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Advances in green extraction methods, biological properties, and applications of betanin and vitexin: An updated review and bibliometric analysis

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ABSTRACT

This systematic review and bibliometric analysis investigated the research gaps, trends, and updates in the recovery and applications of betanin and vitexin, focusing on describing the sustainable extraction methods and biological properties. The bibliometric analysis revealed considerable growth in publications in the last two years. The keywords network analysis demonstrated that antioxidant activity, betalain, betanin, and betacyanin are the main research clusters, highlighting that the recovery of vitexin from by-products is a potential theme for investigation. The demand for betanin and vitexin has been increasing in the last years, mainly due to the beneficial biological properties (anti-inflammatory, antioxidant, antimicrobial, and anticancer activity) and pharmaceutical applications for replacing synthetic drugs in the development of nutraceutical food products. Hence, the application of ultrasound-assisted extraction, pulsed electric field extraction, pressurized liquid extraction, and subcritical water extraction are the sustainable extraction methods most suitable for the recovery of betanin and vitexin, which support the application in the food, pharmaceutical, and health industries.

1. Introduction

Bioactive compounds are phytochemicals naturally produced by plants and algae with biological properties. Bioactive compounds generally have positive benefits for human health. Unlike macro- and micronutrients considered fundamental (carbohydrates, minerals, proteins, fats, and vitamins), phytochemicals are not crucial for the functioning of life and the human body (Vettorazzi et al., 2020). Bioactive compounds are classified into the three most relevant types: (i) terpenes and terpenoids with approximately 25,000 compounds; (ii) phenolic compounds with approximately 8000 compounds; and (iii) alkaloids with approximately 12,000 compounds. Fig. 1 presents the chemical structure of these main types of bioactive compounds. In the secondary metabolism of plants, the synthesis of bioactive compounds has four routes: (i) the malonic acid pathway; (ii) the mevalonic acid pathway; (iii) the shikimic acid pathway; and (iv) the non-mevalonate pathway. The main groups of bioactive compounds present in foods are phytosterols (i.e., stigmasterol in soy), terpenoids (i.e., limonene in citrus fruits), polyphenols (i.e., chlorogenic acids found in raspberries), glucosino-

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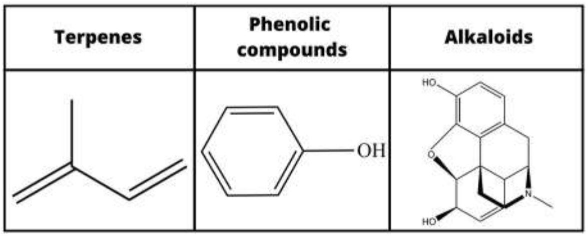

Fig. 1. Chemical structure of the main types of bioactive compounds.

lates (i.e., sulforaphane in broccoli), alkaloids (i.e., caffeine in coffee beans), capsaicinoids (i.e., capsaicin found in peppers), and carotenoids (i.e., β-carotene found in carrots) (Azmir et al., 2013; Essien et al., 2020).

Notwithstanding, the industrial processing of fruits is increasing with population growth, consequently increasing the generation of by-products (Fierascu et al., 2021; Saha et al., 2018). However, the agri-food by-products contain a high amount of bioactive compounds in their composition, being a valuable feedstock for producing and isolating phytomedicines (Martins and Ferreira, 2017; Vilas-Boas et al., 2021).

Betalains are associated with antioxidant, anti-inflammatory, and chemopreventive features in vitro and *in vivo* (de Oliveira et al., 2021). Betalains are compounds with water-soluble characteristics derived from ammonium and betalamic acid and are found in several plants of the Caryophyllales family. Betalains are separated into yellow betaxanthin pigments and red–violet betacyanin pigments. Betacyanin pigments, mostly found in beetroots, are divided into betanin, amaranine, ganfrenine, and 2-descarboxy-betanin (Fig. 2). Approximately 85% of betacyanins are composed of betanin (betanidin-5-*O*-glucoside), the most substantial pigment of red beets (Chandran et al., 2014).

The European Union and the Food and Drug Administration validated betanin as a red dye for food that is identified in greater amounts on the surface, i.e., on the skin, than inside the beet (Slatnar et al., 2015). Since skins are discarded during beet processing, the interest in obtaining betanin from this source increases due to the costs and waste generation reduction. For instance, during beetroot processing about 300–600 mg betanin/kg can be recovered (Schieber, 2019). The characteristics of betanin can be altered by different conditions, such as light, temperature, high water activity, and pH variations (below 3 and above 7). This pH range shows that betanin can be used as a pH-sensitive pigment. When combined with oxygen, betanin showed more stability when the pH was between 5.5 and 5.8 without oxygen. Because these characteristics significantly influence the stability of betanin, it is recommended to keep it as an extract (Cejudo-Bastante et al., 2019). Betanin is increasingly used in food as a coloring and additive in cake mixes, beverages, fruit yogurt, ice cream, sauces, jellies, dairy products, soups, chewing gum, and ready-to-eat icings, and is also used in pharmaceuticals and cosmetics (Esatbeyoglu et al., 2015; Ravichandran et al., 2013).

Vitexin is a flavonoid glycoside derived from apigenin, identified mainly in beet leaves and stalks, which makes its application of great importance for the reduction of by-products produced by the food industry (Lorizola et al., 2018; Vissers et al., 2017) (Fig. 2). Vitexin has several pharmacological and biological properties, such as antioxidant, antithyroid, antitumor, antimicrobial, antibacter-

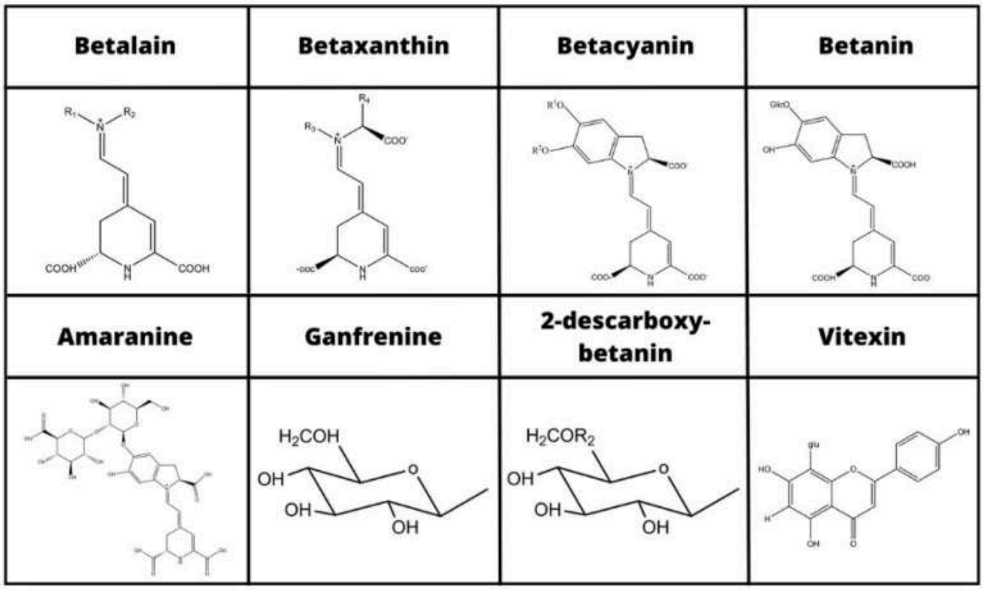

Fig. 2. The chemical structure of the compounds: betalain, betaxanthin, betacyanin, betanin, amaranine, ganfrenine, 2-descarboxy-betanin, and vitexin.

ial, radioprotective, hypotensive, anti-arteriosclerotic, antispasmodic, antihypertensive, antiglycation, antiviral, antihepatotoxic and anti-inflammatory (Borghi et al., 2013; Lee et al., 2012; Lindsay and Cooksey, 2014). Among the anti-inflammatory effects attributed to vitexin, it is responsible for increasing the reaction of low-density lipoprotein (LDL) against oxidation and inhibiting α-glucosidase (Ninfali and Angelino, 2013; Sharma et al., 2012).

Notwithstanding, bibliometric analysis is based on recognizing publications in the general scope, covering a specific area, where statistical methods can be employed as part of the analysis working set. Initially, bibliometric analysis includes primarily bibliographic syntheses of highly mentioned scientific works. Bibliometric tools have been used to provide quantitative diagnoses of literature production. These analyses are presented as one of the most used techniques to consider the reliability and the effect of academic work. One of the quantities used to carry out bibliometrics is the mention of periodicity, which associates the number of mentions of a particular article by researchers, in which the one most mentioned is undoubtedly the most relevant. Although bibliometric analysis is not a perfect technique, it is an important method to guide the allocation of resources by funding agencies and encompasses numerous classes of archives, such as books, theses, and journal articles (Akmal et al., 2020; Ellegaard and Wallin, 2015).

Recent studies show bibliometrics as an essential tool in accessing information from a great number of sources, such as in the case of the application of nanomaterials to produce biogas from natural waste. A bibliometric analysis of the last 50 years concluded that nanomaterials had transformed the branch of anaerobic digestion, methane, and waste production (Khan et al., 2022). In surveys such as the development of elicitation techniques to enrich edible plant shoots with bioactive compounds, bibliometric was designed to facilitate the understanding of scientific production and research directions (Toro et al., 2021). The results presented a considerable evolution in studies on this topic. Other work-related aims are to consider the most relevant opportunities and challenges of products derived from microalgae, in this case, astaxanthin, a carotenoid bioactive compound and trends of investigations concerning astaxanthin (Villaro et al., 2021).

In this context, this systematic review advanced the knowledge in green extraction methods, biological properties, and applications of betanin and vitexin. For this, a systematic search and bibliometric analysis elucidated the research trends, publication evolution, and bibliometric network of keywords, authors, institutions, and countries.

2. Overview of bioactive compounds: biological activity and health

Bioactive compounds from fungi, plants, or vegetables have been used for many years as drugs, most of which have become pharmaceuticals (Vettorazzi et al., 2020). Currently, bioactive compounds of natural origin (plants, fruits, and vegetables) have been gaining attention due to their strong biological properties, such as anti-inflammatory, antimicrobial, and antioxidant capacity, which are responsible for helping to protect against human diseases (Dias et al., 2015; dos Reis et al., 2015; Kammerer et al., 2014; Karim, 2013; Martins and Ferreira, 2017; Petrovska, 2012; Verma and Srivastav, 2020). It is worth mentioning that, in addition to these bioactive ingredients being able to provide therapeutic benefits, they are also capable of incorporating value and improving nutritional functionalities of various foods, gaining a role of great relevance in the cosmetics, pharmaceuticals, food, and biotechnology industries (dos Reis et al., 2015; Gammone et al., 2015; Martins and Ferreira, 2017; Nasri et al., 2014; Rodriguez-Amaya, 2016).

The demand for bioactive compounds for different applications is growing increasingly, stimulated mainly by studies that are in progress and have the purpose of defining the applicability to improve health (Vilas-Boas et al., 2021). The use and application of natural bioactive compounds have great potential to promote the replacement of synthetic medicines. Some studies have proven that medicinal plants are a source of bioactive compounds that can act as a substitute for synthetic drugs in traditional treatments of diseases such as hepatitis, acquired immunodeficiency syndrome, and cancer (Ahmed and Wang, 2021; Fierascu et al., 2020; Guaadaoui et al., 2014; Mukherjee et al., 2013; Siddiqui et al., 2017). Natural bioactive compounds have high anticancer potential, and research indicates that more than 50% of anticancer drugs come from natural components or derivatives. Studies reported that bioactive compounds (phenols, terpenoids, alkaloids, flavonoids) from marine sources have anticancer characteristics against several types of cancer (Gomes et al., 2016; Patra et al., 2022, 2020).

