Biomedicine & Pharmacotherapy 161 (2023) 114337

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Natural sources, biological effects, and pharmacological properties of cynaroside

Abdelhakim Bouyahya [a,*], Douae Taha [b], Taoufiq Benali [c], Gokhan Zengin [d], Nasreddine El Omari [e], Naoufal El Hachlafi [f], Asaad Khalid [g,h], Ashraf N. Abdalla [i], Chrismawan Ardianto [j], Ching Siang Tan [k,*], Long Chiau Ming [j,l,m], Narjis Sahib [n]

[a] Laboratory of Human Pathologies Biology, Department of Biology, Faculty of Sciences, Mohammed V University in Rabat, Morocco
[b] Laboratory of Spectroscopy, Molecular Modelling Materials, Nanomaterials Water and Environment–CERNE2D, Faculty of Sciences, Mohammed V University in Rabat, Morocco
[c] Environment and Health Team, Polydisciplinary Faculty of Safi, Cadi Ayyad University, Marrakesh-Safi 46030, Morocco
[d] Department of Biology, Science Faculty, Selcuk University, Konya 42250, Turkey
[e] Laboratory of Histology, Embryology and Cytogenetic, Faculty of Medicine and Pharmacy, Mohammed V. University in Rabat, B.P. 6203, Rabat 10000, Morocco
[f] Microbial Biotechnology and Bioactive Molecules Laboratory, Sciences and Technologies Faculty, Sidi Mohmed Ben Abdellah University, Fez B.P. 2626, Morocco
[g] 7 Substance Abuse and Toxicology Research Center, Jazan University, Jazan 45142, Saudi Arabia
[h] Medicinal and Aromatic Plants and Traditional Medicine Research Institute, National Center for Research, P.O. Box 2404, Khartoum, Sudan
[i] Department of Pharmacology and Toxicology, College of Pharmacy, Umm Al-Qura University, Makkah 21955, Saudi Arabia
[j] Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya 60115, Indonesia
[k] School of Pharmacy, KPJ Healthcare University College, 71800 Nilai, Malaysia
[l] PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Gadong, Brunei Darussalam
[m] School of Medical and Life Sciences, Sunway University, Sunway City 47500, Malaysia
[n] Laboratoire d'Amélioration des Productions Agricoles, Biotechnologie et Environnement (LAPABE), Faculté des Sciences, Mohammed Premier University, Oujda 60000, Morocco

ARTICLE INFO

Keywords:
Cancer cell
Diabetes
Infectious disease
Biological properties
Anticancer
Bioactive compound

ABSTRACT

Cynaroside is a flavonoid, isolated from several species belonging to the Apiaceae, Poaceae, Lamiaceae, Solanaceae, Zingiberaceae, Compositae and other families and it can be extracted from seeds, roots, stems, leaves, barks, flowers, fruits, aerial parts, and the whole plant of these species. This paper discloses the current state of knowledge on the biological/pharmacological effects and mode of action to better understand the numerous health benefits of cynaroside. Several research works revealed that cynaroside could have beneficial effects on various human pathologies. Indeed, this flavonoid exerts antibacterial, antifungal, antileishmanial, antioxidant, hepatoprotective, antidiabetic, anti-inflammatory, and anticancer effects. Additionally, cynaroside exhibits its anticancer effects by blocking MET/AKT/mTOR axis by decreasing the phosphorylation level of AKT, mTOR, and P70S6K. For antibacterial activity, cynaroside reduces biofilm development of *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Moreover, the incidence of mutations leading to ciprofloxacin resistance in *Salmonella typhimurium* was reduced after the treatment with cynaroside. In addition, cynaroside inhibited the production of reactive oxygen species (ROS), which reduced the damage to mitochondrial membrane potential caused by hydrogen peroxide (H_2O_2). It also enhanced the expression of the anti-apoptotic protein Bcl-2 and lowered that of the pro-apoptotic protein Bax. Cynaroside abrogated the up-regulation of c-Jun N-terminal kinase (JNK) and p53 protein expression triggered by H_2O_2. All these findings suggest that cynaroside could be used to prevent certain human diseases.

* Corresponding author.
E-mail addresses: bouyahya@um5r.ac.ma (A. Bouyahya), douae.taha02@gmail.com (D. Taha), benali.taoufiq@gmail.com (T. Benali), gokhanzengin@selcuk.edu.tr (G. Zengin), nasrelomari@gmail.com (N. El Omari), naoufal.elhachlafi@usmba.ac.ma (N. El Hachlafi), akahmed@jazanu.edu.sa (A. Khalid), anabdrabo@uqu.edu.sa (A.N. Abdalla), chrismawan-a@ff.unair.ac.id (C. Ardianto), tcsiang@kpjuc.edu.my (C.S. Tan), longchiauming@gmail.com (L.C. Ming), n.sahib@ump.ac.ma (N. Sahib).

https://doi.org/10.1016/j.biopha.2023.114337
Received 18 November 2022; Received in revised form 19 January 2023; Accepted 27 January 2023
Available online 20 February 2023

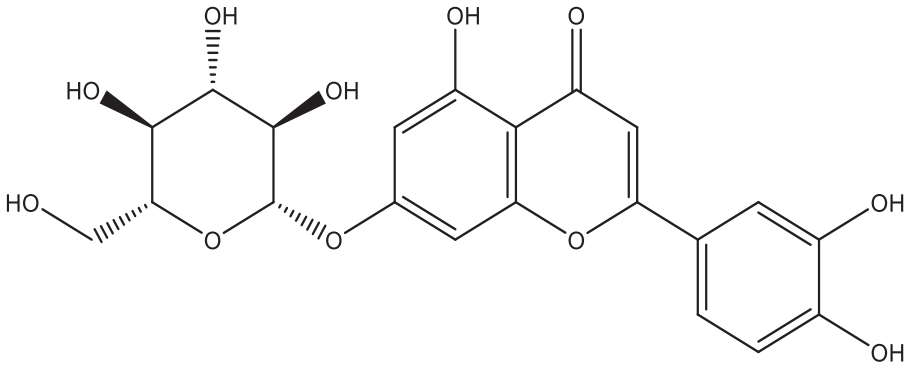

Fig. 1. Chemical structure of Cynaroside.

1. Introduction

Since antiquity, natural products have been used to prevent and treat pathologies of human health systems. The importance of these herbal products in human society has increased due to: i) low toxicity, ii) easy availability, and iii) fewer adverse effects than chemically synthesized drugs [1]. Several studies have demonstrated the bioactivity of plant extracts rich in polyphenols, flavonols, flavonoids, saponins, and carotenes [2–10]. This prompted researchers to isolate and identify the molecule responsible for the biological activities of plant extracts; thus several compounds such as morin, carvone, chalcones, chrysoeriol, grifolin, pinosylvin, quercetin, and others are tested for their biological properties, the results of which have shown that these molecules exert antioxidant, anti-free radical, anticancer, anti-inflammatory, antimicrobial, anti-arthritic, antidiabetic, neuroprotective, cardioprotective, hepatoprotective, and nephroprotective effects [11–24]. Currently, a large number of drugs based on natural compounds are available in the market such as morphine, cannabidiol, and taxal extracted from *Papaver somniferum*, *Cannabis sativa*, *Salix* spp., and *Taxus brevifolia* plants, respectively [25–28].

