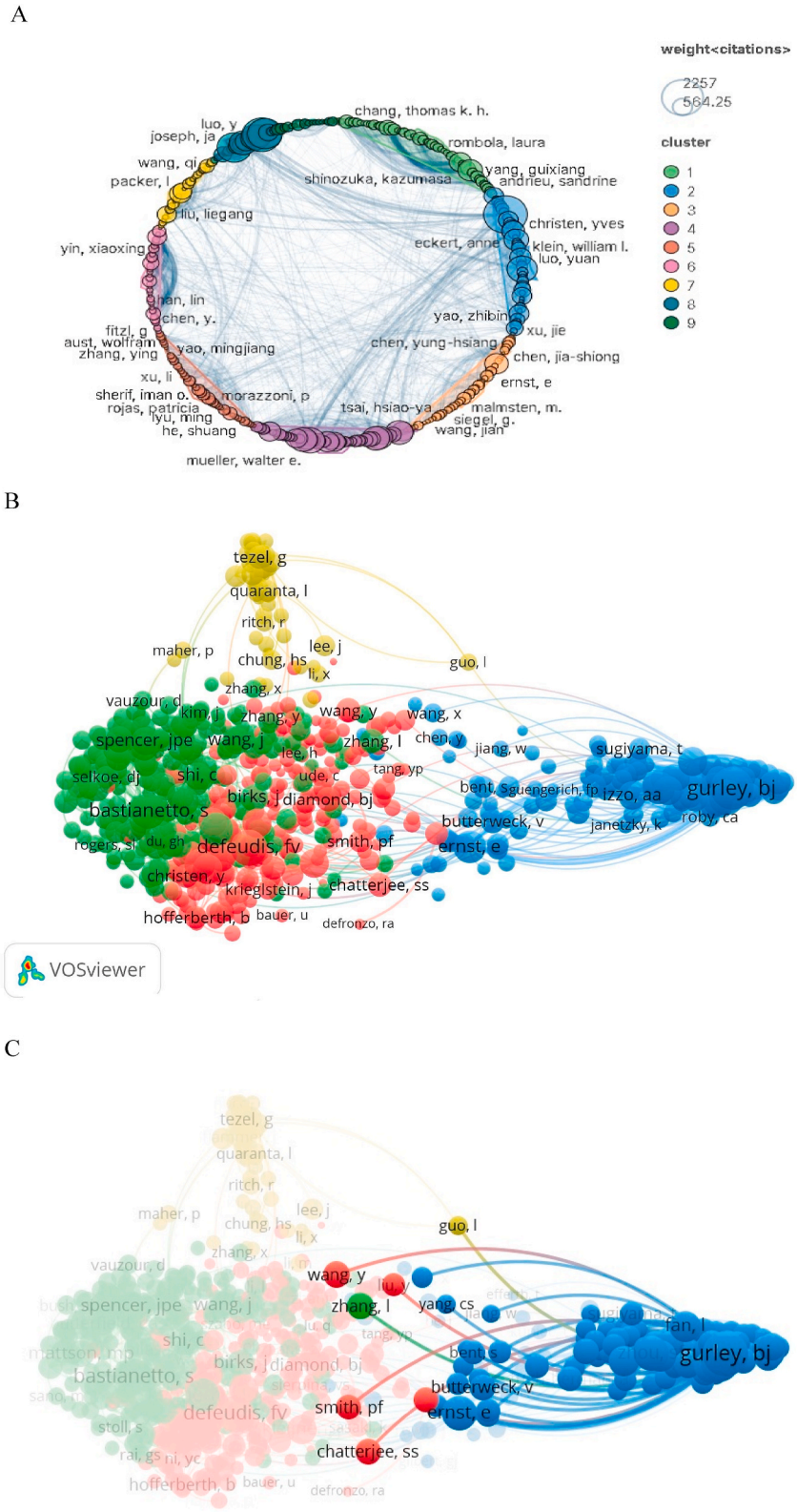

Fig. 4. A.Visualization map of authors citation in GBE research
Fig. 4B.VOSviewer visualization map of co-cited authors in GBE research
Fig. 4C.VOSviewer visualization map of co-cited author Gurley.bj in GBE research.

Table 2
Top 10 citations and co-cited authors in GBE research.

Rank	Author	Count	Citations	TLS	Co-cited Author	Citations	TLS
1	Christen Yves	16	2257	1065	Gurley.bj	244	12810
2	Umegaki Keizo	12	709	947	Defeudis.fv	409	8245
3	Mueller Walter e.	14	1019	918	Markowitz.js	125	7665
4	Shinozuka Kazumasa	19	577	875	Bastianetto.s	242	7438
5	Drieu.k	22	892	832	Kennedy.do	209	6740
6	Hoerr robert	14	724	745	Zhou.sf	124	6108
7	Luo yuan	10	1081	690	Ernst.e	208	6102
8	Yin Xiaoxing	19	426	641	Ramassamy.c	156	5151
9	Luo Y	6	906	639	Piscitelli.sc	81	4852
10	Smith,jv	4	754	553	Lebars.pl	207	4791

Table 3
Top 10 journals and co-cited journals publishing *Ginkgo biloba* extract research articles. IF, Impact Factor; JCR, Journal Citation Reports.