3. Methodology for the systematic literature search and bibliometric analysis

The literature search used scientific output data from the core collection of Science Citation Index Expanded (SCI-E) – Clarivate Analytics' ISI – Web of Science© (Fig. 3). The following logic operation was used for the search: ("Vitexin" OR "Apigenin 8-C-glucoside" OR "Betanin" OR "phytolaccanin") AND ("waste" OR "by-products" OR "by-product" OR "residue" OR "wastes" OR "by-products" OR "by-product" OR "residue"). This search was conducted to select specific, accurate, and reliable information based on title, abstract, and author's keywords of each document published in the database. There was a selection in the document class for the search, filtering for "article" and "review". A survey was carried out between 2010 and 2022 to observe the expansion of publications in recent years and the more constant branches of study. During the time span, 63 publications were obtained (61 articles and 2 reviews). Bibliometric analysis software allows the data collected from the selected documents to be examined. The three-field graph of the most relevant authors on the timing diagram was performed on the R language package (Bibliometrix). The analysis of the sources, the most cited authors, the keyword clusters of these authors, and the country networks, the data obtained were analyzed in VOSviewer© software. All the data used in the bibliometric analysis were obtained based on the 63 publications. An investigation of the most mentioned documents (articles and reviews) was carried out to understand the relevance and impact of betanin and vitexin from different perspectives.

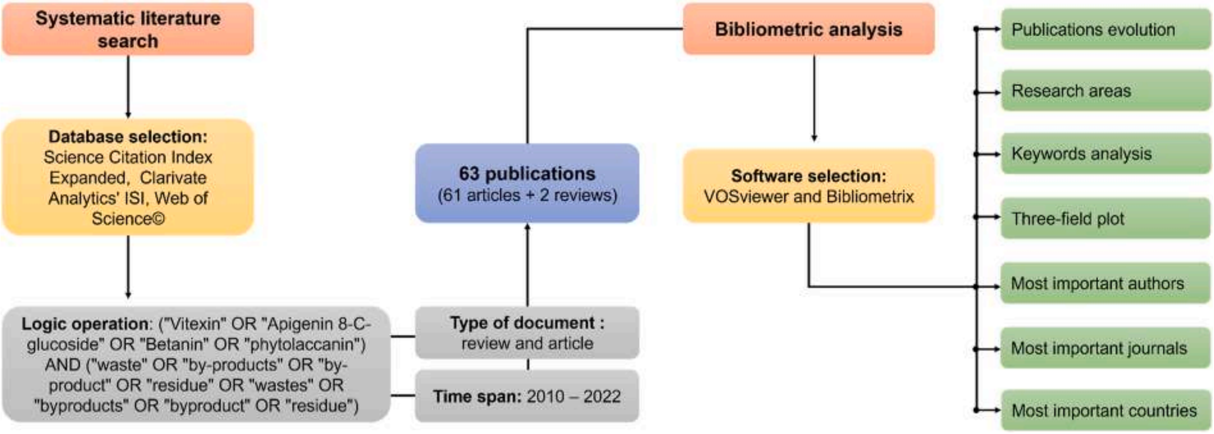

Fig. 3. Flowchart describing the main steps for the systematic literature search and bibliometric analysis.

4. Research trends on betanin and vitexin

4.1. Publication evolution and research areas

Fig. 4 shows the evolution of research involving betanin and vitexin. The research showed that between 2005 and 2022, 63 documents were published (61 articles and 2 reviews). In the first 4 years, publications remained scarce, reaching their highest value in the last year, less than 5. In 2016, there was a significant increase in published articles, presenting their highest value until then. Between 2017 and 2021, the number of publications increased, reaching its peak in 2021 with 13 publications, the highest balance of annual publications in the period evaluated. This increase in publications demonstrates the growing interest in the subject. There is a growing interest in the recovery of bioactive compounds from agri-food by-products, where the interest is expected to continue to increase over the years. The ranking of the ten main areas is presented in Table 1. Among the five main areas of research, *Food Science Technology* is in the first place, responsible for 57.14% of the documents found in the research. The following area was *Chemistry* (28.57%), *Biochemistry Molecular Biology* (20.65%), *Pharmacology Pharmacy* (12.69%), and *Agriculture* (9.52%).

4.2. Bibliometric analysis of keywords

Table 2 shows, through colored circles, the most used keywords. The size of the circles indicates the ones most used by the authors. The relationship between the most used keywords can be seen in Fig. 5a. The circumference area related to the term is directly proportional to the number of occurrences, and the link between the words represents the interaction between the keywords. Terms such as antioxidant activity, betalains, betanin, and betacyanins present the circles with the most significant areas. These keywords have several connections, demonstrating that they are widely used in studies related to the researched topic. The different colors represent groupings with words used together with a particular frequency. Table 3 shows the clusters of the main keywords obtained on VOSviewer software. The main keyword found was antioxidant activity, which is present in cluster 2 (green) and has interactions with clusters 1 (red), 3 (blue), 4 (yellow), and 5 (purple). Initially, the main keywords used were color, stability, biosynthesis, and

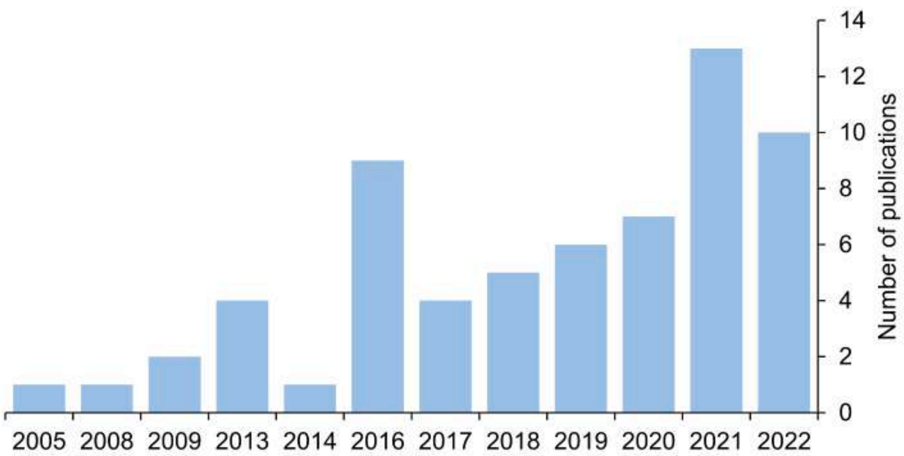

Fig. 4. Evolution of the number of publications related to the research field of betalain and vitexin (2005–2022).

Table 1
Ranking of the top 10 publication areas, affiliations, countries, and journals based on the number of publications related to the systematic search.

Ranking	Research areas	Number	%[a]
1st	Food Science Technology	36	57.14%
2nd	Chemistry	18	28.57%
3rd	Biochemistry Molecular Biology	13	20.63%
4th	Pharmacology Pharmacy	8	12.69%
5th	Agriculture	6	9.52%
6th	Engineering	6	9.52%
7th	Nutrition Dietetics	5	7.93%
8th	Biotechnology Applied Microbiology	4	6.34%
9th	Environmental Sciences Ecology	4	6.34%
10th	Science Technology Other Topics	3	4.76%
Ranking	Affiliations	Number	%[a]
1st	Polytechnic Institute of Bragança	4	6.34%
2nd	University of Auckland	4	6.34%
3rd	University of Novi Sad	4	6.34%
4th	Universiti Putra Malaysia	3	4.76%
5th	Complutense University of Madrid	2	3.17%
6th	Spanish National Research Council	2	3.17%
7th	Council of Scientific Industrial Research	2	3.17%
8th	Central Food Technological Research Institute	2	3.17%
9th	National Agricultural Technology Institute	2	3.17%
10th	Miguel Lillo Foundation	2	3.17%
Ranking	Countries	Number	%[a]
1st	Spain	11	17.46%
2nd	China	10	15.87%
3rd	Brazil	6	9.52%
4th	Italy	6	9.52%
5th	Serbia	6	9.52%
6th	Mexico	5	7.93%
7th	India	4	6.34%
8th	Malaysia	4	6.34%
9th	New Zealand	4	6.34%
10th	Portugal	4	6.34%
Ranking	Journals	Number	%[a]
1st	Molecules	6	9.52%
2nd	Food Chemistry	5	7.93%
3rd	Antioxidants	3	4.76%
4th	Journal of Food Science and Technology Mysore	3	4.76%
5th	Agronomy	2	3.17%
6th	Food Function	2	3.17%
7th	Foods	2	3.17%
8th	LWT Food Science and Technology	2	3.17%
9th	Science of The Total Environment	2	3.17%
10th	Biocatalysis and Agricultural Biotechnology		1.587%
Ranking	Authors	Number	%[a]
1st	Barros L	4	6.34%
2nd	Dias MI	3	4.76%
3rd	Ferreira ICFR	3	4.76%
4th	Lee SY	3	4.76%
5th	Shaari K	3	4.76%
6th	Zain MSC	3	4.76%
7th	Alberto MR	2	3.17%
8th	Alves MJ	2	3.17%
9th	Calhelha RC	2	3.17%
10th	Canadanovic-brunet J	2	3.17%

[a] Percentage of 63 documents (automatically calculated in WoS). The search was conducted on the 6th of October 2022.

pigments, thus demonstrating that research was more focused on the characteristics of the components. The main keywords reveal interest in bioactive capacity, extraction, and purification (Fig. 5b). Fig. 6 highlights the relationship between the most frequent keywords and prominent authors. New terms are found, such as Naviglio extractor and response surface methodology, which are directly related to the study of the extraction of these compounds.

Over the years, the topics and areas researched have changed; some areas have become outdated, while others have gained more focus. With this variation of themes and interests, the keywords also vary. The thematic map classifies the clusters according to their importance in the research area, showing density and centrality in their axes (Fig. 7). The map is divided into quadrants. The first quadrant is the purple cluster with the keyword's anthocyanin, bioactive compounds, and curcumin, which are classified as Niche

Table 2
The top 20 keywords based on publications between 2010 and 2022 (rank based on the occurrences).

Ranking	Keyword	Occurrences	Total link strength
1	Antioxidant activity	17	57
2	Betalains	16	63
3	Betanin	13	33
4	Betacyanins	12	57
5	Polyphenols	10	43
6	By-products	10	41
7	Antioxidant	10	34
8	Extraction	8	38
9	Optimization	8	32
10	Bioactive compounds	7	37
11	Phenolic compounds	7	36
12	Fruits	7	27
13	Acid	7	18
14	Food	6	23
15	Capacity	5	27
16	Phenolic compounds	5	22
17	Stability	5	21
18	Antioxidant properties	5	20
19	Identification	5	19
20	Quantification	5	19

Themes. These keywords present elevated density and few centralities; they are well-developed in their field of study but present few relations with other topics. The keywords isovitexin, mung bean, and vitexin are considered motor themes. This set of keywords present high centrality and density, which are well-developed current themes that influence and interact with other thematic areas. The clusters in the emerging or declining theme quadrant present terms that are in evidence and may become important or are declining or outdated themes. Finally, there is the last quadrant, which presents terms with low development and high centrality. These terms are classified as basic themes, with significant but not yet well-developed and will be the focus of future research.