Cynaroside is a flavonoid compound widely found in plants belonging to the families Apiaceae, Poaceae, Lamiaceae, Solanaceae, Zingiberaceae, Compositae, and others. It has been described to have important pharmacological activities, including antibacterial [29–39], antifungal [30,32,33,36,38–40], antileishmanial [41],[31], antioxidant [35,42–48], hepatoprotective [49], [50], antidiabetic [46,51–53], anti-inflammatory [54–60], and anticancer effects [38], [61–64]. Moreover, cynaroside exhibits its anticancer effects by modulating various cell signaling pathways. Ji et al. [62] demonstrated that this flavonoid decreases the level of phosphorylation of AKT, mTOR, and P70S6K which causes a blockage of the MET/AKT/mTOR axis [62]. Regarding the antibacterial effect, cynaroside reduced biofilm development of *P. aeruginosa* and *Staphylococcus aureus* and increased the incidence of mutations leading to ciprofloxacin resistance in *Salmonella typhimurium* [38].

Despite the richness of the literature by research works, which have valorized the different biological activities of this molecule, to the best of our knowledge, no critical review has been performed to provide suggestions for potential future clinical trials of this bioactive compound. This paper aims to provide a comprehensive review of the natural reservoirs, chemistry, and pharmacological activities of cynaroside.

2. Source of cynaroside

Merremia tridentata (L.) stem and root extracts revealed that cynaroside is the major compound of this plant collected in Vietnam [51], as well as of *Cuminum cyminum* L. collected in China [65] and *Olea europaea* collected in Pakistan [66]. Cynaroside is the major compound of leaf extract of *Anthriscus sylvestris* (L.) Hoffm. harvested in Korea [67], the extract of *Vernonia amygdalina* collected in Vietnam [68], the extract of *Prunus pseudocerasus* harvested in China [69], *Cymbopogon citratus* Stapf leaf extract harvested in Portugal [70], *Thymus migricus* leaf extract harvested in Turkey [71], *Cantharanthus roseus* and *Bryophyllum pinnatum* extracts collected in Nigeria [72], the extract of *Stachys lavandulifolia* Vahl. aerial parts from Iran [73], the extract of *Salvia tesquicola* and *Salvia verticillata* collected in regions of Russia [74], and *Bischofia javanica* leaf extract form Bangladesh [75]. It was found in leaf extracts of *Mentha piperita* and *Mentha longifolia* collected in regions of Saudi Arabia [42].

Cynaroside richness has also been recorded in other plant extracts, including *Capsicum annuum* seeds from Netherlands [76], aerial parts of *Launaea capitata* from Egypt [77], aerial parts of *Salvia dracocephaloides* Boiss. collected in Iran [78], *Canarium patentinervium* Miq. leaves and barks from Malaysia [79], *lpinia blepharocalyx* K. seeds from Vietnam [80], the extracts of *Chrysanthemum morifolium* collected in Korea [81], and the leaves and the flowers of *M. longifolia* (L.) from Hungary [82,83].

Other extracts have also been characterized by the dominance of this component, such as those of the leaves and flowers of *Acantholippia salsoloides* from Portugal [84], the leaves of *Capsicum Cultivars* from Germany [85], of *Lavandula stoechas* collected in Greece [86], *Lonicera japonica* flos [87] and *Elsholtiza bodinieri* [55] from China, *Aronia melanocarpa* and *Aronia arbutifolia*, leaves and fruits of *Aronia prunifolia* collected in Poland [88], *Angelica keiskei* [63], *Salvia plebeia* R. Br. [89], and *Lonicera japonia* Thunb. [90,91] collected in Korea.

Indeed, cynaroside is the main compound of many plant extracts, such as the extracts of the aerial parts of *Bidens cernua* L. colllected in Poland [40], the extract of *Lagotis integrifolia* (Willd.) Schischk from Mongolia [92], also of *Centaurea borysthenica* and *Centaurea daghestanica* from Poland [93], *Artocarpus incisa* L. leaves from Vietnam [61], and *Gentianella azurea* leaves and flowers collected in Russia [94].

This has also been observed with extracts of aerial parts of *Bidens tripartita* from Turkey [46], *B. tripartita* flowers from Poland [95,96], *C. citratus* leaves from Portugal [97], *L. japonica* Thunb. flowers from China [98], *L. japonica* flowers from China [99], extracts of *A. sylvestris* from Romania [100], *Carthamus tinctorius* L. flowers from Russia [101], *Tilia rubra* subsp. *Caucasica* leaves from Iran [102], *Centaurea scoparia* aerial parts from Egypt [103], and *A. sylvestris* (L.) aerial parts from Slovakia [38].

Furthermore, cynaroside is one of the major compounds of *Polygonum orientale* collected in China [104,105], *Veronica longifolia* L. stems from Ukraine [106], *Dracocephalum palmatum* Stephan extracts [107], *Sophora flavescens* Soland. aerial parts from Russia [108], *S. plebeia* leaves from Korea [109], *Agrimonia eupatoria* L. from Russia [110], as well as *Scutellaria immaculata* and *Scutellaria ramosissima* aerial parts and roots from Uzbekistan [32].

Cynaroside was isolated from *Salvia limbata* aerial part extracts from Iran [111], *Ixeris dentata* roots from korea [112], *Sonneratia caseolaris* from Japan [113], *Melissa officinalis* L. from Turkey [114], aerial parts of *Halenia corniculata* L., *Pyrola rotundifolia* L., and *Pyrola incarnate* from Mongolia [57], *A. Keiskei* aerial parts from Korea [50], and *Thermopsis*