Rank	Journal	Count (%)	Citations	TLS	Co-cited journal	Citation	IF (2022)	JCR
1	Phytotherapy Research	47 (2.54)	1873	176	Journal of Ethnopharmacology	1771	5.19	Q1
2	Frontiers In Pharmacology	31 (1.67)	790	139	Journal of Biological Chemistry	1436	5.49	Q2
3	Phytomedicine	26 (1.41)	1010	159	Proceedings of The National Academy of Sciences of The United States of America	1401	12.66	Q1
4	Evidence-Based Complementary and Alternative Medicine	25 (1.35)	379	97	Phytotherapy Research	1363	6.38	Q1
5	Journal of Ethnopharmacology	24 (1.30)	742	116	Brain Research	1313	3.61	Q3
6	Life Sciences	20 (1.08)	969	141	Free Radical Biology and Medicine	1271	8.10	Q1
7	Molecules	20 (1.08)	418	74	Life Sciences	1257	6.78	Q1
8	Nutrients	19 (1.03)	716	65	Investigative Ophthalmology & Visual Science	1122	4.92	Q1
9	Cellular And Molecular Biology	19 (1.03)	594	122	Journal of Neurochemistry	1116	5.55	Q1
10	Acta Pharmacologica Sinica	19 (1.03)	435	83	Jama-Journal of the American Medical Association	1068	157.33	Q1

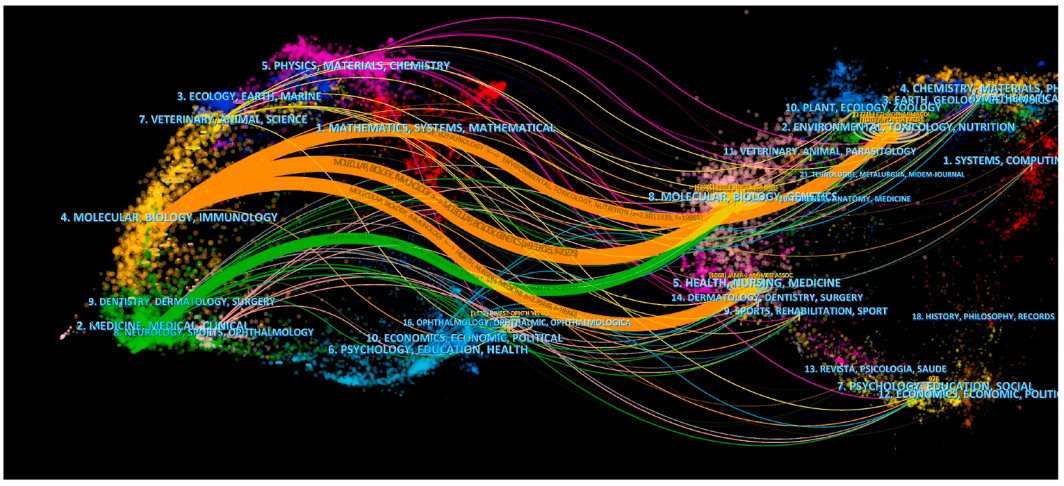

Fig. 5. Dual map overlay of journals with GBE. Note the citing journals are on the left, and the cited journals are on the right.

frequency keywords in Table 5 were oxidative stress, dementia, double-blind, apoptosis, expression, in-vitro, inhibition, flavonoids, brain, neuroprotection, nitric-oxide, mechanisms, cells, rats, antioxidant, quercetin, efficacy, injury, and NFκB. As shown in Fig. 8A, clustered network diagrams can reflect the research area's essential knowledge structure. Most were clustered into three categories:

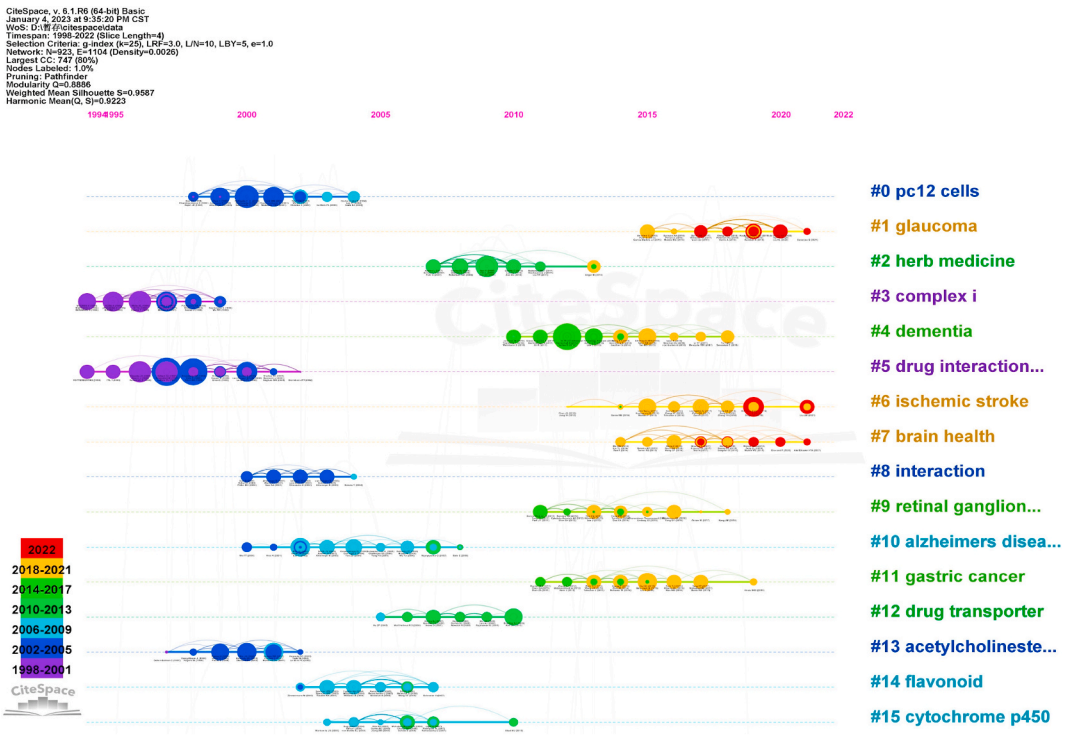

Fig. 6. Timeline of GBE research references. Note the size of the nodes is positively correlated with the frequency of citation, the curve between nodes represents the citation relationship, the straight line represents duration, the color of the lines and nodes corresponds to the color of the year. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 4
Top 10 co-cited references and references with citation bursts related to *Ginkgo biloba* extract.

Rank	Authors	References citation	Journal	Count (%)	Year	Centrality	Bursts
1	Le Bars PL et al. [36]	A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group	JAMA	73	1997	0.06	36.31
2	Vellas B et al. [37]	Long-term use of standardised Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial	Lancet Neurol	43	2012	0.03	23.67
3	Oken BS et al. [10]	The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease	Arch Neurol	40	1998	0.02	17.68
4	Kanowski S et al. [38]	Proof of efficacy of the ginkgo biloba special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia	Pharmacopsychiatry.	30	1996	0.00	17.07
5	Bastianetto S et al. [46]	The Ginkgo biloba extract (EGb 761) protects hippocampal neurons against cell death induced by beta-amyloid	EUR J NEUROSCI	38	2000	0.04	16.50
6	Watanabe CM et al. [48]	The in vivo neuromodulatory effects of the herbal medicine ginkgo biloba	P NATL ACAD SCI USA	36	2001	0.00	15.25
7	DeKosky ST et al. [44]	Ginkgo biloba for prevention of dementia: a randomized controlled trial	JAMA	33	2008	0.00	14.67
8	DeFeudis FV [45]	Ginkgo biloba extract (EGb 761) and CNS functions: basic studies and clinical applications	Curr Drug Targets	32	1998	0.00	14.12
9	Smith JV et al. [47]	Studies on molecular mechanisms of Ginkgo biloba extract	Appl Microbiol Biot	31	2004	0.17	13.66
10	Le Bars PL et al. [49]	A 26-week analysis of a double-blind, placebo-controlled trial of the ginkgo biloba extract EGb 761 in dementia	Dement Geriatr Cogn Disord	31	2000	0.00	13.30

the mechanism of action of GBE, clinical application (including dementia, glaucoma, etc.), and the chemical analysis of GBE; among all of the clusters, the mechanism of action of GBE represents the largest territories of GBE research, indicating that these played a key role on topics in the study of GBE. On the other side, in the overlay visualization map of the keywords co-occurrence analysis graph, a

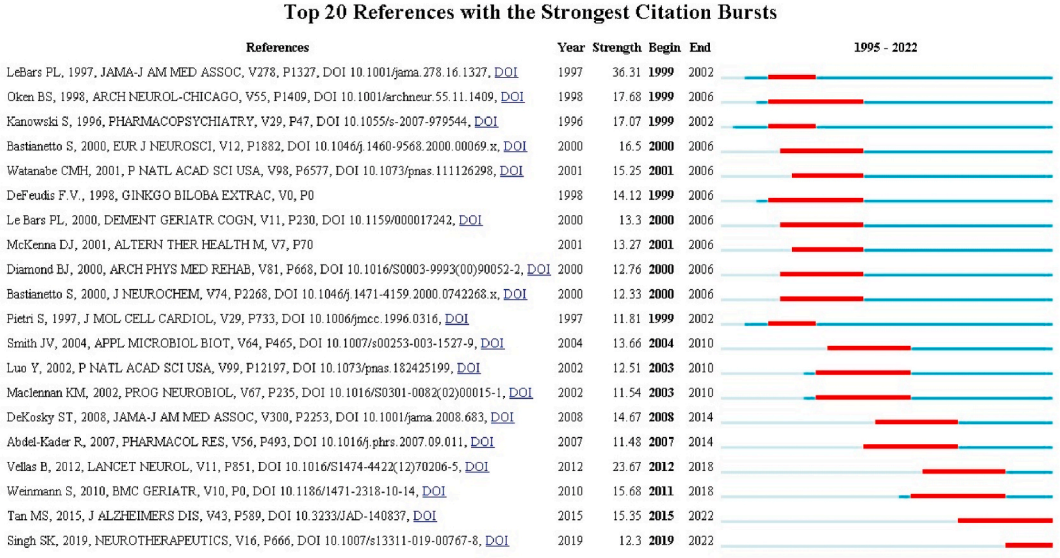

Fig. 7. CiteSpace map of the 20 references of GBE research with the strongest citation bursts.

Table 5
Top 20 keywords related to *Ginkgo biloba* extract.