4.3. Most cited publications

The bibliometric included classifying the most mentioned papers in the field over the last 12 years. Table 4 presents the most cited articles on vitexin, betanin, and by-product research. The most cited article (87 citations) was *"Phytochemical and therapeutic potential of cucumber"* published by (Mukherjee et al., 2013) in *Fitoterapia Journal*. This article reviews the therapeutic application, the pharmacological and phytochemical profile of different parts of *Cucumis sativus* L. which shows that plant leaves are sources of some of the main phytoconstituents, such as vitexin-6-(4-hydroxy-1-ethylbenzene) and isovitexin-8-(4-hydroxy-1-ethylbenzene). The second most cited article was *"Recovery of colorants from red prickly pear peels and pulps enhanced by pulsed electric field and ultrasound"* (74 citations), published in 2016 at *Innovative Food Science & Emerging Technologies* (Koubaa et al., 2016). This study aimed to determine the potential of unconventional pretreatments, such as pulsed electric fields (PEFs) and ultrasound (USNs), to improve the extraction of red dyes from prickly pear (*Opuntia stricta* Haw.) peels and pulps. Opuntia fruit processing by-products have many potential food additives, such as betanin and isobetanin, which could be an alternative to replace synthetic colorants.

The third most cited article (60 citations) was *"Antiradical, antimicrobial and cytotoxic activities of commercial beetroot pomace"*, published in 2013 in *Food & Function* by Vulic et al. (2013). The study evaluated the phytochemical profile and the antiradical, antimicrobial, and cytotoxic activities of industrial beet pomace extract and concluded that beet by-products are a good source of bioactive compounds. Other research carried out by Tran et al. (2017) (59 citations), Tumbas Šaponjac et al. (2016) (38 citations), and Hidalgo et al. (2018) (29 citations) presents beetroot as a good source of bioactive compounds. This last article shows a direct application since adding beetroot pomace to water biscuits had a positive effect on betanin, isobetanin, total phenols, and antioxidant capacity. Moreover, other authors explore other by-products in their research to produce bioactive compounds, as Melgar et al. (2017) (55 citations). Through the chemical characterization of the by-products (*Opuntia ficus-indica* and *Opuntia engelmanni* peels), it was possible to identify the phenolic and betalain profiles and show the advantages of the by-products as a new source of functional ingredients. Vigano et al. (2016) (44 citations) identified and quantified five phenolic compounds in passion fruit peel extracts, isoorientin, vicenin, vitexin, orientin, and isovitexin, with pressurized liquid extraction (PLE) with ethanol:water, being the most efficient extraction method. On the other hand, Liew et al. (2018) (37 citations) evaluated the antioxidant activity, total phenolic content, and flavonoids of the peels of *Camelia sinensis*, finding high antioxidant activities, total phenolic content, and flavonoids in this raw material. Finally, Cattaneo et al. (2016) (30 citations) identified constituents such as C-glycosyl flavones, including schaftoside, isoschaftoside, vicenin II, vitexin and isovitexin, in polyphenolic extracts. Based on the above, it is possible to establish that there are a wide variety of opportunities for by-products since they have many bioactive compounds that may be of interest to the agri-food industry.

4.4. Study of authors, journals, institutions, and countries

The bibliometric analysis of vitexin, betanin, and by-product research presented the study of authors, journals, institutions, and countries. Table 1 shows the ranking of the 10 top publication areas, affiliations, countries, and journals based on the number of pub-

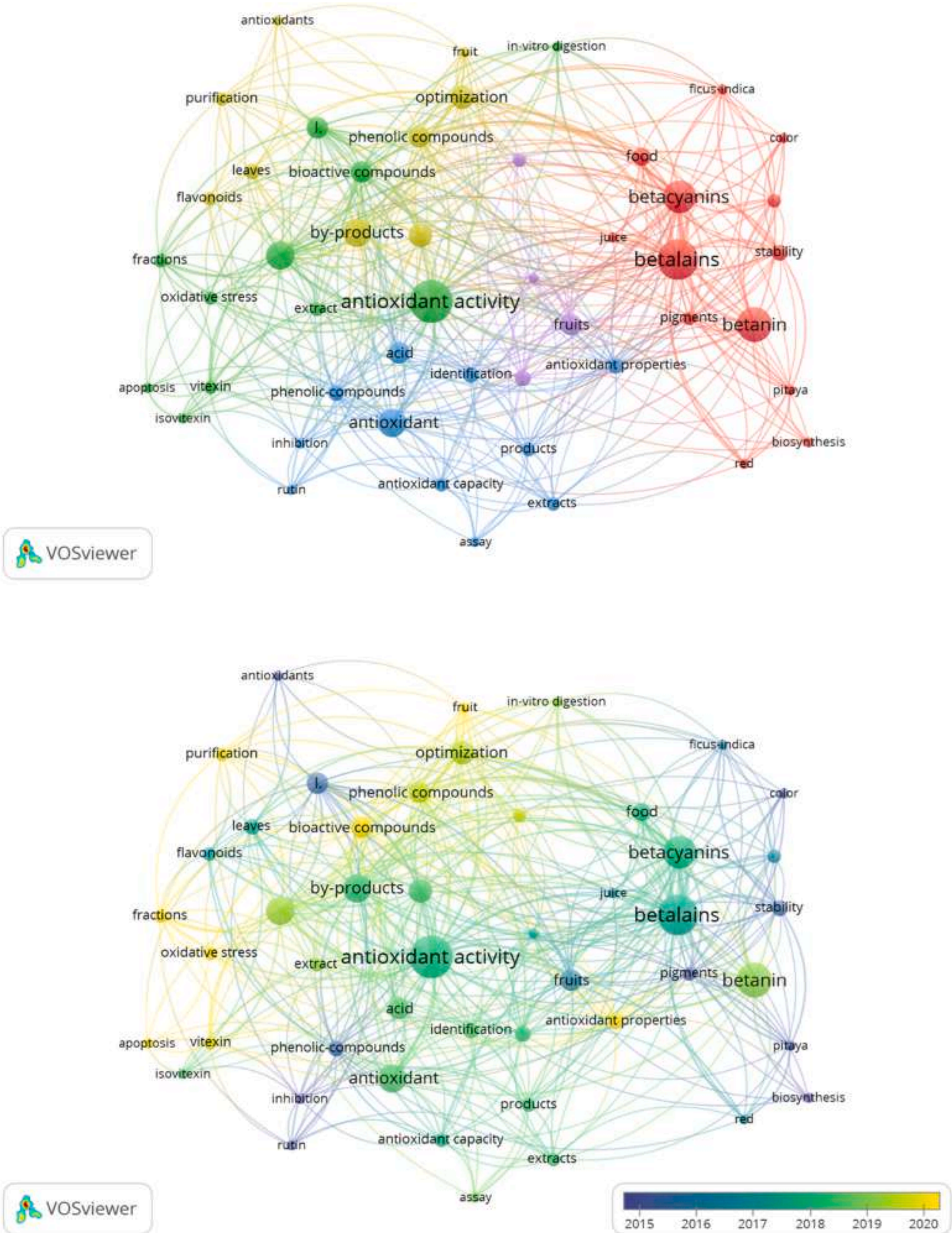

Fig. 5. Clustering of the most frequent keywords based on the publications between the years 2010–2022: term map based on different clusters and term average year map.

lications. Fig. 8 shows the three-field graph of the most relevant authors, keywords, and sources. The main research area was *Food Science Technology*, which was the most relevant area, with 36 publications, followed by *Chemistry* (18 publications), *Biochemistry Molecular Biology* (13 publications), and *Pharmacology Pharmacy* (8 publications). The leading country in these research topics is Spain (11 publications), China (10 publications), Brazil, Italy, and Serbia (6 publications each). According to the number of publications from the leading countries in the area, it is possible to establish that research is being carried out in parallel throughout the world, which allows the extraction of betaine and vitexin from agri-food by-products. The most productive institutions were the Polytechnic Institute of Bragança (Portugal), University of Auckland (New Zealand), and University of Novi Sad (Serbia) (4 publications each), followed by the Universiti Putra Malaysia (3 publications), Complutense University of Madrid (2 publications), and Spanish National Research Council (2 publications). The most relevant journals were *Molecules* (9.52%), *Food Chemistry* (7.93%), *Antioxidants* (4.76%), and *Journal of Food Science and Technology Mysore* (4.76%).

Table 3
Clusters of the main keywords obtained on VOSviewer software.

Cluster	Keywords on VOSviewer Network
1	Betacyanins, betalains, betanin, biosynthesis, color, ficus indica, food, food colorants, juice, pigments, pitaya, red, stability.
2	Antioxidant activity, apoptosis, bioactive compounds, extract, fractions, in vitro digestion, isovitexin, oxidative stress, polyphenols, vitexin.
3	Acid, antioxidant, antioxidant capacity, antioxidant properties, assays, extracts, identification, inhibition, products, rutin.
4	Antioxidants, by-products, extraction, flavonoids, fruit, leaves, optimization, phenolic compounds, purification.
5	Capacity, fruits, plants, ultrasound-assisted extraction
6	Phenolic compounds, antioxidant capacity, by-products, polyphenols, antioxidant, beetroot, cactus, extraction, flavonoids.
7	Betanin, betlains, antioxidant, betacyanins, food colorants, color, pitaya.
8	Antioxidant activity, buckwheat hull, flavonoid, oil palm leaves.
9	Antocyanin, bioactive compounds, curcumin, natural colorants.
10	Isovitexin, mung bean, vitexin.

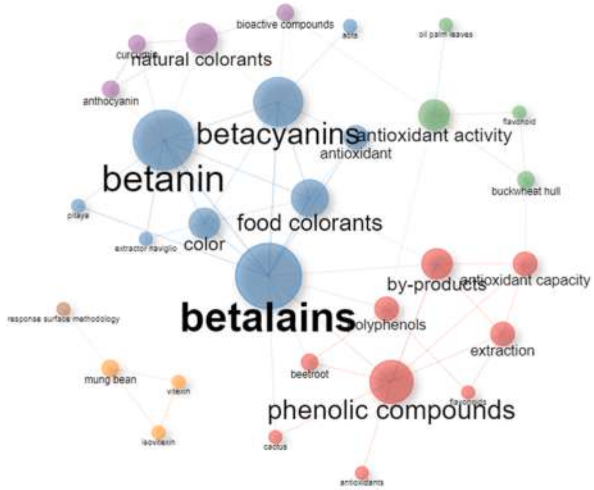

Fig. 6. Network analysis and thematic map of the clusters from the most frequent authors' keywords based on the publications between the years 2010–2022.