Table 1
Source of cynaroside

Plants Families	Countries	Parts used	References
Merremia tridentata (L.) Convolvulaceae	Vietnam	Stems and roots	[51]
Cuminum cyminum L. Apiaceae	China	Not reported	[65]
Olea europaea Oleaceae	Pakistan	Not reported	[66]
Vernonia amygdalina Asteraceae	Vietnam	Not reported	[68]
Anthriscus sylvestris (L.) Hoffm. Apiaceae	Korea	Leaves	[67]
Prunus pseudocerasus Rosaceae	China	Not reported	[69]
Cymbopogon citratus Stapf. Poaceae	Portugal	Leaves	[70]
Thymus migricus Lamiaceae	Turkey	Leaves	[71]
Cantharanthus roseus Crassulaceae	Nigeria	Not reported	[72]
Bryophyllum pinnatum Crassulaceae			
Stachys lavandulifolia Vahl. Lamiaceae	Iran	Aerial parts	[73]-
Salvia tesquicola Lamiaceae	Russia	Aerial parts (leaves and stems)	[74]
Salvia verticillata Lamiaceae			
Bischofia javanica Euphorbiaceae	Bangladesh	Leaves	[75]
Mentha piperita Lamiaceae	Saudi Arabia	Leaves	[132]
Mentha longifolia Lamiaceae			
Capsicum annuum Solanaceae	Netherlands	Seeds	[76]
Launaea capitata Asteraceae	Egypt	Aerial parts	[77]
Salvia dracocephaloides Boiss. Lamiaceae	Iran	Aerial parts	[78]
Canarium patentinervium Miq. Burseraceae	Malaysia	Leaves and barks	[79]
Alpinia blepharocalyx K. Zingiberaceae	Vietnam	Seeds	[80]
Chrysanthemum morifolium Asteraceae	Korea	Not reported	[81]
Scutellaria baicalensis Labiatae			
Mentha longifolia (L.) Lamiaceae	Hungary	Leaves and flowers	[82,83]
Acantholippia salsoloides Verbenaceae	Portugal	Leaves and flowers	[84]
Capsicum Cultivars Solanaceae	Germany	Leaves	[85]
Lavandula stoechas Lamiaceae	Greece	Not reported	[86]
Lonicera japonica flos Caprifoliaceae	China	Not reported	[87]
Elsholtiza bodinieri Lamiaceae	China	Not reported	[55]
Aronia melanocarpa Rosaceae	Poland	Leaves and fruits	[88]
Aronia arbutifolia Rosaceae			
Aronia prunifolia Rosaceae			
Angelica keiskei Apiaceae	Korea	Not reported	[90]
Salvia plebeia R. Br. Lamiaceae	Korea	Aerial parts	[89]
Lonicera japonia Thunb. Caprifoliaceae	Korea	Not reported	[90,91]
Lagotis integrifolia (Willd.) Schischk Scrophulariaceae	Mongolia	Not reported	[92]
Centaurea borysthenica Asteraceae	Poland	Not reported	[93]
Centaurea daghestanica Asteraceae			
Bidens cernua L. Asteraceae	Poland	Aerial parts	[40]
Artocarpus incisa L. Moraceae	Vietnam	Leaves	[61]
Gentianella azurea Gentianaceae	Russia	Leaves and flowers	[94]
Bidens tripartita Asteraceae	Turkey Poland	Aerial parts Flowers	[46] [96]
Bidens tripartitus Asteraceae	Poland	Not reported	[95]
Cymbopogon citratus Poaceae	Portugal	Leaves	[97]
Lonicera japonica Thunb. Caprifoliaceae	China	Flowers	[98]
Lonicera japonica Caprifoliaceae	China	Flowers	[99]
Anthriscus sylvestris Apiaceae	Romania	Not reported	[100]
Carthamus tinctorius L. Asteraceae	Russia	Flowers	[101]
Tilia rubra subsp. *Caucasica* Tiliaceae	Iran	Leaves	[102]
Centaurea scoparia Asteraceae	Egypt	Aerial parts	[133]
Anthriscus sylvestris (L.) Apiaceae	Slovakia	Aerial parts	[38]
Polygonum orientale Polygonaceae	China	Not reported	[104,105]
Veronica longifolia L. Scrophulariaceae	Ukraine	Stems	[106]
Dracocephalum palmatum Stephan. Lamiaceae	Not reported	Not reported	[108]
Sophora flavescens Soland. Fabaceae	Russia	Aerial parts	[107]
Salvia plebeia Labiatae	Korea	Leaves	[109]
Agrimonia eupatoria L. Rosaceae	Russia	Not reported	[110]
Scutellaria immaculata Lamiaceae	Uzbekistan	Aerial parts and roots	[32]
Scutellaria ramosissima Lamiaceae			
Salvia limbata Lamiaceae	Iran	Aerial parts	[111]
Ixeris dentata Asteraceae	Korea	Roots	[112]
Sonneratia caseolaris Sonneratiaceae	Japan	Not reported	[113]
Melissa officinalis L. Labiatae	Turkey	Not reported	[114]
Halenia corniculata L. Gentianaceae	Mongolia	Aerial parts	[57]
Pyrola rotundifolia L. Ericaceae			
Pyrola incarnate Ericaceae			
Angelica Keiskei Apiaceae	Korea	Aerial parts	[50]
Thermopsis alterniflora Fabaceae	Uzbekistan	Not reported	[115]
Cynara scolymus L. Asteraceae	Portugal Vietnam Not reported Egypt Bulgaria Italy	Not reported Leaves Leaves Not reported Leaves and seeds	[116] [61] [117] [118] [119] [120]

(*continued on next page*)

Table 1 (*continued*)

Plants Families	Countries	Parts used	References
		Leaves, outer bracts, heads, and stems	
	Brazil	Leaves	[121]
	Germany		[122]
	United States		[123]
	Austria		[124]
	Germany	Not reported	[125]
	Egypt	Seeds	[126]
	Italy	Whole plants	[127]
Digitalis ciliata Plantaginaceae	Not reported	Leaves	[128]
Symphyandra pendula Campanulaceae	Not reported	Leaves and flowers	[129]
Phlomis tuberosa (L.) Labiatae	Russia	Leaves and fruits	[130]

altherniflora from Uzbekistan [115],

Cynaroside is the major compound of *Cynara scolymus* L. extracts from many parts of plants and regions such as Portugal [116], plant leaves from Vietnam [61], [117], and Egypt [118], plant leaves and seeds from Bulgaria [119], leaves, outer bracts, flower heads, and stems from Italy [120], *C. Scolymus* L. leaves from Brazil [121], plant leaves from Germany [122], [125], United States [123], and Austria [124], as well as seeds from a plant collected in Egypt [126], and the whole plant with various parts collected in Italy [127].

Cynaroside has also been recorded in other plant extracts, *Digitalis ciliata* leaves [128], *Symphyandra pendula* Leaves and flowers [129], and *Phlomis tuberosa* (L.) leaves and fruits from Russia [130].

We can conclude that this molecule is chemotype although most of the plants with cynaroside as main constituent correspond to the Asteraceae/Compositae family [46,61,68,77,81,95,96,101,103,112, 116–127,131], the Lamiaceae family [32,55,71,73,74,78,82,83,89,108, 111,132] and Apiaceae family [38,50,65,67,90,100].

Cynaroside (Fig. 1) is a flavone widely present in plants (Table 1). It is called by various names (Luteolin-7-*O*-glucoside, Luteoloside, Cinaroside).

3. Extraction, identification, and isolation process of cynaroside

As shown in Table 2, several research groups have isolated and purified cynaroside from a variety of medicinal plants.

Spectroscopic techniques such as UPLC-Q-TOF-MS, and elemental analysis have been used to elucidate the structure of cynaroside isolated and purified from *C. cyminum* L. extract [65], and also from *T. migricus* leaves obtained by the methods of maceration [71], HPLC-PDA-ESI/MSn and ^{1}H NMR of *Cymbopogon citratus* Stapf. [70] were been used to elucidate this molecule from *Stachys lavandulifolia* Vahl. with ^{1}H NMR, ^{13}C NMR, and UV spectral analysis [73], *M. piperita* and *M. longifolia* used HPLC-DAD [132], *C. annuum* seed extract [77].

It was by-product from *S. dracocephaloides* Boiss. obtained with the maceration method using ^{1}H and ^{13}C NMR [78], *A. blepharocalyx* K. using MS, IR, and NMR analysis [80], *M. longifolia* (L.) leaves and flowers obtained with soxhlet, maceration, and ultrasonic using the HPLC-DAD method [82], *C. morifolium* and *Scutellaria baicalensis* using LC-MS/MS [81], *A. salsoloides* using Ion-trap mass spectrometry with flame ionization detection *via* gas chromatography [84] *C. Cultivars* [85], *L. stoechas* [86], *L. japonica* flos [87], leaves and fruits of *A. melanocarpa*, *A. arbutifolia*, and *A. prunifolia* using HPLC-DAD [88].

Cynaroside eluted from *E. bodinieri* by HPLC, ESI-MS, and NMR [55], *S. plebeia* R. Br. [89], *L. integrifolia* (Willd.) Schischk obtained with soxhlet method using MS, ^{1}H, ^{13}C, HSQC, HMBC, and ^{1}H-1 H COSY NMR [92], *C. Scolymus* L. [116,117,120,123,124,126] *C. citratus* [97], *G. azurea* [94], *B. tripartita* [46], from leaves of *T. rubra* subsp. *Caucasica* obtained by maceration using UV, ^{1}H NMR, and ^{13}C NMR [102], flowers of *C. tinctorius* L. [101], and *L. japonica* [99]. The complete interpretation of ^{1}1D and ^{2}D NMR, UV, IR, and mass spectroscopy allowed the identification of cynaroside in *C. scoparia* aerial part extracts obtained by maceration [103], *A. sylvestris* (L.) [38], *P. orientale* [104,105], *D. palmatum* Stephan. [107], *S. flavescens* Soland. using ^{1}H and ^{13}C NMR [108], aerial parts and roots of *S. immaculata* and *S. ramosissima* [32], *S. limbata* [111], from *B. tripartita* L. flowers obtained by maceration using HPLC analysis [96], *H. corniculata* L., *P. rotundifolia* L., *P. incarnate* [57], and *D. ciliata* [128], from leaves and fruits of *P. tuberosa* (L.) using IR spectrum [130].