Rank	Keyword	Count	TLS	Rank	Keyword	Count	TLS
1	Oxidative Stress	361	1093	11	Activation	89	292
2	Dementia	305	874	12	Nitric-Oxide	92	290
3	Double-Blind	220	591	13	Mechanisms	88	277
4	Apoptosis	157	516	14	Cells	86	265
5	Expression	125	376	15	Rats	84	260
6	In-Vitro	132	362	16	Antioxidant	77	253
7	Inhibition	100	356	17	Quercetin	87	250
8	Flavonoids	108	317	18	Efficacy	81	249
9	Brain	88	300	19	Injury	73	239
10	Neuroprotection	85	297	20	NFκB	71	218

deeper shade of orange color corresponds with a higher score of average normal citations; Fig. 8B showed an overlay visualization map of the keywords co-occurrence analysis graph, dementia, oxidative stress, and NFκB reflect future trends in GBE research. Furthermore, Fig. 8C highlight displayed overlay visualization map of dementia (Fig. 8C(1)), oxidative stress (Fig. 8C(2)), and NFκB (Fig. 8C(3))as keywords co-occurrence analysis graph.

In this study, the 20 most frequent keywords are presented for three phases based on the data produced by the Web of Science Core Collection (Fig. 9). The difference between the three phases appeared to be a significant change, which could support the division into these phases. Thus, the relations and differences between the keywords in all three stages were observed. As for the search words, "*Ginkgo Biloba* Extract" and "oxidative stress" undoubtedly ranked top 2 in each stage. Some keywords superimposed during the three phases, although the sequence was different, such as the frequencies of the two keywords (i.e., "double blind" and "neuroprotection") in Phase I, Phase II, and Phase III continuously on the rise, however, "pharmacokinetics" and "flavonoids" in Phase I declined in number in the Phase III, which are also demonstrated through timeline visualization generated by CiteSpace.

Keywords belonged to the chemistry category in Phase I, such as "quercetin", "metabolism", "pharmacokinetics", and "flavonoids". In addition, "nitric-oxide" is a unique keyword in Phase I because it is the only word describing the pharmacological activity of flavonoid kaempferol found in GBE in the early stage in the top 20 most frequent keywords, which shows that GBE was considered a potential anti-inflammatory agent, inhibit nitric oxide production under tissue-damaging inflammatory conditions from the initial stages of research [50,51] (Fig. 9). Compared with Phase I, keywords about the signal path involved the GBE as anti-inflammatory agent emerges in Phase II (i.e., "NFκB", and "inflammation"). This means that activation of NFκB is one of the critical events in the signal transduction pathways mediating inflammation induction [51]. Furthermore, words related to the glaucoma of GBE (e.g., "glaucoma" and "open-angle glaucoma") only emerge in Phase III. An article published in 2022 demonstrated that GBE had been shown to improve optic nerve head perfusion and decrease oxidative stress in the treatment of glaucoma [52].