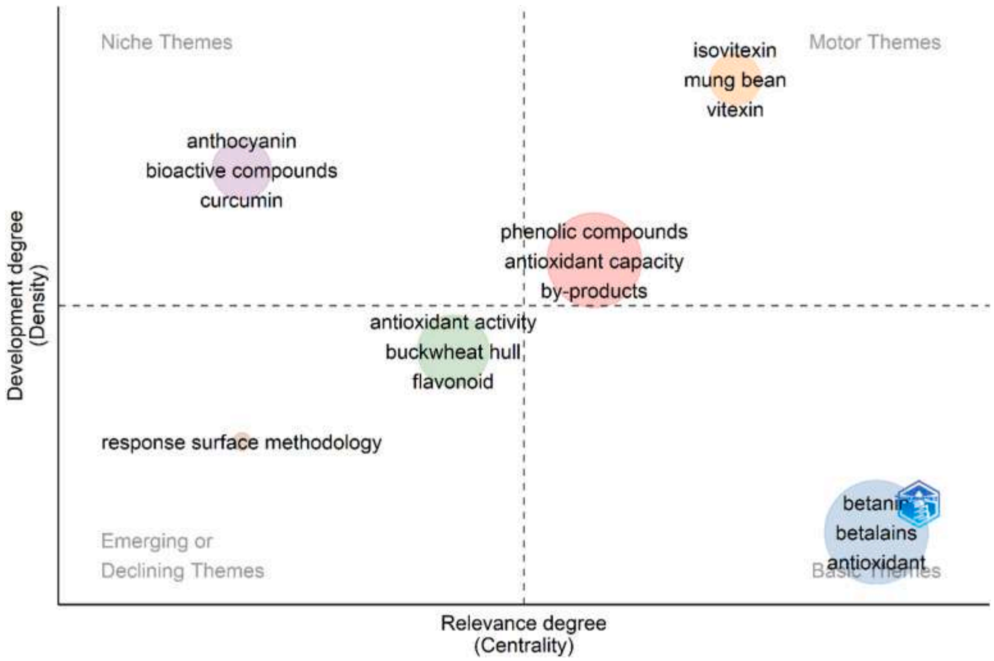

Fig. 7. Thematic map of the clusters from the most frequent authors' keywords based on the publications between the years 2010–2022.

Table 4
Top 10 most cited documents based on publications between 2010 and 2022.

Ranking	Title	Journal	Publication year	Total Citations	Reference
1st	Phytochemical and therapeutic potential of cucumber	Fitoterapia	2013	87	Mukherjee et al. (2013)
2nd	Recovery of colorants from red prickly pear peels and pulps enhanced by pulsed electric field and ultrasound	Innovative Food Science & Emerging Technologies	2016	74	Koubaa et al. (2016)
3rd	Antiradical, antimicrobial and cytotoxic activities of commercial beetroot pomace	Food & Function	2013	60	Vulic et al. (2013)
4th	Starch-based bio-elastomers functionalized with red beetroot natural antioxidant	Food Chemistry	2017	59	Tran et al. (2017)
5th	By-products recovery of *Opuntia* spp. peels: Betalainic and phenolic profiles and bioactive properties	Industrial Crops and Products	2017	55	Melgar et al. (2017)
6th	Pressurized liquids extraction as an alternative process to readily obtain bioactive compounds from passion fruit rinds	Food and Bioproducts Processing	2016	44	Vigano et al. (2016)
7th	Encapsulation of Beetroot Pomace Extract: RSM Optimization, Storage and Gastrointestinal Stability	Molecules	2016	38	Tumbas Šaponjac et al. (2016)
8th	Phytochemical composition and in vitro antioxidant activities of *Citrus sinensis* peel extracts	PeerJ	2018	37	Liew et al. (2018)
9th	Flour from *Prosopis alba* cotyledons: a natural source of nutrient and bioactive phytochemicals	Food Chemistry	2016	30	Cattaneo et al. (2016)
10th	Microencapsulates and extracts from red beetroot pomace modify antioxidant capacity, heat damage and colour of pseudocereals-enriched einkorn water biscuits	Food Chemistry	2018	29	Hidalgo et al. (2018)

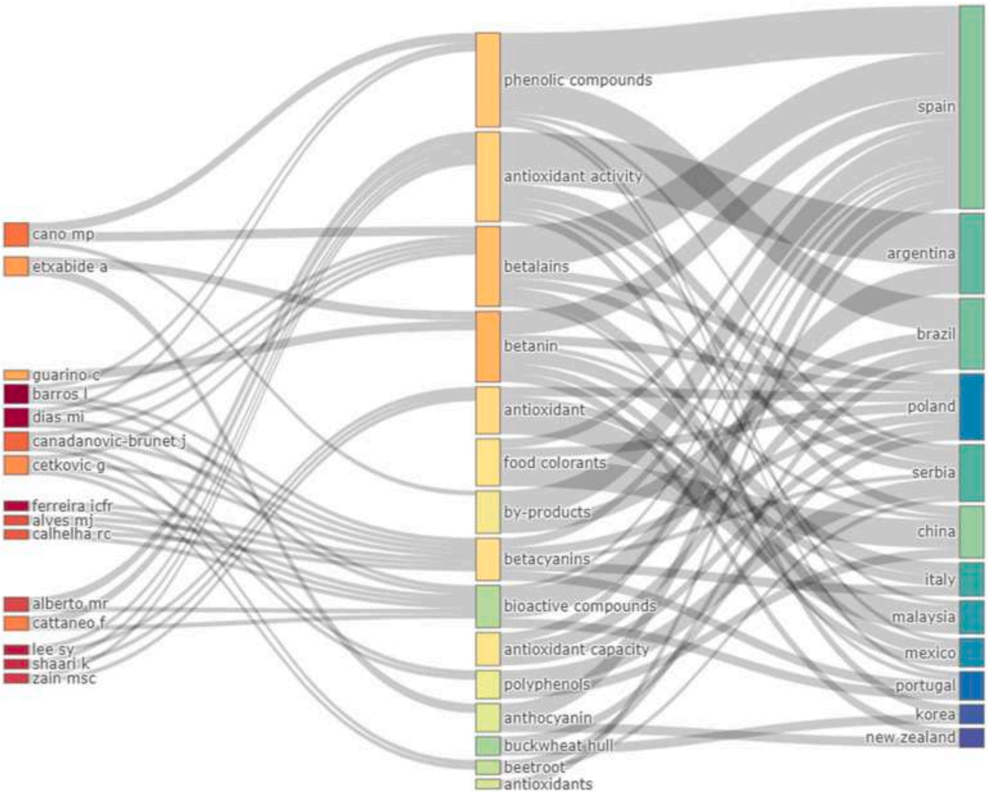

Fig. 8. The three-field plot correlates the most expressive authors, keywords, and sources based on the publications between the years 2010–2022.

Finally, the most cited authors in the area are Barros L (4 publications), Dias MI, Ferreira ICFR, Lee SY, Shaari K, and Zain MSC (3 publications each). The results indicate that several authors are investigating the extraction of vitexin and betanin from agri-food by-products, which makes it possible to obtain different alternatives for extracting these compounds.

5. Biological applications of betanin and vitexin

Research has shown that betanin can inhibit membrane lipid peroxidation and LDL oxidation. In addition, it prevented H_2O_2 (hydrogen peroxide) and ONOO (peroxynitrite), through RSA (radical scavenging activity), from causing any anomaly in DNA. Betanin compounds may inhibit enzymes such as lipoxygenase. Betanin can also inhibit ICAM-1 (cell adhesion molecule), which can mediate inflammation. (Esatbeyoglu et al., 2014; Sakihama et al., 2012).

Betanin also has an antihepatotoxic property by stimulating the enzyme quinone reductase II. In tests applied to rats, it attenuated the toxicity caused by carbon tetrachloride, for example. Among the properties of betanin, the antioxidant capacity proved significant. It can prevent nitrosative stress by inhibiting IC_{50} (Sakihama et al., 2012). Still, regarding antioxidant activity, betanin can inhibit free radicals (ROS and RNS) produced due to contact with radiation, leading to mutation and even lethality. Studies have shown that betanin can reduce generators of cardiac fibrosis, which is associated with hyperglycemia. This aspect is because betanin can reduce the number of collagen crosslinks by increasing soluble collagen and decreasing Maillard reaction products (Han et al., 2015; Khan, 2016).

The research described below using betanin as a treatment in animal model revealed considerable anticancer potential (Khan, 2016). Betanin applied at a dose of 2.5 mg/100 mL of water is responsible for inhibiting tumors, such as skin tumors induced by 7,12-dimethylbenz(*a*)anthracene (DMBA) and developed by UV-B light. Furthermore, betanin decreased the occurrence of a type of two-stage hepatocarcinogenesis stimulated by *N*-nitrosodiethylamine (NDEA) and developed by phenobarbital. Studies have shown that the anticancer property is related to a decrease in the amount of endothelial microvessels ($CD31^+$) to prevent angiogenesis ptosis (Zhang et al., 2013).

Betanin has also shown antiproliferative characteristics with several cell genera with IC_{50} values between 142 and 164 μmol/mL. The cytotoxicity (IC_{50} of 40 μmol/L) that betanin exhibited concerning human chronic myeloid leukemia (K562) was developed through cellular events, such as decreases in mitochondrial membrane properties. Betanin is capable of inhibiting TrxR1 (selenoprotein thioredoxin reductase), which leads to an increase in the concentration of reactive oxygen species (ROS) and the elimination of cancer cells, such as lung and breast cancer (Sun et al., 2021; Zhang et al., 2017).

The anti-inflammatory property of vitexin is due to its *anti*-bradykinin, antihistamine, and anti-serotonin activities. Regarding anticancer activity, vitexin can be used as a therapeutic resource against leukemia, acting in the development of the expression of cleaved caspase-3 and cleaved caspase-9, used in leukemia cells (Lee et al., 2012). Studies indicated that vitexin has an antiaging capacity in the skin (Hao et al., 2022). Vitexin is also responsible for reducing liver anomalies caused by a diet rich in lipids and for causing an improvement in metabolic properties. Furthermore, vitexin induced inhibition of adipogenesis in lipid concentration. The hypotensive activity of vitexin is due to its characteristics that obstruct the ganglia, and the anti-inflammatory activity is due to its *anti*-bradykin, antihistamine, and anti-serotonin characteristics (Lorizola et al., 2018).

Regarding the antiviral property, vitexin showed a considerable result in the fight against parainfluenza virus type 3 (leads to respiratory infection), with IC_{50} values of 20.8 g/mL (inhibited concentration at 50%) and 16.0 g/mL of selectivity index. The antithyroid activity of vitexin was evidenced because it can significantly inhibit thyroid peroxidase. Furthermore, vitexin acts on the enzyme iodothyronine deiodinase to inhibit the metabolism of thyroid hormones. Vitexin showed radioprotective properties of great relevance for people with breast cancer who underwent radiotherapy. About 70% of patients who had vitexin in their bodies did not lose weight during the radiotherapy process. In comparison, 73% of those who did not have vitexin in their bodies lost weight from 1 to 2 kg after approximately one month (Lindsay and Cooksey, 2014).

6. Green extraction methods of betanin and vitexin

The bibliometric analysis covered several documents referring to extraction methods, revealing certain trends related to this field of study. Table 5 contains these articles, presenting the extraction method, the solvent used, the compound obtained, and the references. There are two technologies, high-pressure processing and high-temperature treatments, to analyze the stability of betalain from red beet stalk extract (dos Santos et al., 2018). The solid-liquid extraction method is applied (the process exemplified in Fig. 9) using a domestic blender, which contributes to the stability of the red beet pigment. The PLE was applied with ethanol as solvent to beetroot (leaves and stems) to analyze the yield of the process, the total phenolic content, and the antioxidant of the recovered extracts. The study verified that PLE (process exemplified in Fig. 10) contributed considerably to the recovery of compounds present in the residues, where vitexin was one of the most abundant compounds found in the beet residue, showing excellent results (0.65 mg/g of extract) when compared to other methods, Soxhlet, and supercritical fluid, for example (Lasta et al., 2019).