4. Biological properties

4.1. Antibacterial activity

Several investigations have tested the antimicrobial effects of cynaroside in their various solvent forms, including acetone, ethanol, methanol, hexane, and ethyl acetate from a wide range of plant species [29–39]. As summarized in Table 3, from the literature, the antibacterial potential of cynaroside (effective against both Gram-positive and Gram-negative bacteria) was detailed according to the plants of origin, antibacterial assay, tested strains, and the main results. Indeed, Žemlička et al. [38] extracted cynaroside from the aerial parts of wild chervil, *A. sylvestris* (L.) Hoffm. The results of antibacterial activity test against *S. aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Bacillus cereus*, *Escherichia coli*, *Serratia marcescens*, *Proteus* sp., *S. typhimurium*, and *P. aeruginosa* showed inhibition effect only on *S. marcescens* and *S. typhimurium*. Additionally, the cynaroside suppresses the increased incidence of mutations leading to ciprofloxacin resistance in *S. typhimurium* and promotes biofilm development of *P. aeruginosa* and *S. aureus*. Zhu et al. [39] used the dried leaves of *C. scolymus* extracted with 75% ethanol. Cynaroside's antimicrobial properties were tested using the diffusion technique at a concentration of 10.0 mg/mL of the extract, and it was shown to have an antibacterial effect on all bacteria tested. Indeed, *Bacillus subtilis*, *S. aureus*, *Agrobacterium tumefaciens, Micrococcus luteus, E. coli*, *S. typhimurium*, and *P. aeruginosa* were sensitive to cynaroside with MIC values of *100,* 50, 200, 200, 200, 200, and 100 μg/mL, respectively.

In contrast, the Akroum et al. [29] studied the antibacterial activity of cynaroside isolated from *M. longifolia* methanolic and ethanolic extracts against certain clinical bacteria. The ethanolic extract was more active than the methanolic extract. However, it showed no growth inhibition against *E. coli* and *P. aeruginosa*. While the minimal inhibitory concentrations (MICs) for the strains tested using the ethanolic extracted were 0.070, 0.095, and 0.050 mg/mL for *S. aureus*, *B. cereus*, and *B. subtilis*, respectively. *In vitro*, the study of Mamadalieva et al. [32] demonstrate that the cynaroside from *S. immaculata* and *S. ramosissima* exerts antibacterial effectiveness against various types of bacteria tested including *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *Staphylococcus pyogenes* ATCC 12344, Methicillin-resistant *Staphylococcus aureus* (MRSA), and *S. aureus* NTCC 10442 with equal MIC values of 0.5 mM. Confirmed by the study of Xiong et al. [37], the antibacterial activity of cynaroside isolated from *L. japonica* leaves was demonstrated against *S. aureus* and *E. coli*. Indeed, the diameters of inhibition zone against *E. coli* and *S. aurens* are 22.9 ± 0.2 mm and 27.4 ± 0.4 mm, respectively. In fact, the cynaroside was the most common constituent in half of the samples EE in the extract of *Chimonanthus salicifolius* S. Y.Hu. [36] improving the sensitivity of bacteria such as *E. coli* (MIC=2.8 μg/mL), *S. aureus* (MIC=317.5 μg/mL), and *B. subtilis* (MIC=1250 μg/mL). Cynaroside purified from the ethanol extract of *Youngia japonic*a was also isolated by Ooi et al. [33] and studied for its antibacterial effect against *Vibrio cholera*, *Vibrio parahaemolyticus*, *B. cereus*, *S. aureus*, *P. aeruginosa*, and *S. typhimurium*. The results showed that this molecule inhibits strain growth with an inhibition zone diameter of 0.7 and 0.8 mm against *V. cholera* and *V. parahaemolyticus*, respectively, while

Table 2
Extraction, identification, and isolation process of cynaroside.

Plants Families	Parts used	Extraction methods	Extraction and isolation parameters	Identification and isolation methods	References
Cuminum cyminum L. Apiaceae	Not reported	Not reported	Not reported	UPLC-Q-TOF-MS	[65]
Thymus migricus Lamiaceae	Leaves	Maceration	Plants were extracted using both water and methanol *Thymus migricus* water extract is prepared by combining 20 g of the powdered air-dried leaves of the plant with 200 mL of distilled water For 12 h, it was fltered and stirred at room temperature A lyophilizer was used to lyophilize the filtrate at 5 mmHg and 50 °C 20 g of air-dried *Thymus migricus* leaves were ground into a powder and combined with 200 mL of methanol to create *Thymus migricus* methanol extract For 12 h, it was stirred at room temperature before being fltered Rotary evaporators were used to evaporate the fltrate (Heidolph 94200)	LC-MS/MS	[71]
Cymbopogon citratus Stapf. Poaceae	Leaves	Infusion	Not reported	HPLC-PDA-ESI/MSn and ^{1}H NMR	[70]
Stachys lavandulifolia Vahl. Lamiaceae	Aerial parts	Maceration	At room temperature, 0.5 kg of shade-dried and ground plant aerial parts were macerated in methanol-water (7:3) (38 L each) The concentrated hydroalcoholic extract was diluted with water and then liquid-liquid fractionated using chloroform and n-butanol The fractions were then dried at 45 °C in a low-pressure rotary evaporator	^{1}H NMR,^{13}C NMR, and UV spectral analysis	[73]-
Mentha piperita Lamiaceae *Mentha longifolia* Lamiaceae	Leaves	Not reported	Not reported	HPLC-DAD	[132]
Capsicum annuum Solanaceae	Seeds	Not reported	Not reported	HPLC	[76]
Launaea capitata Asteraceae	Aerial parts	Maceration	Air-dried aerial portions of *Launaea capitata* ground to a fine powder The sample (500 g) was transferred to a suitable container and soaked using pure methanol and the eluate was concentrated *in vacuo* to obtain 18.37 g of the crude extract Using the gradient elution method, thin layer chromatography (TLC), and high performance liquid chromatography (HPLC), the residue was separated on a silica gel column After loading the extract (4.0 g) onto a silica gel chromatography column (2.5 × 60 cm), it was eluted with methylene chloride followed by a linear gradient of methylene chloride and methanol to 100% MeOH	^{1}H and^{13}C NMR	[77]
Salvia dracocephaloides Boiss. Lamiaceae	Aerial parts	Maceration	We used the maceration technique to extract powder from 300 g of air-dried *Salvia dracocephaloides* aerial parts in three and a half liters of methanol water (8:2) The crude extract (71.68 g) was divided into water (1 L) and organic solvents (31 L) in order of increasing polarity; n-hexane, chloroform, ethyl acetate, and n-butanol The solvent was then evaporated using a rotary evaporator The organic layers were condensed while the residual water portion was frozen at − 20 °C	^{1}H and^{13}C NMR	[78]
Alpinia blepharocalyx K. Zingiberaceae	Seeds	Maceration	At room temperature, 9.0 kg were mercerized with methanol (3 × 20 L) to extract the desired substance A crude methanol extract was obtained by evaporating the solvent extract at low pressure between 40 and 50 °C (950 g) Hexane, ethyl acetate, and butanol were then used in a liquid-liquid extraction technique to separate the crude methanol extract Three crudes were produced when the solvent was	MS, IR, and NMR	[80]