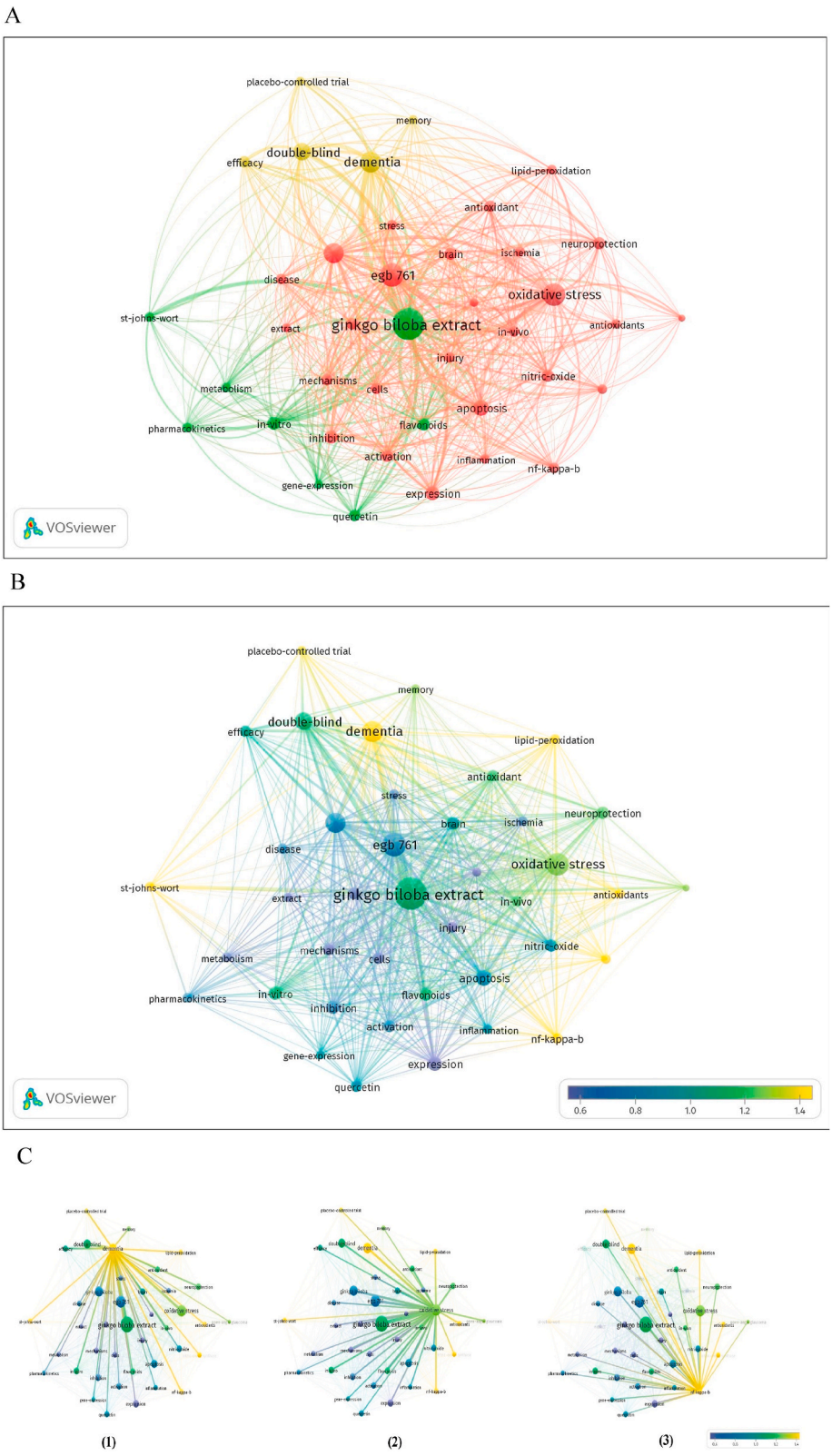

Fig. 8. A.VOSviewer visualization map of clustered network diagrams of keywords
Fig. 8B.An overlay visualization map of the keyword co-occurrence analysis graph
Fig. 8C.An overlay visualization map of dementia (1), oxidative stress (2) and NF-κB (3) co-occurrence analysis graph.

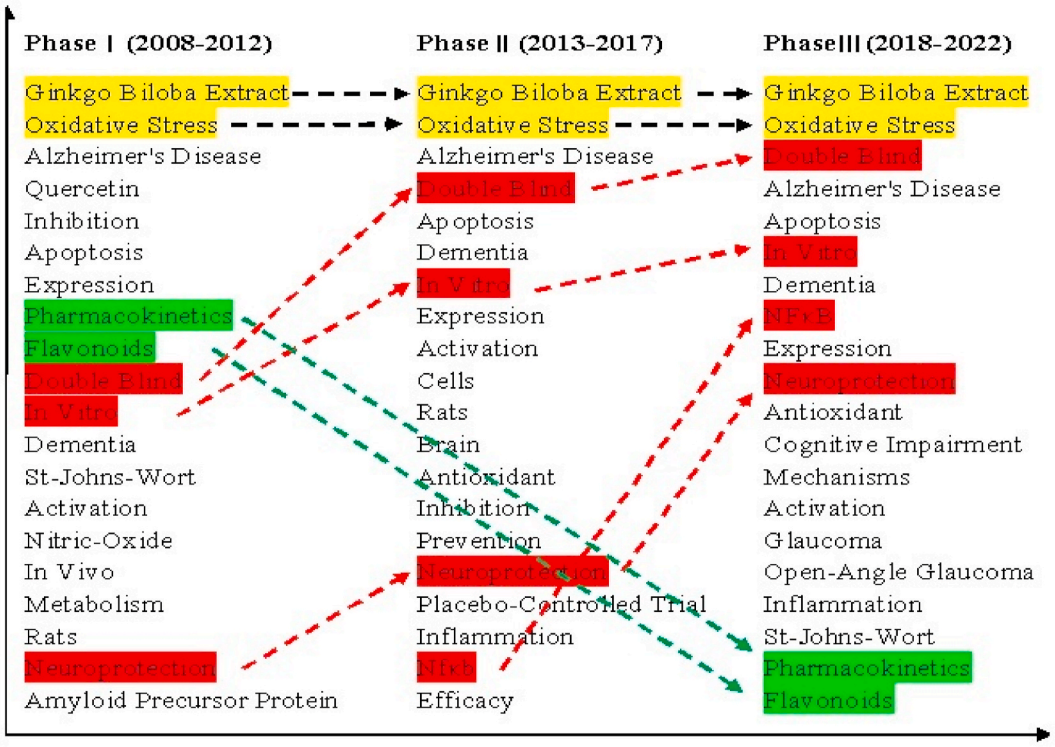

Fig. 9. TOP 20 co-occurrenc keywords in three phases of past15 years.

4. Discussion

The trends in the number of literature and article citations reflect the exploration rate and research progress in a field [53]. Fig. 2 indicates that the number of articles and citations on GBE is generally at a relatively high level, indicating that GBE has been a significant research direction in the last few years and has a remarkable development trend in the future. Furthermore, 2015 articles published from 1985 to 2022 were analyzed, and these publications encompass 815 journals, 80 countries/regions, 1855 institutions, and 3333 authors, demonstrating that the GBE has captured the attention of scholars worldwide. The contribution of China in this field is particularly prominent, which may be related to the fact that GBE, as a traditional Chinese medicine, is widely used in China [11,22]. Another significant contributor is the USA, whose status may be related to the superior biotechnology it applies to GBE research. (Fig. 3A). The China Academy of Chinese Medical Sciences cooperated most frequently with other organizations, and it cooperated most closely with Peking Union Medical College in China (Fig. 3B). Christen Yves, who is from the United States, has been cited most frequently and cooperates most closely with other researchers. These findings show that the USA holds an outstanding position in this field. The total number of publications and citations. Phytotherapy Research (n = 47; 1873 citations) and Phytomedicine (n = 26; 1010 citations) were the top two journals in this area. The Journal of Ethnopharmacology is the most co-cited among of the top 10 journals; it is also ranked as Q1 by the Journal Citation Reports (Table 3); these conclusions echo the dual map of overlay of journals with GBE, which suggests that published articles on GBE are mainly oriented toward medical and clinical applications. (Fig. 5). With the assistance of these data, researchers can swiftly create a knowledge architecture that is based on existing and significant contents in this field that are identified by our study.