The extraction methods employing ultrasound-assisted, subcritical water extraction (SWE), and subcritical water assisted by ultrasound using water as solvent had a considerable influence on the yield of polyphenols (which is composed of phenolic acids and flavonoids, as is the example of vitexin) from buckwheat, in which, among these methods, the one that obtained the highest yield was SWE (Dzah et al., 2020). Just like the previous work, ultrasound was applied as an extraction method to mung bean shells to obtain extracts that proved to be extremely efficient in protecting against skin aging, such as vitexin, which showed great results (3926.00 μg/g dried mung bean hull) when compared to other phenolic compounds (Hao et al., 2022). However, unlike the previous method, a 60% ethanol solution was used as the solvent. The effect of adding red beet bagasse extracts, pure or microencapsulated, on the antioxidant properties, thermal damage, and color of einkorn biscuits enriched with pseudocereals was analyzed, in which the mi-

Table 5
Description of the main extraction methods based on selected publications between the years 2010–2022 and their respective solvents and main compounds.

Extraction method	Solvent(s)	Main compounds	Reference
Ultrasound	Water	Flavonoids, (flavan-3-ols), flavonols (kaempferol-3-*O*-glycoside), flavones (vitexin) and anthocyanins (cyanidin-3-*O*-rutinoside)	Dzah et al. (2020)
	Ethanol	Protocatechuic acid, isovitexin, vitexin, caffeic acid, 4-coumaric acid, ferulic acid, rutin, and chlorogenic acid	Hao et al. (2022)
	Ethanol	Betanin, isobetanine, total phenolics	Hidalgo et al. (2018)
	Water, methanol, ethanol, 70% aqueous methanol, 70% aqueous ethanol, or DESs	Flavone C-glycosides (vicenin-2, vicenin-3, schaftoside, vitexin and isovitexin)	Jeong et al. (2017)
	Ethanol	Isoorientin, orientin, and vitexin	Li et al. (2013)
	Ethanol	Orientin, vitexin, luteolin 7-*O*-glucoside, apigenin, luteolin, apigenin and luteolin	Ren et al. (2016)
	Ethanol	Vicenin II, isoschaftoside, schaftoside, vitexin and isovitexin	Uriburu et al. (2022)
	Methanol	Orientin/isoorientin and vitexin/isovitexin	Zain et al. (2021b)
	Acetona	Rutin, orientin, homoorientin, vitexin, and isovitexin	Kalinova et al. (2014)
	Water	Betanin and isobetanin	Koubaa et al. (2016)
	Ethanol	Vitexin	Maravic et al. (2022)
	MeOH	Isoorientin, orientin, vitexin and isovitexin	Zain et al. (2021a)
	–	Red beet pigment	Cao et al. (2022)
	Ethyl acetate, ethyl acetate-methanol, absolute methanol, and methanol-water	Catechin, epicatechin, orientin, isoorientin, vitexin, and isovitexin	Zain et al. (2020)
	H20/EtOH	Phyllocactin, isobetanine, isophylocactin, and betanin	Roriz et al. (2022)
Pressurized liquid extraction	Ethanol	Ferulic acid, vitexin, and synapaldehyde	Lasta et al. (2019)
	–	Vitexin e isovitexin	Supasatyankul et al. (2022)
	–	Isoorientin, vicenin, vitexin, orientin, and isovitexin	Vigano et al. (2016)
	Ethanol	Vitexin	Maravic et al. (2022)
Solid liquid extraction	Ethanol	Vitexin	Maravic et al. (2022)
	Ethanol and water	Betanin and isobetanin	Scarano et al. (2020)
	–	Betalain	dos Santos et al. (2018)
Subcritical water	Water	Flavonoids, (flavan-3-ols), flavonols (kaempferol-3-*O*-glycoside), flavones (vitexin) and anthocyanins (cyanidin-3-*O*-rutinoside)	Dzah et al. (2020)
	Ethanol	Vitexin	Maravic et al. (2022)
Microwave	Ethanol	Vitexin	Maravic et al. (2022)
	Water	Betanin	Ciriminna et al. (2019)
Bain marie	Methanol, ethanol, and acetone	Catechin, epigallocatechin, vitexin, rutin, luteolin and apigenin	Liew et al. (2018)
	Ethanol, methanol, water, and acetone	Vitexin, isovitexin, isoorientin, ori entin, rutin, isoquercetin and quercetin	Park et al. (2019)
Ultrasonic-assisted subcritical water	Water	Flavonoids, (flavan-3-ols), flavonols (kaempferol-3-*O*-glycoside), flavones (vitexin) and anthocyanins (cyanidin-3-*O*-rutinoside)	Dzah et al. (2020)
Pulsed electric fields	Water	Betanin and isobetanin	Koubaa et al. (2016)
Soxhlet Extraction	Methanol	Vitexin	Bhardwaj et al. (2022)
Anel de agitação magnética	Ethanol	Malic acids, ascorbic acid, citric acid, betanin, and isobetaine	Garcia-Saavedra et al. (2019)
Juice extractor	Ethanol	Betanin	Aztatzi-Rugerio et al. (2019)
Self-hydrolysis	Ethanol	Phenolic acids (protocatechuic and ferulic acids) and flavonoids (orientin, vitexin, and naringenin)	Rico et al. (2022)
Deep Eutectic Solvent Extraction	Ethanol	Phenolic acids (protocatechuic and ferulic acids) and flavonoids (orientin, vitexin, and naringenin)	Rico et al. (2022)

(*continued on next page*)

Table 5 (*continued*)

Extraction method	Solvent(s)	Main compounds	Reference
Magnetic stirrer	Acetone and methanol	Gallic acid, ferulic acid, sinapic acid, vitexin and isovitexin	Basha and Rao (2017)
Others	Ethanol/water	Camphor, ethyl acetate, citric acid, linoleic acid and lauric acid, α-tocopherol, quercetin-3-*O*-rutinoside, quercetin-*O*-(deoxyhexoside-rutinoside), betanin and isobetanin	Chahdoura et al. (2019)
	Methanol	Vitexina, orientina e isoorientina	Czemplik et al. (2016)
	Ethanol	Octanol, ellagic acid, epicatechin, quercetin, betanin, ascorbic acid, limonene, hexanal, car-3-ene and myrcene	Bulkan et al. (2022)
	Acetone/water	*C*- glicosil flavonas (schaftoside, isoschaftoside, vicenin II, vitexin e isovitexin)	Cattaneo et al. (2016)
	Ethanol, deionized water, and *n*-hexane	Betanin	Lee et al. (2022)
	Ethanol	Vitexin	Lorizola et al. (2021)
	Methanol	Vitexin and isovitexin	Ni et al. (2022)
	Methanol	*ß*-carotene	Silos-Espino et al. (2020)
	Ethanol	*P*-hydroxybenzoic acid, catechin, and vitexin	Sun et al. (2022)
	Deionized water	Phyllocactin and betanin	Thaiudom et al. (2021)
	Methanol	Rutin and vitexin	Zielinska et al. (2013)
	Methanol	Caffeic acid, ferulic acid, rosmarinic acid, vitexin, luteolin-*O*-glucuronide	Zuniga-Lopez et al. (2021)

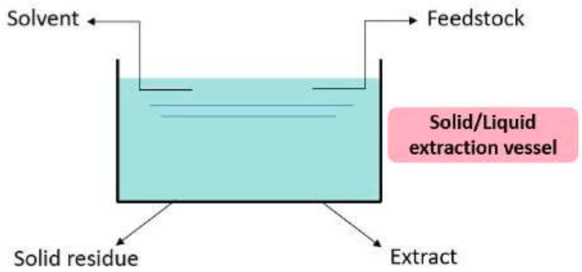

Fig. 9. Example of solid-liquid extraction method. Adapted from da Gabriel da Rosa et al. (2022).

croencapsulated biscuit enriched with water was considered the richest in betanin showing good values (1377 mg/kg). As in previous studies, the extraction method used was ultrasound, differing in that it used 0.5% ethanol as the solvent (Hidalgo et al., 2018). Different solvents were evaluated, such as water, methanol, ethanol, 70% aqueous methanol, 70% aqueous ethanol, and deep eutectic solvents (DES), applied to the ultrasonic bath technique to analyze the presence of flavone C-glycosides. Through the study, it was proved that the use of ultrasound for more extended periods and also the use of solvents with lower water contents generated a greater yield of flavone C-glycosides, such as vitexin, where the solvent that presented the best result was the DES (0.087 mg/g) (Jeong et al., 2017). Extraction methods not commonly used were analyzed, such as pulsed electric fields (PEF) and ultrasound-assisted extraction (UAE) (process exemplified in Fig. 11), to increase the extraction of red dyes (such as betanin) from the peel and pulp of prickly pear (*Opuntia stricta* Haw.). Both evaluated methods used water as a solvent and showed good results compared to traditional methods (Koubaa et al., 2016). Similar to the previous work, the present study aimed to evaluate different types of unconventional extraction methods, solid/liquid extraction, microwave- and ultrasound-assisted extraction, pressurized liquid extraction, and subcritical extraction with water (process exemplified in Fig. 12), to extract polyphenols from sugar beet leaves. Among the polyphenols, vitexin was one of the best results, 627–681 mg/100 g using solid-liquid, microwave, and ultrasound extraction. This study differed from the previous one because all methods used ethanol as a solvent, in which extractions assisted by ultrasound and microwaves showed better results (Maravic et al., 2022). The UAE was evaluated method using 60% ethanol as solvent to obtain flavonoids (such as vitexin) compared to a conventional method, in which the ultrasonic bath obtained considerably higher yields (Li et al., 2013).

The high-speed counter-current chromatography (HSCCC) method was evaluated, and it was proved efficient in separating flavonoids (such as vitexin) from *Spirodela polyrhiza* (aquatic plant), reaching a purity level of more than 90% for all flavonoids analyzed. Ethanol was used as the solvent in an ultrasonic bath (Ren et al., 2016) to extract dry *Spirodela polyrhiza*,. Seeds of *Prosopis alba* (white algarrobo) were obtained through the flour and enriched phenolic extracts, and their characterization was evaluated to use them as non-traditional sources of nutritional ingredients. These enriched extracts were passed through an ultrasonic bath using 70% ethanol as a solvent, in which vitexin was among the most found compounds in this extract (Uriburu et al., 2022). The ultrahigh-

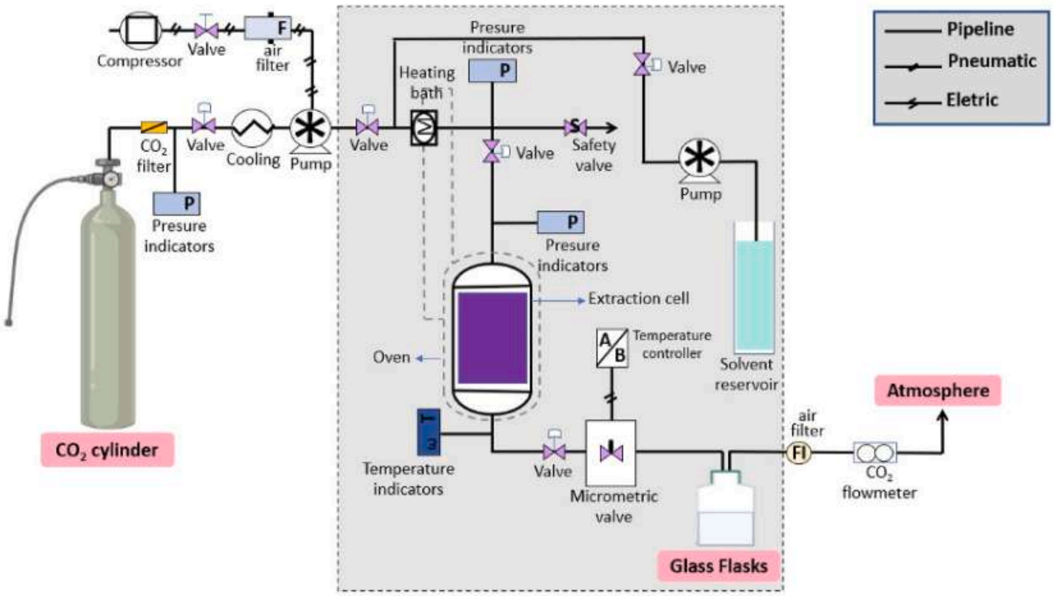

Fig. 10. Example of pressurized liquid extraction. Reproduced from Vigano et al. (Vigano et al., 2016), with modifications.