(*continued on next page*)

Table 2 (*continued*)

Plants Families	Parts used	Extraction methods	Extraction and isolation parameters	Identification and isolation methods	References
			recovered at low pressure: crude hexane (20 g), crude ethyl acetate (345 g), crude butanol (189 g), and crude water (126 g) The ethyl acetate crude was isolated by silica gel column chromatography (CC) with hexane/ethylacetate step gradient system (100/1 – 0/1, *v/v*) to yield eight fractions Compound 1 was obtained by further separating the eluted hexane/acetone (10/1, *v/v*) eluted fraction (9.8 g) by CC and purifying it by preparative HPLC (12 mg) Six subfractions were obtained from the initial fraction (43 g) by CC eluting with a hexane/ethyl acetate solvent mixture of 15/1		
Mentha longifolia (L.) Lamiaceae	Leaves and flowers	Soxhlet, maceration, and ultrasonic	Methanol, a 7:3 ethanol and water combination, and water were used as solvents Metabolites were separated chromatographically using an ACQUITY UPLC® BEH C18 column (2.1 150 mm, 1.7 m) with water (mobile phase A) and acetonitrile with 0.1% formic acid (mobile phase B) at 40 °C Holding for 0.5 min the starting gradient composition of 95% A/5% B, increasing to 80% B in 10 min, decreasing to 0% A in 10.01 min, and holding for 1.90 min	HPLC-DAD method	([82]
Chrysanthemum morifolium Compositae *Scutellaria baicalensis* Labiatae	No reported	Decoction	Not reported	LC-MS/MS	[81]
Acantholippia salsoloides Verbenaceae	Leaves and flowers	Infusion	Not reported	Ion-trap mass spectrometry with flame ionization detection *via* gas chromatography	[84]
Capsicum Cultivars Solanaceae	Leaves	Not reported	Not reported	HPLC-MS	[85]
Lavandula stoechas Lamiaceae	Not reported	Not reported	Not reported	HPLC/ESI-MS	[86]
Lonicera japonica flos Caprifoliaceae	Not reported	Not reported	Not reported	HPLC	[87]
Aronia melanocarpa Rosaceae *Aronia arbutifolia* Rosaceae *Aronia prunifolia* Rosaceae	Leaves and fruits	Not reported	Air dried sample sizes (0.5 g) were taken from stems and leaves harvested at the end of three separate 4-week growth cycles A modified HPLC-DAD technique was used to estimate the levels of the polyphenols under investigation These are the test conditions: Mobile phase: A-methanol: 0.5% acetic acid (1:4 *v/v*); B-methanol (gradient program); flow rate: 1 mL min-1; injection volume: 10 l; detection wavelength: 254 nm; analytical column: Purospher RP-18e; 4 mm 250 mm 5 mL; Merck)	HPLC-DAD	[88]
Elsholtiza bodinieri Lamiaceae	Not reported	Not reported	Not reported	HPLC, ESI-MS, and NMR	[55]
Salvia plebeia R. Br. Lamiaceae	Aerial parts	Maceration	Powder (1.0 g) was suspended in extract solvents (methanol: water: formic acid, 50:45:5, *v/v/v* for flavonoids and methanol: water: formic acid, 80:15:5, *v/v/v* for phenolic acids) containing the internal standard, and the mixture was extracted for 5 min at 200 rpm on an orbital shaker The mixture was centrifuged at 4 °C for 10 min at 3000 rpm Each supernatant was filtered using a 0.2 μm polyvinylidene fluoride (PVDF) syringe filter (Whatman, Kent, England), and then 0.5 mL of phenolic extract was mixed with 4.5 mL of water to make 5 mL of a phenolic-containing crude extract Finally, the phenolic concentration was separated from the crude extract using the solid phase extraction technique using a Sep-pak C18 cartridge (Waters Co., Milford, MA, USA) Sep-pak cartridges were conditioned with 2 mL of water, then activated with 2 mL of methanol After the flavonoid extract was diluted, it was placed into a cartridge and washed with 2 cc of	UPLC-DAD-QTOF/MS	[89]

(*continued on next page*)

Table 2 (*continued*)

Plants Families	Parts used	Extraction methods	Extraction and isolation parameters	Identification and isolation methods	References
			water to eliminate contaminants. We next used 3 mL of methanol to elute the cartridge and recover the whole phenolic mixture		
Lagotis integrifolia (Willd.) Schischk Scrophulariaceae	Not reported	Soxhlet	Dried and powdered plant material (600 g) was extracted six times with 1 L 70% EtOH using the Soxhlet equipment, and the combined extract was concentrated under decreased pressure The residue was first suspended in H_2O, then split into four 0.5 L volumes of hexane, chloroform, ethyl acetate, and butanol The ethyl acetate extract (6.4 g) was subjected to chromatography on silica gel and eluted with chloroform/methanol (100:1→1:1) Fractions containing similar content was combined and concentrated The E-1 compound was isolated with 10 mg yield	MS,^{1}H,^{13}C, HSQC, HMBC, and^{1}H-1 H COSY NMR	[92]
Cynara scolymus L. Asteraceae	Not reported	Decoction	Not reported	RP-HPLC-DAD	[116]
	Leaves	Ultrasonic	The leaves of a frozen artichoke were pulverized using a mortar and a pestle and some liquid nitrogen Following 30 min in an ultrasonic bath, the powder (20 mg) was homogenized with 4 mL 60% MeOH containing 10 g/mL umbelliferone (as internal standard) The extracts were then filtered through a 22 mL Millipore filter after being vortexed and centrifuged at 10,000 g for 10 min to get rid of any remaining plant debris	UHPLC–PDA-MS	[117]
	Leaves, outer bracts, heads, and stems	Maceration	Not reported	HPLC-DAD and HPLC-MS	[120]
	Leaves	Infusion	Two extractions of 300 g of dried Green Globe artichoke heads each in 2000 mL of 70% methanol were performed Under vacuum, the extract was concentrated until dry, and then the residue was mixed with water (300 mL) and chloroform (3 × 300 mL) to be separated The water layer was then extracted thrice using ethyl acetate (3 × 300 mL) and n-butanol (3 300 mL) in that order	MS and NMR ^{1}H NMR and^{13}C NMR	[123]
	Leaves	Ultrasonic	The 80 mg of dried extract used in the quantification tests was dissolved in 2.00 mL of methanol solution containing 15% (*v/v*) water using a sonicator for 5 min Before injection, each solution was filtered through 0.45 μm cellulose acetate membrane filters (Sartorius, G6ttingen, Germany)	HPLCMS and by 1D and ^{2}D NMR	[124]
	Seeds	Not reported	Not reported	Ultra-voilet absorption spectra	[126]
Cymbopogon citratus Poaceae	Leaves	Infsion	150 mL of boiling water were added to 5 g of dried leaves were ground into a powder and then steeped in boiling water for 15 min The polyphenol-rich fractions follow	HPLC-PDA-ESI/MSn	[97]
Gentianella azurea Gentianaceae	Leaves and flowers	Maceration	Air-dried, ground herb of *Gentianella azurea* (sample GaH3; 1.7 kg) was extracted with 70% EtOH (60 °C, ×3), and the combined extracts were partitioned with $CHCl_3$ (Ga-F1, 108.3 g), EtOAc (Ga-F2, 159.8 g), and n-BuOH (Ga-F3, 283.9 g), respectively	HPLC	[94]
Bidens tripartita Asteraceae	Aerial parts	Maceration	For the LC-MS and HPLC analyses, we employed chromatographic grade double-distilled water, analytical grade trifluoroacetic acid, and HPLC grade methanol and acetonitrile	LC-MS and HPLC analysis	[46]
Tilia rubra subsp. *Caucasica* Tiliaceae	Leaves	Maceration	Macerating powdered, shade-dried leaves (170 g) in a solution of 80% methanol in water (5 × 1 L) yielded a complete hydroalcoholic extract After defatting the whole extract using sufficient amounts of petroleum ether and chloroform, it was concentrated using a rotary evaporator at 45 °C	UV,^{1}H NMR, and^{13}C NMR	[102]
Carthamus tinctorius L. Asteraceae	Flowers	Infusion	The August 2013 harvest of 100 g of air-dried safflower flowers was subjected to three extractions with 70% EtOH: the first two took place at room temperature for 24 h each, while the third was conducted in a boiling water bath for 30 min	1 H NMR-, UV-spectroscopy, and mass spectrometry	[101]