We can determine the information that investigators emphasize from an analysis of references. CiteSpace was used to analyze references. The years per slice in the time slicing module was set to four, and the top 20 references were listed (Figs. 6 and 7). Timeline view analysis is shown, including the topics “flavonoid”, “cytochrome p450”, “drug transporter”, “interaction”, “ischemic stroke”, “dementia”, and“glaucoma”. The rate of development is still generally slow across the entire spectrum. The research background of this domain can be divided into four stages, according to the theme by analyzing the references of literature with a timeline view, including chemical analysis, pharmacokinetics, pharmacological mechanism and clinical application of GBE.

To the beginning of December 2022, 516 GBE-related review articles were retrieved from the Web of Science Core Collection; 37 were directly related to GBE, as characterized by the inclusion of GBE in the title.

The earliest review article related to the topic of GBE was published in 1999 [54]; however, the first review article directly related to GBE (with a title containing GBE) was published in 2000 and detailed the molecular mechanism of GBE as a potential strategy for dementia, stroke, and macular degeneration; proposed optimization of dose, component activity, mechanisms, and clinical applications were the hotspot of future research [55], which was consistent with the roadmap of GBE in different subdivisions of the field in Fig. 10.

4.1. Milestone reviews of chemical analysis of GBE

GBE exhibits various pharmacological actions based on chemical constituents, which are the foundation of pharmaceuticals [56]. Van Beek conducted two reviews of chemical analysis and quality control of GBE in 2002 and 2009, respectively [57,58]. He pointed out that the separation and detection of ingredients of GBE can mainly depend on HPLC with RI, ELSD, or MS. Then, several relevant articles focused on chemical analysis were published later [59,60]. All of them classified the chemical composition of GBE into several different types based on chemical structure patterns as follows flavonoids, terpenoids, alkylphenols and alkyl phenolic acids, carboxylic acids, lignans, proanthocyanidins, polyprenols, and polysaccharides [56–58].

Quantitative analysis of multi-index components of GBE often requires sufficient chemical reference substances; however, many reference substances are difficult to obtain. To obtain higher contents and chemical reference substances for quantitative determination, several methods, such as extraction with supercritical carbon dioxide [13], extraction with ionic liquids [61], graphene oxide-assisted extraction [62], separation of polyprenols by adsorbents containing silver ions [63], enrichment and purification with macroporous resin [64], and ultrasound-assisted enzymatic extraction [65,66], have been developed to extract and purify specific constituents from GBE. All of the methods mentioned above possess disadvantages in the efficiency of the content and purity of the isolated active compounds, making it challenging to meet the massive demand of the international market. Recently, Liu et al. proposed that synthesis and biosynthesis may become potential strategies for the preparation of characteristic compounds from *Ginkgo biloba* [3].

The detection of flavonol glycosides, terpenoid lactones (the active constituents), and ginkgolic acids (the toxic constituents) has received increasing attention [56]. In addition, the contents in GBE have different rules in mainstream countries; the pharmacopeia of the People's Republic of China (Chin. Ph.) total flavonol glycosides≥24 %, sum of BB, GA, GB, and GC ≥ 6 % (BB: bilobalide GA: ginkgolide A; GB: ginkgolide B; GC: ginkgolide C), total ginkgolic acids≤10 mg/kg; European Pharmacopeia (Eur. Ph.) total flavonol glycosides 22 ~ 27 %, total ginkgolic acids≤5 ppm, and United States Pharmacopeia (US. Ph.) total flavonol glycosides 22 ~ 27 %, sum of BB, GA, GB, and GC ≥ 6 % 5.4 ~ 12 %, total ginkgolic acids≤5 mg/g [3]. Then, an increasing number of qualitative and quantitative analyses of the constituents in GBE were established [67–84]. Nevertheless, the literature published on the topic of analytical chemistry has declined significantly over the past decade. In 2015, an article reviewed the advances in chemical analysis and quality control of flavonoids in GBE [59]; up to 2021, the review focused on chemical constituents and detection techniques for GBE [56]. These reviews summarize most analytical methods and provide references for research on the quality control and discovery of effective constituents for GBE. Due to the slow iteration of analytical methods in recent years, reviews in this research in this territory are contracting.

Fig. 10. Roadmap of the milestone reviews of GBE in different subdivided fields.

4.2. Milestone reviews of the pharmacokinetics of GBE

Extensive knowledge about the pharmacokinetic characteristics of GBE, including absorption, excretion, and metabolism of active pharmacodynamic compounds such as flavonoids, helps to evaluate and discuss the pharmacological mechanisms. In 1986, Moreau et al. first reported the pharmacokinetics of GBE. The half-life of specific activity is 4–5 h. The primary active substance of GBE is distributed in glandular and neuronal tissues and eyes, with high absorption and bioavailability [85], Rangel-Ordóñez L et al. reported that after administration of GBE, flavonoids in the rat brain were distributed in the hippocampus, frontal cortex, striatum, and cerebellum [86], Bhattaram et al. described the pharmacokinetics and bioavailability of active ingredients of GBE; the mean elimination half-life of terpene lactones and flavonols were in the range of 2–3 h and 2–4 h, respectively. The bioavailability values of ginkgolides and bilobalide were more than 70 % [87]. Then, the absorption, excretion, and metabolism of pharmacokinetic characteristics of GBE were summarized by Diamond BJ et al. [55].