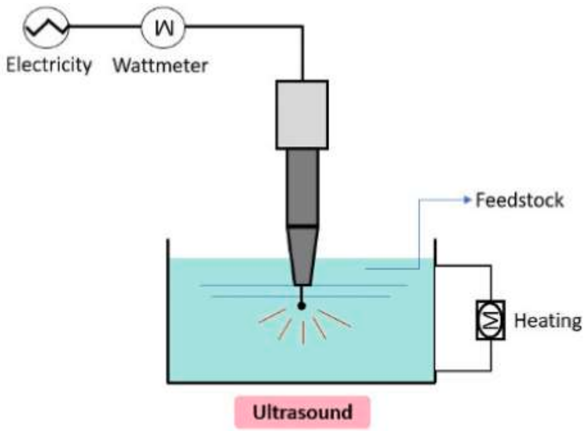

Fig. 11. Example of extraction method using ultrasound. Reproduced from da Rosa et al. (Gabriel da Rosa et al., 2022), with modifications.

performance liquid chromatography with an ultraviolet/photodiode array (UHPLC-UV/PDA) was analyzed to determine luteolin and apigenin derivatives in compounds extracted from oil palm leaves using methanol as a solvent in an ultrasonic bath. Ultrasound showed excellent results (244.35 μg/mL) in the extraction of vitexin, derived from apigenin, when compared with other compounds, such as isovitexin (Zain et al., 2021b).

The potential antioxidant activity of *Camelia sinensis* (sweet orange) peel extracts and their relationship with their phytochemical content was analyzed using methanol, ethanol, and acetone solutions in a water bath as an extraction method. The research concluded that the extraction method contributed to obtaining extracts with a high phytochemical content (phenolics and flavonoids), such as vitexin (Liew et al., 2018). The effect of solvents, ethanol (in different percentages), methanol, water, and acetone employees in a water bath and applied to common buckwheat and tartar hulls was evaluated (Park et al., 2019). The extract obtained through the solvents had a high yield, such as the methanol and 80% ethanol extracts, which had good amounts of flavonoids such as vitexin (12.2 mg/g). Purified melon peel extracts obtained by two nonconventional methods (hydrothermal treatment and alkaline DES extraction) were evaluated. Both methods obtained good results concerning pectin using ethanol from 85% as a solvent. It is also possible to quantify phenolic acids and flavonoids, such as vitexin, which showed better results (6 mg/g) using phenolic fraction recovered with resin water wash liquor after extraction and pectin precipitation adsorption (Rico et al., 2022).

The effect of natural dyes (such as betanin) extracted by the Naviglio method from residues of *Opuntia ficus-indica* (L.) Miller was evaluated (Scarano et al., 2020). This method is considered an ecologically correct and current technique of solid-liquid extraction that uses a solution of ethanol and water as solvents. The study proved that compared to other conventional methods under the same conditions, the Naviglio method obtained better yields concerning the extraction of pigments, such as betanin. The PLE was utilized

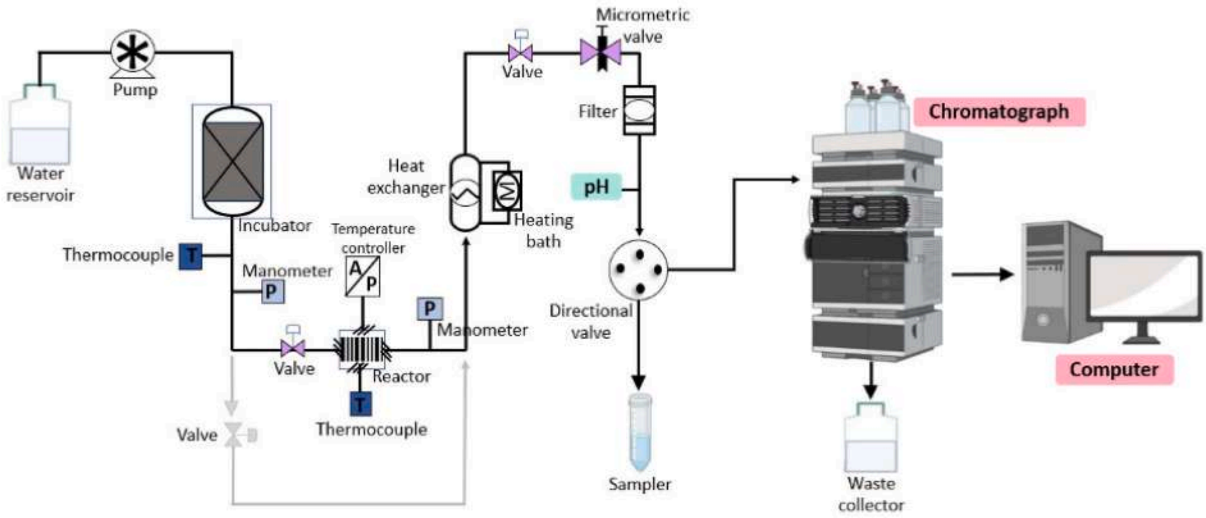

Fig. 12. Example of extraction method using subcritical water.

to evaluate the conditions for extracting phenolic compounds and flavonoids from mung bean seed husks. The extract obtained from PLE was compared with conventional extraction methods used, such as the Soxhlet method, proving to be superior in several aspects, such as the extraction speed and the yield of phenolic compounds and flavonoids, such as vitexin (130.53 mg/g of extract) (Supasatyankul et al., 2022). Similar to a previous study, the PLE was compared with the usual methods of extraction (Soxhlet and maceration) to obtain bioactive compounds, such as vitexin, from passion fruit peel (Vigano et al., 2016). Additionally, a previous study found that PLE obtained the best yields for the extraction of bioactive compounds. The 80% acetone was used as a solvent in ultrasound to extract e-caprolactam from germinated achenes, unlike cases cited previously that used ethanol (Kalinova et al., 2014). According to the previous information, it was possible to verify that most works described used an ultrasonic bath and pressurized liquid extraction as extraction methods. With this, it is possible to observe a growing trend in using ecologically correct extraction methods and green technologies.

7. Conclusion

Bibliometric analysis was applied as a tool for evaluating the advances in the green extraction methods and the biological properties of betanin and vitexin over the last 12 years. The number of publications related to this area has been increasing in recent years, reaching its peak in 2021. This trend demonstrates that the interest in these fields has been increasing, mainly due to the intensified waste use demand and interest in bioactive compounds expansion. The bibliographical analysis showed that vitexin is among the words identified as motor themes. That is, it is considered a current and well-developed theme. Studies related to betanin began in 2005, therefore, conceptualized as basic themes considerably explained. In addition, bibliometrics indicated that one of the most used keywords was betanin in studies associated with inflammation properties and food dyes. Through the studies used to generate the analysis, it was found that most of the warranty processes used as a method were ultrasound, pressurized liquid generation, solid-liquid generation, and subcritical water generation, thus demonstrating a determined tendency to use methods of responsibility that do not harm the environment, that is, clean technologies. Finally, the green extraction of betanin and vitexin from agri-food by-products are promising bioactive compounds for application in the food, pharmaceutical, and health industries, due to the relevant biological properties, such as antioxidant, anti-inflammatory, and anticancer activity.

CRediT authorship contribution statement

Leonardo de Freitas Marinho: Conceptualization; Data curation; Writing – Original draft; review & editing. William Gustavo Sganzerla: Data curation; Writing – Original draft; review & editing. Vanessa Cosme Ferreira: Data curation; Writing. Juver Andrey Jimenez Moreno: Data curation; Writing –. Mauricio Ariel Rostagno: Writing – Review of original draft & editing; Supervision. Tânia Forster-Carneiro: Writing – Review of original draft & editing; Supervision.

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.

Data availability

Data will be made available on request.