(*continued on next page*)

Table 2 (*continued*)

Plants Families	Parts used	Extraction methods	Extraction and isolation parameters	Identification and isolation methods	References
			Evaporating the water-alcoholic extract under vacuum reduced the volume to 50 mL, which was then combined with 30 g of silica gel L 40/100 and dried A powdered version of a chloroform solution (dried extract with silica gel), applied to a silica gel layer (5 cm in height and 8 cm in diameter) $CHCl_3$ and $CHCl_3$-EtOH mixtures of varying concentrations were used to elute the chromatographic column (99:1; 98:2; 97:3; 95:5; 93:7; 90:10; 85:15; 80:20; 70:30, 60:40, 50:50) TLC analysis was used to track progress in 100-mL increments (Sorbfil PTLC-AF-A-UV, solvent systems $CHCl_3$-EtOH, 9:1; CHCl3-EtOH-H2O, 26:16:3; and n-butanol-glacial acetic acid-water, 4:1:2) Precipitate from compound 1 that had fallen into one of the mixed fractions was collected, and then the compound was crystallized from EtOH water		
Lonicera japonica Caprifoliaceae	Flowers	Soxhlet and ultrasonic	1 g of dried plant material was rehydrated in fifty milliliters of 70% (*v/v*) ethanol over the course of 24 h The sample was then transferred to a clean polyethylene bag After bringing the extracts to room temperature, they were centrifuged at 2000 rmn1 for 5 min, and the resulting supernatants were combined and kept at 4 °C for later HPLC analysis	HPLC-DAD	[99]
Centaurea scoparia Asteraceae	Aerial parts	Maceration	At room temperature, 5 kg of dried, powdered *Centaurea scoparia* leaves and stems were extracted four times (10 L each) with 70% EtOH The combined extracts' solvent was evaporated under reduced pressure at a temperature no higher than 40 °C until dry, yielding a crude residue of 275 g This was then partitioned three times with one liter each of hexane, ethyl acetate, and n-butanol to produce 70 g of hexane, 50 g of ethyl acetate, and 30 g of n-butanol (75 g) A column (150 × 4 cm) packed with 600 g of polyamide 6 S was used to fractionate the ethyl acetate extract The elution gradient began with water and progressed through a series of progressively less polar H_2O/EtOH solutions (10: 0, 9: 1, 8: 2, 7: 3, 6: 4, 5: 5, 4: 6, 3: 7, 2: 8, 1: 9, and 0: 10)	1D and ^{2}D NMR, UV, IR, and mass spectroscopy	[103]
Anthriscus sylvestris (L.) Apiaceae	Aerial parts	Not reported	Not reported	The use of ^{1}H,^{13}C, attached proton test (APT), heteronuclear single quantum correlation (HSQC), and heteronuclear multiple bond correlation (HMBC) NMR spectroscopy, as well as EPR spectroscopy	[38]
Polygonum orientale Polygonaceae	Not reported	Not reported Infusion	Not reported Extraction solutions were mixed, filtered, concentrated under decreased pressure, and ethanol was precipitated from dried *Polygonum orientale* that had been refluxed with boiling water (3 times, 1:10, *w/v*) for 1 h Precipitate was discarded after ethanol was extracted at low pressure Four times, residue was dissolved in water and extracted with n-butanol (2:1, *v/v*) to get an extract with a concentration of 1 g/mL After removing the nbutanol at a lower pressure, the residue was dissolved in 80% ethanol, put onto a polyamide column, and then eluted with the same solvent The *Polygonum orientale* extract was obtained by drying the plant under low pressure	UPLC–ESI-MS/MS UPLC–MS/MS	[134] [104]
Dracocephalum palmatum Stephan. Lamiaceae	No reported	Not reported	A 60% EtOH extract of the *Dracocephalum palmatum* plant was partitioned with $CHCl_3$, EtOAc, and n-BuOH to obtain three fractions, which were separated by CC (gel permeation, normal phase silica gel (NP-SiO_2) and reverse phase silica gel (RP-SiO_2), XAD, polyamide chromatography), preparative (prep)	HPLC-UV	([107]

(*continued on next page*)

Table 2 (*continued*)

Plants Families	Parts used	Extraction methods	Extraction and isolation parameters	Identification and isolation methods	References
Sophora flavescens Soland. Fabaceae	Aerial parts	Infusion	Subterranean component (raw material no. TsH0702) Five times in a boiling water bath, the powdered raw material (400 g) was extracted with 70% EtOH (1:15) Liquid-phase extraction with C_6H_{14}, $CHCl_3$, and EtAc was performed on the water residual after the alcohol fraction had been concentrated there Hexane (at 5.28 g, 1.32% of the air-dried raw material mass), chloroform (at 26.24 g, 6.56%), ethylacetate (at 5.92 g, 1.48%), and water (at 117.68 g, 29.42%) were the resulting fractions After separating the chloroform fraction (20 g) using CC on SiO_2 (3 40 cm) in a hexan EtAc (100: 0 60: 40) gradient system, the resultant fractions were rechromatographed on Sephadex LH20 (2 × 50 cm) in a $CHCl_3$ EtOH (100: 0 85: 15) system, and preparative TLC was performed (solvent systems 1 and 2)	^{1}H and^{13}C NMR	[108]
Scutellaria immaculata Lamiaceae *Scutellaria ramosissima* Lamiaceae	Aerial parts and roots	Maceration	The final concentration of all samples was 20 mg per 1 mL of methanol Rheodyne injectors were used with the HPLC system (Merck-Hitachi L-6200A) (20 mL loop) A 5 mm RP-C18e LichroCART 250–4 column was used for separation (Merck, Darmstadt, Germany). A) HPLC grade water from VWR (Fontenay-Sous-Bois, France) containing 0.5% formic acid (Merk (Darmstadt, Germany)), and B) acetonitrile made up the mobile phase (J. T. Backer, Deventer, Holland) For the methanol and chloroform fractions, the gradient program ran from 0% to 50% B in 50 min, and then to 100% in 5 min; for the water fraction, the program ran from 0% to 25% B in 50 min, and then to 100% in 5 min	LC-MS	[32]
Salvia limbata Lamiaceae	Aerial parts	Maceration	*Salvia limbata* (836 g) dried aerial parts were chopped into pieces and extracted with ethyl acetate and methanol at room temperature Hexane: acOEt (19:1, 9:1, 1:1, 0:1) was used in silica gel CC on the ethyl acetate extract (38.4 g) to produce nine fractions (A–I) After passing 1 g of fraction G through silica gel CC in a 1:1 hexane: acOEt mixture, we obtained five different fractions (G1–G5) After submitting fraction G5 to sephadex LH20 CC using methanol as the eluent, we were able to isolate pure component 1. (235 g) Pure compounds 2, 3, 4, and 5 were obtained by passing Fraction H through sephadex LH20 CC twice using AcOEt: MeOH (1: 4) as eluent (5.5 mg)	^{1}H- and^{13}C NMR	[111]
Bidens tripartita L. Asteraceae	Flowers	Maceration	2 g of dried, powdered plant material was extracted using petrol (5 × 50 mL) and chloroform (5 × 50 mL) in that order Second, 6 × 50 mL of 70% methanol was added to the plant remains and heated at a reflux for 2 h After evaporating the mixed extracts until dry, they were redissolved in 20 mL of 40% methanol containing 0.5% ortho-phosphoric acid An aliquot (20 L) was injected onto the HPLC column after a 5 mL sample of the solution was filtered *via* a Chromafil O-45/25 (PTFE 25 mm, 0.45 m, Macherey-Nagel, Germany)	HPLC analysis	[96]
Halenia corniculata L. Gentianaceae *Pyrola rotundifolia* L. Ericaceae *Pyrola incarnate* Ericaceae	Aerial parts	Not reported	All flavonoids were isolated from the ethylacetate fraction of the related plants according to the general procedure for the isolation of phenolic compounds from plant origins The purification of isolated compounds was done by CC and crystallization from methanol or ethanol following the determination of purity by TLC on pre-coated Silicagel 60 F 254 aluminium sheets gradually spraying with 1% of methanol diphenylboric acid-β-ethylamino ester (NP) and 5% of ethanol polye	^{13}C NMR	[57]
Digitalis ciliata Plantaginaceae	Leaves	Not reported	Not reported	NMR and mass spectroscopy	[128]