Due to their wide use and ease of availability, and gradually revealing their safety, the interaction between GBE and drugs has attracted extensive attention. In 2001 and 2009, Izzo AA reviewed GBE and drug interactions and detailed that GBE influenced the plasma concentrations of omeprazole, ritonavir and tolbutamide; clinical cases indicate interactions of GBE with antiepileptics, aspirin, diuretics, ibuprofen, risperidone, rofecoxib, trazodone and warfarin, and the above mentioned interactions have serious clinical consequences [88,89]. Several subsequent several reports have shown that GBE fed to rats significantly increased the concentration of hepatic cytochrome P450, the expression of various cytochrome P450 RNAs, and the activity of some enzymes [90,91]. Even so, until now, the effect of *Ginkgo biloba* components on cytochrome P450 enzymes has been controversial and far from conclusive [90,92–94]. Chatterjee et al. detailed that GBE is mainly metabolized by CYP3A4 and proposed that the effects of GBE on drug-metabolizing enzymes were specific for rats and may not be extrapolated to humans [95]. Then Gougis et al. recently reviewed documents on GBE and pointed out that due to the inconsistent results in different trials, GBE as an inducer or inhibitor has been controversial, classifying GBE as having a mild interaction with cytochromes for predicted interaction with drugs [21]. Based on published data, most scholars believe that it is impossible to assess whether the interactions of GBE compounds and cytochrome P450 enzymes exhibit clinical relevance for humans. Further investigations into humans are necessary to draw a definite conclusion.

4.3. Milestone reviews of the pharmacological mechanism of GBE

Over the past decade, GBE treatment diseases have received considerable attention. An increasing number of studies have focused on the mechanism of GBE treatment of various types of diseases [96–98], which partially supports the last consequence drawn from the analysis of keywords and literature that scholars are paying attention to the mechanism of GBE treatment of clinical diseases. Since the discovery of the effect of GBE, including neuroprotective, antioxidation, and anti-inflammatory effects [99], the discussion on its mechanisms has been ongoing by scholars. Some are mainly relevant to inhibiting the aggregation of amyloid-beta, which is thought to be the primary mechanism of dementia; others have focused on antioxidative stress and anti-inflammation [39,100–102].

The first review detailed that flavonoids, as the main components of GBE are mediated by exerting antioxidative properties by delivering electrons to free radicals, blocking ROS accumulation and inhibiting neuroinflammation to treat age-related neurodegenerative diseases [103]. Youdim K A et al., Cybulska-Heinrich et al., Song et al. and Młynarczyk et al. successively summarized the antioxidant, antiplatelet, and antiapoptotic and anti-inflammatory effects of GBE, including inhibiting NADPH oxidase subunits p47 (Phox) and rac-1, reducing gp91 and p22 (Phox) expression caused by ox-LDL induced AMPK and PKC activation, enhancing HO-1 expression through the Akt/eNOS and p38/MAPK pathways, reducing adhesion molecules such as monocyte chemokine-1 (MCP-1) and VCAM-1 mediated by ROS, preventing the adhesion of monocytes to endothelial cells, protecting endothelial cells function, reducing ROS generation, thereby preventing endothelial dysfunction, and considering GBE as a potential therapeutic approach in the treatment of nervous lesions, glaucoma and atherosclerosis [104–107].

Additionally, Alzheimer's disease, which is known as the most common cause of dementia, has attracted widespread attention across the world. GBE not only exerts antioxidant effects but also prevents amyloid-beta and tau aggregation and enhances spatial learning and memory to relieve the symptoms of Alzheimer's disease [39,100,108].

According to the distribution of countries/regions, China is the most productive country, suggesting that it is a leading country in GBE research. Surprisingly, the United States has the highest TLS, which means that the USA has the closest cooperation with other countries and even plays a significant bridging role in global cooperation. Among the top 10 institutions, seven were from China, which explains why China has the largest number of publications. Although there are different extents of collaboration in the middle of countries, the TLS of cooperation among some of the top 10 institutions can be meliorated. Therefore, we hope that countries and institutions can cooperate even further. The publication count of Drieu.K from Japan is the first in the author list and had a high TLS. Christen Yves had the highest number of citations, indicating significant academic impact and outstanding scientific achievement in GBE research in recent decades. The TLS of Gurley.BJ ranked first in co-cited authors, reflecting his powerful academic influence on GBE research. Of the published and cited journals, dementia ranked first with the most significant number of publications and citations of GBE research.

4.4. Milestone reviews of the clinical application of GBE

Despite GBE having a wide range of pharmacological effects, its clinical application is limited and controversial [37,109–112]. The first meta-analysis confirmed the efficacy and good tolerability of GBE was patients who suffered from dementia [111], then effects on tinnitus and dizziness were demonstrated [113], but showed no prevention of acute mountain sickness [114]; subsequently, GBE in

mono-therapy showed greater scientific evidence as a therapeutic option for vitiligo [115]; then, Ji HJ et al. reported GBE appears to improve neurological function and dependence compared with conventional therapy for ischemic stroke at different stages, however not ameliorate in recurrence rate for ischemic stroke patients [11]; Kuo CY summarized several conflicting studies exploring the neuroprotective effect of GBE in the clinical treatment of glaucoma, drawing the conclusion that whether GBE is effective in the treatment of glaucoma further large clinical trials still need to be justified [116]; Liang N et al. reported GBE could help mild cognitive impairment patients to prevent progression into dementia and to improve the ability of daily living activities [117]; Xie et al. showed GBE relieves dementia symptoms in early-stage Alzheimer's disease sufferers after high doses and long-term use of GBE from clinical studies [118]. Ahmad et al. summary of randomized control trials determined that the combination of GBE and pharmaceuticals has far better effects than only allopathic treatment for dementia; they also report that consider different herbal remedies in combination with FDA approved drugs are effective and more promising than monotherapy in the treatment of Alzheimer's disease [119].