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References

Ahmed, T., Wang, C.K., 2021. Black garlic and its bioactive compounds on human health diseases: a review. Molecules 26.
Akmal, M., Hasnain, N., Rehan, A., Iqbal, U., Hashmi, S., Fatima, K., Farooq, M.Z., Khosa, F., Siddiqi, J., Khan, M.K., 2020. Glioblastome multiforme: a bibliometric analysis. World Neurosurg. 136, 270–282.
Azmir, J., Zaidul, I.S.M., Rahman, M.M., Sharif, K.M., Mohamed, A., Sahena, F., Jahurul, M.H.A., Ghafoor, K., Norulaini, N.A.N., Omar, A.K.M., 2013. Techniques for extraction of bioactive compounds from plant materials: a review. J. Food Eng. 117, 426–436.
Aztatzi-Rugerio, L., Granados-Balbuena, S.Y., Zainos-Cuapio, Y., Ocaranza-Sánchez, E., Rojas-López, M., 2019. Analysis of the degradation of betanin obtained from beetroot using Fourier transform infrared spectroscopy. J. Food Sci. Technol. 56, 3677–3686.
Basha, S.A., Rao, U., 2017. Bioactivities of fractions obtained from green gram (Vigna radiata) milled by-products. Food Biosci. 19, 134–141.
Bhardwaj, N., Sharma, P., Guo, L., Dagdag, O., Kumar, V., 2022. Molecular dynamic simulation and Quantum chemical calculation of phytochemicals present in Beta vulgaris and electrochemical behaviour of Beta vulgaris peel extract as green corrosion inhibitor for stainless steel (SS-410) in acidic medium. Colloids Surf., A. 632.
Borghi, S.M., Carvalho, T.T., Staurengo-Ferrari, L., Hohmann, M.S.N., Pinge-Filho, P., Casagrande, R., Verri, W.A., 2013. Vitexin inhibits inflammatory pain in mice by targeting TRPV1, oxidative stress, and cytokines. J. Nat. Prod. 76, 1141–1146.
Bulkan, G., Sitaresmi, S., Yudhanti, G.T., Millati, R., Wikandari, R., Taherzadeh, M.J., 2022. Enhancing or inhibitory effect of fruit or vegetable bioactive compound on Aspergillus Niger and A. oryzae. J. Fungi 8.
Cao, Y.Y., Wang, X.R., Bai, H.J., Jia, P., Zhao, Y.J., Liu, Y.N., Wang, L., Zhuang, Y.T., Yue, T.L., 2022. Fluorescent detection of tetracycline in foods based on carbon dots derived from natural red beet pigment. LWT--Food Sci. Technol. 157.
Cattaneo, F., Costamagna, M.S., Zampini, I.C., Sayago, J., Alberto, M.R., Chamorro, V., Pazos, A., Thomas-Valdes, S., Schmeda-Hirschmann, G., Isla, M.I., 2016. Flour from Prosopis alba cotyledons: a natural source of nutrient and bioactive phytochemicals. Food Chem. 208, 89–96.
Cejudo-Bastante, M.J., Hurtado, N., Muñoz-Burguillos, P., Heredia, F.J., 2019. Stenocereus griseus (Haw) pitaya as source of natural colourant: technological stability of colour and individual betalains. Int. J. Food Sci. Technol. 54, 3024–3031.
Chahdoura, H., Barreira, J.C.M., Barros, L., Dias, M.I., Calhelha, R.C., Flamini, G., Sokovic, M., Achour, L., Ferreira, I., 2019. Bioactivity, hydrophilic, lipophilic and volatile compounds in pulps and skins of Opuntia macrorhiza and Opuntia microdasys fruits. LWT--Food Sci. Technol. 105, 57–65.
Chandran, J., Nisha, P., Singhal, R.S., Pandit, A.B., 2014. Degradation of colour in beetroot (Beta vulgaris L.): a kinetics study. J. Food Sci. Technol. 51, 2678–2684.
Ciriminna, R., Chavarria-Hernandez, N., Rodriguez-Hernandez, A.I., Pagliaro, M., 2019. Toward unfolding the bioeconomy of nopal (Opuntia spp.). Biofuels, Bioprod. Biorefin. 13, 1417–1427.
Czemplik, M., Mierziak, J., Szopa, J., Kulma, A., 2016. Flavonoid C-glucosides derived from flax straw extracts reduce human breast cancer cell growth in vitro and induce apoptosis. Front. Pharmacol. 7.
de Oliveira, S.P.A., do Nascimento, H.M.A., Sampaio, K.B., de Souza, E.L., 2021. A review on bioactive compounds of beet (Beta vulgaris L. subsp. vulgaris) with special emphasis on their beneficial effects on gut microbiota and gastrointestinal health. Crit. Rev. Food Sci. Nutr. 61, 2022–2033.
Dias, M.I., Ferreira, I.C.F.R., Barreiro, M.F., 2015. Microencapsulation of bioactives for food applications. Food Funct. 6, 1035–1052.
dos Reis, L.C.R., de Oliveira, V.R., Hagen, M.E.K., Jablonski, A., FlÔres, S.H., de Oliveira Rios, A., 2015. Carotenoids, flavonoids, chlorophylls, phenolic compounds and antioxidant activity in fresh and cooked broccoli (Brassica oleracea var. Avenger) and cauliflower (Brassica oleracea var. Alphina F1). Lwt 63, 177–183.
dos Santos, C.D., Ismail, M., Cassini, A.S., Marczak, L.D.F., Tessaro, I.C., Farid, M., 2018. Effect of thermal and high pressure processing on stability of betalain extracted from red beet stalks. J. Food Sci. Technol. 55, 568–577.
Dzah, C.S., Duan, Y.Q., Zhang, H.H., Authur, D.A., Ma, H.L., 2020. Ultrasound-, subcritical water- and ultrasound assisted subcritical water-derived Tartary buckwheat polyphenols show superior antioxidant activity and cytotoxicity in human liver carcinoma cells. Food Res. Int. 137.
Ellegaard, O., Wallin, J.A., 2015. The bibliometric analysis of scholarly production: how great is the impact? Scientometrics 105, 1809–1831.
Esatbeyoglu, T., Wagner, A.E., Motafakkerazad, R., Nakajima, Y., Matsugo, S., Rimbach, G., 2014. Free radical scavenging and antioxidant activity of betanin: electron spin resonance spectroscopy studies and studies in cultured cells. Food Chem. Toxicol. 73, 119–126.
Esatbeyoglu, T., Wagner, A.E., Schini-Kerth, V.B., Rimbach, G., 2015. Betanin-A food colorant with biological activity. Mol. Nutr. Food Res. 59, 36–47.
Essien, S.O., Young, B., Baroutian, S., 2020. Recent advances in subcritical water and supercritical carbon dioxide extraction of bioactive compounds from plant materials. Trends Food Sci. Technol. 97, 156–169.
Fierascu, R.C., Fierascu, I., Baroi, A.M., Ortan, A., 2021. Selected aspects related to medicinal and aromatic plants as alternative sources of bioactive compounds. Int. J. Mol. Sci. 22, 1–20.
Fierascu, R.C., Fierascu, I., Ortan, A., Georgiev, M.I., Sieniawska, E., 2020. Innovative approaches for recovery of phytoconstituents from medicinal/aromatic plants and biotechnological production. Molecules 25.
Gabriel da Rosa, R., Sganzerla, W.G., Barroso, T.L.C.T., Buller, L.S., Berni, M.D., Forster-Carneiro, T., 2022. Sustainable production of bioactive compounds from jabuticaba (Myrciaria cauliflora): a bibliometric analysis of scientific research over the last 21 years. Sustain. Chem. Pharm. 27, 1–17.
Gammone, M.A., Riccioni, G., D'Orazio, N., 2015. Carotenoids: potential allies of cardiovascular health? Food Nutr. Res. 59.
Garcia-Saavedra, N.M., Barros, L., Reis, F.S., Roriz, C.L., Alves, M.J., Garcia-Hernandez, M., Perez-Rodriguez, M.L., Sanchez-Mata, M.D., Ramirez-Moreno, E., Ferreira, I., 2019. Chemical characterization and biological activities of two varieties of xoconostle fruits Opuntia joconostle FAC Weber ex Diguet and Opuntia matudae Scheinvar. Food Funct. 10, 3181–3187.
Gomes, N.G.M., Dasari, R., Chandra, S., Kiss, R., Kornienko, A., 2016. Marine invertebrate metabolites with anticancer activities: solutions to the "supply problem.". Mar. Drugs 14.
Guaadaoui, A., Benaicha, S., Elmajdoub, N., Bellaoui, M., Hamal, A., 2014. What is a bioactive compound? A combined definition for a preliminary consensus. Int. J. Food Sci. Nutr. 3, 17–179.
Han, J., Tan, C., Wang, Y., Yang, S., Tan, D., 2015. Betanin reduces the accumulation and cross-links of collagen in high-fructose-fed rat heart through inhibiting non-enzymatic glycation. Chem. Biol. Interact. 227, 37–44.
Hao, R.L., Li, M.Q., Li, F., Sun-Waterhouse, D.X., Li, D.P., 2022. Protective effects of the phenolic compounds from mung bean hull against H2O2-induced skin aging through alleviating oxidative injury and autophagy in HaCaT cells and HSF cells. Sci. Total Environ. 841.
Hidalgo, A., Brandolini, A., Canadanovic-Brunet, J., Cetkovic, G., Saponjac, V.T., 2018. Microencapsulates and extracts from red beetroot pomace modify antioxidant capacity, heat damage and colour of pseudocereals-enriched einkorn water biscuits. Food Chem. 268, 40–48.
Jeong, K.M., Yang, M., Jin, Y., Kim, E.M., Ko, J., Lee, J., 2017. Identification of major flavone C-glycosides and their optimized extraction from cymbidium kanran using deep eutectic solvents. Molecules 22.
Kalinova, J.P., Triska, J., Vrchotova, N., Moos, M., 2014. Verification of presence of caprolactam in sprouted achenes of Fagopyrum esculentum Moench and its influence on plant phenolic compound content. Food Chem. 157, 380–384.
Kammerer, D.R., Kammerer, J., Valet, R., Carle, R., 2014. Recovery of polyphenols from the by-products of plant food processing and application as valuable food ingredients. Food Res. Int. 65, 2–12.
Karim, R., 2013. Endogenous Lebanese plants treating diabetes and related complications. Nat. Prod. Chem. Res. 1.
Khan, M.I., 2016. Plant betalains: safety, antioxidant activity, clinical efficacy, and bioavailability. Compr. Rev. Food Sci. Food Saf. 15, 316–330.