(*continued on next page*)

Table 2 (*continued*)

Plants Families	Parts used	Extraction methods	Extraction and isolation parameters	Identification and isolation methods	References
Phlomis tuberosa (L.) Labiatae	Leaves and fruits	Not reported	Not reported	IR spectrum	[130]

no inhibition was exerted against *B. cereus, S. aureus*, *P. aeruginosa*, and *S. typhimurium*. The *Echium arenarium* plant was also used as a plant source for cynaroside extraction. Kefi et al. [31] studied *in vitro* its antibacterial activity against *Listeria monocytogenes* (ATCC 19115), MRSA ATCC 2592, *Salmonella*, *E. coli, S. aureus* (ATCC 29212), *B. cereus* (ATCC 14579), *P. aeruginosa* (ATCC 27853), *E. coli* (ATCC 35214), and *Klebsiella pneumonia* (CIP 104727). The MIC of *E. arenarium cynaroside* extract were 1000 μg/mL for *L. monocytogene;* 62 μg/mL for both MRSA; 125 μg/mL for *S. aureus*, 500 μg/mL for both *Enterrococcus faecalis* and *B. cereus* MIC= 500 ug/mL, while it was above 1000 μg/mL for *P. aeruginosa, E. coli,* and *K. pneumonia*.

Salawu et al. [34] examined the antibacterial effects of *V. amygdalina* phenolic extracts. The phenolic compound was characterized by reversed phase HPLC/DAD/MS. Luteolin, luteolin 7-*O*-glucoside (cynaroside), and luteolin 7-O-glucuronide were the most important chemicals found in *V. amygdalina*, with the latter being the most abundant flavonoid. The powdered sample was extracted with ethanol-water (7/3) and filtered. Additionally, *B. cereus*, *E. coli*, *Salmonella* spp., *P. aeruginosa*, *Staphylococcus aeruginosa*, *Shigella* spp., *Enterobacter*, *Clostridium sporogenes*, *B. subtilis*, and *Proteus vulgaris* were used to test the antimicrobial properties of the extracts using the agar-well diffusion technique. Results indicate that, except *S. aereus* and *Shigella* spp, the three different concentrations tested (10 mg/mL; 25 mg/mL and 50 mg/mL) of cynoroside are active against the rest of strains tested.

4.2. Antileishmanial activity

Tabrez et al. [41] evaluated the antileishmanial properties of a purchased cynaroside through test-tube experiments. The 50% inhibitory concentration (IC_{50}) value of cynaroside against leishmanial cells *in vitro* was 49.49 ± 3.515 M, and this activity decreased with time. Associated with miltefosine, even at a dose of 20 M, it severely blocked parasite development. Kefi et al. [31] investigated the *in vitro* antileishmanial activity of *E. arenarium.* The ethyl acetate extract yielded the highest concentration of cynoroside (288 60.56 g/mg), making it the most abundant constituent in the organic extracts. Two species of Leishmania, *Leishmania infantum* and *Leishmania major*, were used to test the extract. The MTT (3-(4,5- dimethylthiazol-2-yl)− 2,5-diphenyl tetrazolium bromide) assay was used to determine parasite vitality. The active extract showed action against *L. infantum* (IC_{50} = 8.66 ± 0.24 g/mL) and *L. major* (IC_{50} = 10.7 ± 0.59 g/mL). It also showed a strong antiamastigote action against both *L. major* (IC_{50} = 22.48 ± 0.14 g/mL) and *L. infantum* (IC_{50} = 18.59 ± 0.09 g/mL).

4.3. Antifungal activity

The antifungal activity of cynaroside against many fungi was reported in several works [30,32,33,36,38–40]. Table summarizes all studies that have evaluated the antifungal activity of cynaroside, including its origin, type of assay, tested strains, and key results.

The antifungal efficacy of the extracts will be evaluated. Indeed, concerning *B. tripartita* herbs, Tomczykowa et al. [40] subjected the plant to three different extraction methods, including those using water, methanol/water, acetone/water, and methanol. The dominant flavonoid in *B. tripartita* herb was cynaroside. *Candida albicans* ATCC 10231, *C. parapsilosis* ATCC 22019, *Aspergillus fumigatus*, and *A. terreus* were the organisms challenged in this experiment. The tested organisms used in this study were *C. albicans* ATCC 10231, *C. parapsilosis* ATCC 22019, *A. fumigatus*, and *A. terreus*. Fungies were tested by the disc diffusion test and broth microdilution method. Therefore, for each fungi tested, different results were recorded according to the three concentrations of the extract: *C. albicans* [MIC > 100 mg/mL (Water extract); I. Z. Φ = 0 mm (Water extract); MIC > 100 mg/mL (Methanol/Water extract); I. Z. Φ = 0 mm (Methanol/Water extract); MIC > 100 mg/mL (Acetone/Water extract); I. Z. Φ = 0 mm (Acetone/Water extract)], *C. parapsilosis* [MIC > 100 mg/mL (Water extract); I. Z. Φ = 0 mm (Water extract); MIC > 100 mg/mL (Methanol/Water extract); I. Z. Φ = 0 mm (Methanol/Water extract); MIC > 100 mg/mL (Acetone/-Water extract); I. Z. Φ = 0 mm (Acetone/Water extract)], *A. fumugatus* [MIC > 100 mg/mL; (Water extract); I. Z. Φ = 0 mm (Water extract); MIC > 100 mg/mL; (Methanol/Water extract); I. Z. Φ = 0 mm (Methanol/Water extract); MIC > 100 mg/mL; (Acetone/Water extract); I. Z. Φ = 0 mm (Acetone/Water extract)], *A. terreus* [MIC > 100 mg/mL; (Water extract); I. Z. Φ = 0 mm (Water extract); MIC > 100 mg/mL; (Methanol/Water extract); I. Z. Φ = 0 mm (Methanol/Water extract); MIC > 100 mg/mL (Acetone/Water extract); I. Z. Φ = 0 mm (Acetone/Water extract)].