The risk of bias for meta-analyses of GBE in the treatment of dementia was evaluated by the ROBIS. Then the assessment was divided into three stages: (1)assessing relevance; (2) identifying concerns with the review process; (3) assessing relevance [120].

All published meta-analyses assessed by ROBIS for dementia had low risk in Phase 1 (assessing relevance) and Phase 2 (identifying concerns with the review process) in the first domain (study eligibility criteria), interestingly opposite results were gotten in Phase 3. The results of the ROBIS assessments for dementia are presented in Table 6. Of the Stage 2 assessments, several published in meta-analysis literature were rated high risk in the second area (identification and selection of studies), rated high risk in the third area (collection and study appraisal), and rated as high risk in Phase 3 (risk of bias in the review) (Table 6). Of the Stage 2 assessments, several published in meta-analysis literature were rated high risk in the second area (identification and selection of studies) [117,121,122], rated high risk in the third area (collection and study appraisal) [111,117,121,122,123], and rated as high risk in Phase 3 (risk of bias in the review) [111,117,121,122] (Table 6). The disadvantages of the abovementioned reviews were the poor quality of the methods, which should arouse clinicians' attention [15]. The results hinted that more qualified RCTs were needed to confirm the conclusion due to the low quality of current trials.

All of the above mentioned clinical application supports the consequence generated from the analytic visualizations of keywords and references by CiteSpace and VOSviewer software that scholars are becoming paying attention to GBE treatment clinical diseases.

Although GBE has been used in dementia for more than 50 years, it is still an essential topic in dementia therapy, and high-quality RCTs are urgently needed for dementia by ROBIS analysis. Furthermore, both mechanism and RCTs of GBE are also meaningful directions. From the reference bursts, clustering of references, frequent keywords, keyword clustering, and keyword hotspot changes, it can be speculated that the mechanism of action of GBE (inhibiting amyloid protein aggregate, neuroprotection, anti-inflammation and anti-oxidative stress) and its application in disease (especially in prevent and effective dementia, glaucoma) are the two directions of research focus and future development.

5. Limitations

There are several limitations to this study. First, because of the different algorithms of clustering and calculation methods incorporated in the bibliometric software, the results will be slightly different when different model types are chosen. Due to the limitations of the software, some emerging fields or rare diseases with less literature may not be exhibited. High-quality research that has just been delivered may have less of an impact because they have not had enough time to gather enough citations. Second, a minute proportion of the publications from other databases have not been incorporated into the literature that we searched, as this research is based only on the Web of Science Core Collection. However, it is generally believed that the Web of Science Core Collection is the best database for bibliometric analysis and should be used; data from this database can provide the majority of the information about a particular topic [32]. In the early stages of this study, we used the search term "extracts of *Ginkgo biloba* leaves" and retrieved 25 articles. All these articles referenced GBE had very few citations. We believe that removing this literature would not affect the conclusion, and the results

Table 6
Results of the ROBIS assessments.

Author, year	Phase 1	Phase 2				Phase 3
	Assessing relevance	Domain 1: Study eligibility criteria	Domain 2: Identifification and selection of studies	Domain 3: Collection and study appraisal	Domain 4: Synthesis and fifindings	Risk of bias in the review
Gauthier S et al., 2014 [111]	L	H	L	H	H	H
Liang N et al., 2022 [117]	L	H	H	H	H	H
Ihl R., 2013 [121]	L	L	H	H	H	H
Savaskan E et al., 2018 [122]	L	L	H	H	H	H
Liu H et al., 2020 [124]	L	L	L	L	H	L
Zhan M et al., 2021 [123]	L	L	L	H	H	L

Note: L,low risk; U,unclear; H,high risk.

will not change much. Third, the results for the period from 1985.1.1 to 2022.12.1 do not cover the whole month of 2022.12. Nevertheless, there is little doubt that the visual analysis of the retrieval literature and topic reviews can provide a solid framework and comprehensive analysis for comprehending the GBE study. Fourth, the ROBIS tool was used in this study to evaluate the meta-analysis of GBE in clinical application, and it can be seen from the study that there are significant quality differences. However, quality assessment is a subjective process, and although this overview was assessed by two independent researchers, there were inevitably subjective differences in the assessment results.

6. Conclusion

This study performed a comprehensive bibliometric and theme analysis of GBE between 1985 and 2022. Our findings suggest that China and the USA occupy a leading position in the number of publications or the academic level. Of all the authors and co-cited authors, Drieu.K, Christen Yves, and Gurley.BJ contributed the most in the number of publications, citations, and TLS. Researchers in the future should improve international collaboration. Most of the GBE-related articles were published or cited in globally renowned journals, which suggests that it has attracted much interest. Currently, the research on GBE primarily focuses on dementia, RCT, glaucoma and neuroprotective mechanism, which may also be the focus of future research.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data availability statement

The data used to support the findings of this study were supplied by the Web of Science Core Collection under license and so cannot be made freely available. Requests for access to these data should be made to the Web of Science, Email at Contract.Admin@clarivate.com.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21214.

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