Khan, S.Z., Zaidi, A.A., Naseer, M.N., AlMohamadi, H., 2022. Nanomaterials for biogas augmentation towards renewable and sustainable energy production: a critical review. Front. Bioeng. Biotechnol. 10, 1–29.
Koubaa, M., Barba, F.J., Grimi, N., Mhemdi, H., Koubaa, W., Boussetta, N., Vorobiev, E., 2016. Recovery of colorants from red prickly pear peels and pulps enhanced by pulsed electric field and ultrasound. Innov. Food Sci. Emerg. Technol. 37, 336–344.
Lasta, H.F.B., Lentz, L., Rodrigues, L.G.G., Mezzomo, N., Vitali, L., Ferreira, S.R.S., 2019. Pressurized liquid extraction applied for the recovery of phenolic compounds from beetroot waste. Biocatal. Agric. Biotechnol. 21.
Lee, C.Y., Chien, Y.S., Chiu, T.H., Huang, W.W., Lu, C.C., Chiang, J.H., Yang, J.S., 2012. Apoptosis triggered by vitexin in U937 human leukemia cells via a mitochondrial signaling pathway. Oncol. Rep. 28, 1883–1888.
Lee, T.W., Tsai, I.C., Liu, Y.F., Chen, C.Y., 2022. Upcycling fruit peel waste into a green reductant to reduce graphene oxide for fabricating an electrochemical sensing platform for sulfamethoxazole determination in aquatic environments. Sci. Total Environ. 812.
Li, H., Li, Y.A., Li, G., Tan, X.Z., Chen, G.X., Zhang, Y.K., 2013. Ultrasonically assisted simultaneous extraction of isoorientin, orientin, and vitexin from leaves of neosinocalamus affinis (rendle) Keng f. (N-affinis). Separ. Sci. Technol. 48, 1987–1997.
Liew, S.S., Ho, W.Y., Yeap, S.K., Bin Sharifudin, S.A., 2018. Phytochemical composition and in vitro antioxidant activities of Citrus sinensis peel extracts. PeerJ 6.
Lindsay, H., Cooksey, C., 2014. Antithyroid Effects in Viuo and in Vitro in Millet of Vitexin: Ilr, vols. 6–9.
Lorizola, I.M., Furlan, C.P.B., Portovedo, M., Milanski, M., Botelho, P.B., Bezerra, R.M.N., Sumere, B.R., Rostagno, M.A., Capitani, C.D., 2018. Beet stalks and leaves (Beta vulgaris L.) protect against high-fat diet-induced oxidative damage in the liver in mice. Nutrients 10.
Lorizola, I.M., Miyamoto, J.E., Vieira, A.L.F., Sumere, B.R., Bezerra, R.M.N., Torsoni, M.A., Torsoni, A.S., Rostagno, M.A., Milanski, M., Capitani, C.D., 2021. Beet (Beta vulgaris L.) stalk and leaf supplementation changes the glucose homeostasis and inflammatory markers in the liver of mice exposed to a high-fat diet. Food Chem. Mol. Sci. 2.
Maravic, N., Teslic, N., Nikolic, D., Dimic, I., Seres, Z., Pavlic, B., 2022. From agricultural waste to antioxidant-rich extracts: green techniques in extraction of polyphenols from sugar beet leaves. Sustain. Chem. Pharm. 28.
Martins, N., Ferreira, I.C.F.R., 2017. Wastes and by-products: upcoming sources of carotenoids for biotechnological purposes and health-related applications. Trends Food Sci. Technol. 62, 33–48.
Melgar, B., Dias, M.I., Ciric, A., Sokovic, M., Garcia-Castello, E.M., Rodriguez-Lopez, A.D., Barros, L., Ferreira, I., 2017. By-product recovery of Opuntia spp. peels: betalainic and phenolic profiles and bioactive properties. Ind. Crop. Prod. 107, 353–359.
Mukherjee, P.K., Nema, N.K., Maity, N., Sarkar, B.K., 2013. Phytochemical and therapeutic potential of cucumber. Fitoterapia 84, 227–236.
Nasri, H., Baradaran, A., Shirzad, H., Kopaei, M.R., 2014. New concepts in nutraceuticals as alternative for pharmaceuticals. Int. J. Prev. Med. 5, 1487–1499.
Ni, R., Liu, X.Y., Zhang, J.Z., Fu, J., Tan, H., Zhu, T.T., Zhang, J., Wang, H.L., Lou, H.X., Cheng, A.X., 2022. Identification of a flavonoid C-glycosyltransferase from fern species Stenoloma chusanum and the application in synthesizing flavonoid C-glycosides in Escherichia coli. Microb. Cell Factories 21.
Ninfali, P., Angelino, D., 2013. Nutritional and functional potential of Beta vulgaris cicla and rubra. Fitoterapia 89, 188–199.
Park, B.I., Kim, J., Lee, K., Lim, T., Hwang, K.T., 2019. Flavonoids in common and tartary buckwheat hull extracts and antioxidant activity of the extracts against lipids in mayonnaise. J. Food Sci. Technol. 56, 2712–2720.
Patra, S., Mishra, S.R., Behera, B.P., Mahapatra, K.K., Panigrahi, D.P., Bhol, C.S., Praharaj, P.P., Sethi, G., Patra, S.K., Bhutia, S.K., 2022. Autophagy-modulating phytochemicals in cancer therapeutics: current evidences and future perspectives. Semin. Cancer Biol. 80, 205–217.
Petrovska, B.B., 2012. Historical review of medicinal plants' usage. Pharm. Rev. 6, 1–5.
Ravichandran, K., Saw, N.M.M.T., Mohdaly, A.A.A., Gabr, A.M.M., Kastell, A., Riedel, H., Cai, Z., Knorr, D., Smetanska, I., 2013. Impact of processing of red beet on betalain content and antioxidant activity. Food Res. Int. 50, 670–675.
Ren, D.B., Han, B.S., Xin, Z.Q., Liu, W.B., Ma, S.S., Liang, Y.Z., Yi, L.Z., 2016. Computation-aided separation of seven components from Spirodela polyrrhiza (L.) via counter-current chromatography. Sep. Purif. Technol. 165, 160–165.
Rico, X., Gullon, B., Yanez, R., 2022. A comparative assessment on the recovery of pectin and phenolic fractions from aqueous and DES extracts obtained from melon peels. Food Bioprocess Technol. 15, 1406–1421.
Rodriguez-Amaya, D.B., 2016. Natural food pigments and colorants. Curr. Opin. Food Sci. 7, 20–26.
Roriz, C.L., Heleno, S.A., Alves, M.J., Oliveira, M., Pinela, J., Dias, M.I., Calhelha, R.C., Morales, P., Ferreira, I., Barros, L., 2022. Red pitaya (Hylocereus costaricensis) peel as a source of valuable molecules: extraction optimization to recover natural colouring agents. Food Chem. 372.
Saha, A., Tripathy, V., Basak, B.B., Kumar, J., 2018. Entrapment of distilled palmarosa (cymbopogon martinii) wastes in alginate beads for adsorptive removal of methylene blue from aqueous solution. Environ. Prog. Sustain. Energy 37, 1942–1953.
Sakihama, Y., Maeda, M., Hashimoto, M., Tahara, S., Hashidoko, Y., 2012. Beetroot betalain inhibits peroxynitrite-mediated tyrosine nitration and DNA strand cleavage. Free Radic. Res. 46, 93–99.
Scarano, P., Naviglio, D., Prigioniero, A., Tartaglia, M., Postiglione, A., Sciarrillo, R., Guarino, C., 2020. Sustainability: obtaining natural dyes from waste matrices using the prickly pear peels of Opuntia ficus-indica (L.) Miller. Agronomy 10.
Schieber, A., 2019. By-products of plant food processing as a source of valuable compounds. Ref. Modul. Food Sci. 12, 401–413.
Sharma, K.D., Karki, S., Thakur, N.S., Attri, S., 2012. Chemical composition, functional properties and processing of carrot-A review. J. Food Sci. Technol. 49, 22–32.
Siddiqui, M.H., Alamri, S.A., Al-Whaibi, M.H., Hussain, Z., Ali, H.M., El-Zaidy, M.E., 2017. A mini-review of anti-hepatitis B virus activity of medicinal plants. Biotechnol. Biotechnol. Equip. 31, 9–15.
Silos-Espino, H., Cruz-Macias, F., Reyes-Medina, A., Ortiz-Morales, M., Frausto-Reyes, C., Valera-Montero, L.L., Flores-Benitez, S., Kamaraj, S.K., Perales-Segovia, C., 2020. Effect of agave sap on opuntia SPP. Plant propagation. Pakistan J. Agric. Sci. 57, 1689–1695.
Slatnar, A., Stampar, F., Veberic, R., Jakopic, J., 2015. HPLC-MSn identification of betalain profile of different beetroot (Beta vulgaris L. ssp. vulgaris) parts and cultivars. J. Food Sci. 80, 1952–1958.
Sun, N., Xie, J.Y., Xie, J.H., Chen, Y., Hu, X.B., Yu, Q., 2022. Purification, composition and activity of bound polyphenols from mung bean coat dietary fiber. Food Res. Int. 162.
Sun, S.B., Zhang, Y.C., Xu, W.P., Zhang, Y., Yang, R., Guo, J.L., Guan, S., Ma, Q., Ma, K., Xu, J.Q., 2021. Chlorophyllin inhibits mammalian thioredoxin reductase 1 and triggers cancer cell death. Antioxidants 10.
Supasatyankul, B., Saisriyoot, M., Klinkesorn, U., Rattanaporn, K., Sae-Tan, S., 2022. Extraction of phenolic and flavonoid compounds from mung bean (vigna radiata L.) seed coat by pressurized liquid extraction. Molecules 27.
Thaiudom, S., Oonsivilai, R., Thaiwong, N., 2021. Production of colorant powder from dragon fruit (Hylocerecus polyrhizus) peel: bioactivity, heavy metal contamination, antimutagenicity, and antioxidation aspects. J. Food Process. Preserv. 45.
Toro, M.T., Ortiz, J., Becerra, J., Zapata, N., Fierro, P., Illanes, M., López, M.D., 2021. Strategies of elicitation to enhance bioactive compound content in edible plant sprouts: a bibliometric study. Plants 10, 1–20.
Tran, T.N., Athanassiou, A., Basit, A., Bayer, I.S., 2017. Starch-based bio-elastomers functionalized with red beetroot natural antioxidant. Food Chem. 216, 324–333.
Tumbas Šaponjac, V., Čanadanović-Brunet, J., Ćetković, G., Jakišić, M., Djilas, S., Vulić, J., Stajčić, S.D.S., 2016. Encapsulation of beetroot pomace extract: RSM optimization, storage and gastrointestinal stability. Molecules 21.
Uriburu, F.M.C., Cattaneo, F., Maldonado, L.M., Zampini, I.C., Alberto, M.R., Isla, M.I., 2022. Prosopis alba seed as a functional food waste for food formulation enrichment. Foods 11.
Verma, D.K., Srivastav, P.P., 2020. Bioactive compounds of rice (Oryza sativa L.): review on paradigm and its potential benefit in human health. Trends Food Sci. Technol. 97, 355–365.
Vettorazzi, A., de Cerain, A.L., Sanz-Serrano, J., Gil, A.G., Azqueta, A., 2020. European regulatory framework and safety assessment of food-related bioactive compounds. Nutrients 12, 1–16.
Vigano, J., Brumer, I.Z., Braga, P.A.D., da Silva, J.K., Marostica, M.R., Reyes, F.G.R., Martinez, J., 2016. Pressurized liquids extraction as an alternative process to readily obtain bioactive compounds from passion fruit rinds. Food Bioprod. Process. 100, 382–390.
Vilas-Boas, A.A., Pintado, M., Oliveira, A.L.S., 2021. Natural bioactive compounds from food waste: toxicity and safety concerns. Foods 10.

Villaro, S., Ciardi, M., Morillas-españa, A., Sánchez-Zurano, A., Acién-Fernández, G., Lafarga, T., 2021. Trends and industrial use as food. Foods 10, 1–17.
Vissers, A., Kiskini, A., Hilgers, R., Marinea, M., Wierenga, P.A., Gruppen, H., Vincken, J.P., 2017. Enzymatic browning in sugar beet leaves (beta vulgaris L.): influence of caffeic acid derivatives, oxidative coupling, and coupled oxidation. J. Agric. Food Chem. 65, 4911–4920.
Vulic, J.J., Cebovic, T.N., Canadanovic, V.M., Cetkovic, G.S., Djilas, S.M., Canadanovic-Brunet, J.M., Velicanski, A.S., Cvetkovic, D.D., Tumbas, V.T., 2013. Antiradical, antimicrobial and cytotoxic activities of commercial beetroot pomace. Food Funct. 4, 713–721.
Zain, M.S.C., Lee, S.Y., Nasir, N.M., Fakurazi, S., Shaari, K., 2020. Metabolite characterization and correlations with antioxidant and wound healing properties of oil palm (elaeis guineensis Jacq.) leaflets via H-1-NMR-Based metabolomics approach. Molecules 25.
Zain, M.S.C., Lee, S.Y., Teo, C.Y., Shaari, K., 2021a. Adsorption/desorption characteristics and simultaneous enrichment of orientin, isoorientin, vitexin and isovitexin from hydrolyzed oil palm leaf extract using macroporous resins. Processes 9.
Zain, M.S.C., Osman, M.F., Lee, S.Y., Shaari, K., 2021b. UHPLC-UV/PDA method validation for simultaneous quantification of luteolin and apigenin derivatives from elaeis guineensis leaf extracts: an application for antioxidant herbal preparation. Molecules 26.
Zhang, J., Li, X., Han, X., Liu, R., Fang, J., 2017. Targeting the thioredoxin system for cancer therapy. Trends Pharmacol. Sci. 38, 794–808.
Zhang, Q., Pan, J., Wang, Y., Lubet, R., You, M., 2013. Beetroot red (betanin) inhibits vinyl carbamate- and benzo(a)pyrene-induced lung tumorigenesis through apoptosis. Mol. Carcinog. 52, 686–691.
Zielinska, D., Szawara-Nowak, D., Zielinski, H., 2013. Antioxidative and anti-glycation activity of buckwheat hull tea INFUSION. Int. J. Food Prop. 16, 228–239.
Zuniga-Lopez, M.C., Maturana, G., Campmajo, G., Saurina, J., Nunez, O., 2021. Determination of bioactive compounds in sequential extracts of chia leaf (salvia hispanica L.) using UHPLC-HRMS (Q-Orbitrap) and a global evaluation of antioxidant in vitro capacity. Antioxidants 10.