Žemlička et al. [38] extracted cynoroside from the aerial parts of wild chervil, *A. sylvestris* (L.) Hoffm by acetone and ethyl acetate, and then used in disc diffusion (5 mm) assay was saturated with 20 μg/disc on *Saccharomyces cerevisiae*, *C. albicans*, *Alternaria alternata*, *Aspergillus niger*, *Penicillium purpurogenum*, *Rhizopus oryzae*, *Trichophyton interdigitale*, *Rhodotorula glutinis*, which showed an effect only on *R. glutinis* with an inhibition zone of 12 mm without any inhibition for the rest of the fungi. Zhu et al. [39] used the dried leaves of *C. scolymus* extracted with 75% ethanol. The antifungal potency of cynaroside was investigated by disc (6.0 mm in diameter) using the diffusion method impregnated with 25 μL of the extract at a concentration of 10.0 mg/mL then placed on the inoculated plates. Cynaroside showed antifungal activity against *B. subtilis* (MIC= 100 μg/mL), *S. aureus* (MIC = 50 μg/mL), *A. tumefaciens* (MIC = 200 μg/mL), *M. luteus* (MIC = 200 μg/mL), *E. coli* (MIC = 200 μg/mL), *S. typhimurium* (MIC = 200 μg/mL), and *P. aeruginosa* (MIC = 100 μg/mL). Additionally, Mamadalieva et al. [32] studied the antimicrobial activity of cynaroside from *S. immaculata* and *S. ramosissima*, the antifungal activity was evaluated *in vitro* by diffusion and microdilution methods. The standard strains were *C. albicans* and *Candida glabata*, without any activity on both fungi. Chiruvella et al. [30] used *Soymida febrifuga* (roxb.) A. Juss. root callus extracted with hexane, ethyl acetate, and methanol hexane. These extracts were used separately to extract cynaroside. The disc diffusion method was used to evaluate *A. fumigatus*, *A. niger*, *Alternaria alternate* at two cynaroside concentrations (200 and 400 μg/disc). The results showed that *A. fumigatus* present IZ (200 μg/disc) = 10.2 ± 0.15 and IZ (400 μg/disc) = 17.5 ± 0.42, *A. niger* IZ (200 μg/disc) = 11.7 ± 0.38 and IZ (400 μg/disc) = 14.6 ± 0.13, and *A. alternate* IZ (200 μg/disc) = 15.2 ± 0.83 IZ (400 μg/disc) = 18.2 ± 0.67. Wang et al. [36] prepared ethanol extracts from *Chimonanthus salicifolius* S.Y. Hu. leaves by ethanol gradient elution and evaluated them by high-performance liquid chromatography-diode array detector (HPLC-DAD). Antifungal activity was determined using the broth microdilution technique against several fungal strains, namely *S. cerevisiae* (CICC 1340), *S. cerevisiae* (CICC 1540), *Penicillium digitatum* (AS3.5752), *A. niger*, and *Cephalckiscus Fiagans*. Half of the EE samples tested positive for cynaroside. The results showed for each strain tested promising results; *S. cerevisiae* (CICC 1340) (MIC = 156 μg/mL and MBC = 317.5 μg/mL), *S. cerevisiae* (CICC 1540) (MIC = 156 μg/mL and MBC = 317.5 μg/mL), *P. digitatum* (AS3.5752) (MIC = 156 μg/mL and MBC = 156 μg/mL), and *A. niger* (MIC = 156 μg/mL and MBC = 1250 μg/mL).

Table 3
Antibacterial activity.

Origins	Methods used	Strains tested	Key results	References
Bidens tripartita Fresh herb	Disc diffusion method Broth microdilution method	*Bacillus subtilis* *Micrococcus luteus* *Staphylococcus aureus* *Escherichia coli* *Escherichia coli* (B-lactamase+) *Klebsiella pneumonia* *Pseudomonas aeruginosa*	MIC = 3.1 mg/mL; (Water extract) Inhibition zone (I. Z.) Φ = 15 mm; (Water extract) MIC = 3.1 mg/mL; (Methanol/Water extract) I. Z. Φ = 15 mm(Methanol/Water extract) MIC = 3.1 mg/mL; (Acetone/Water extract) I. Z. Φ = 16 mm; (Acetone/Water extract) MIC = 3.1 mg/mL; (Water extract) I. Z. Φ = 16 mm; (Water extract) MIC = 6.2 mg/mL; (Methanol/Water extract) I. Z. Φ = 14 mm(Methanol/Water extract) MIC = 1.5 mg/mL; (Acetone/Water extract) I. Z. Φ = 16 mm; (Acetone/Water extract) MIC = 1.5 mg/mL; (Water extract) I. Z. Φ = 17 mm; (Water extract) MIC = 3.1 mg/mL; (Methanol/Water extract) I. Z. Φ = 12 mm; (Methanol/Water extract) MIC = 3.1 mg/mL; (Acetone/Water extract) I. Z. Φ = 13 mm; (Acetone/Water extract) MIC = 12.5 mg/mL; (Water extract) I. Z. Φ = 9 mm; (Water extract) MIC = 12.5 mg/mL; (Methanol/Water extract) I. Z. Φ = 8 mm; (Methanol/Water extract) MIC = 6.2 mg/mL; (Acetone/Water extract) I. Z. Φ = 10 mm; (Acetone/Water extract MIC = 12.5 mg/mL; (Water extract) I. Z. Φ = 7 mm; (Water extract) MIC = 25 mg/mL; (Methanol/Water extract) I. Z. Φ = 10 mm; (Methanol/Water extract) MIC = 25 mg/mL; (Acetone/Water extract) I. Z. Φ = 8 mm; (Acetone/Water extract) MIC = 50 mg/mL; (Water extract) I. Z. Φ = 6 mm; (Water extract) MIC = 25 mg/mL; (Methanol/Water extract) I. Z. Φ = 8 mm; (Methanol/Water extract) MIC = 12.5 mg/mL; (Acetone/Water extract) I. Z. Φ = 7 mm; (Acetone/Water extract) MIC = 50 mg/mL; (Water extract) I. Z. Φ = 7 mm; (Water extract) MIC > 100 mg/mL; (Methanol/Water extract) I. Z. Φ = 6 mm; (Methanol/Water extract) MIC > 100 mg/mL; (Acetone/Water extract) I. Z. Φ = 0 mm; (Acetone/Water extract)	[40]
Anthriscus sylvestris (L.) Hoffm	Disc diffusion method	*Escherichia coli* *Proteus* sp. *Salmonella typhimurium* *Pseudomonas aeruginosa*	I. Z. Φ = 12 mm I. Z. Φ = 13 mm Reduced the biofilm development of *Pseudomonas aeruginosa* and *Staphylococcus aureus* and increased the incidence of mutations leading to ciprofloxacin resistance in *Salmonella typhimurium*	[38]
Cynara scolymus L.) leaves	Disc diffusion method	*Bacillus subtilis* *Staphylococcus aureus* *Agrobacterium tumefaciens* *Micrococcus luteus* *Escherichia coli* *Salmonella typhimurium* *Pseudomona aeruginosa*	MIC = 100 μg/mL MIC = 50 μg/mL MIC = 200 μg/mL MIC = 200 μg/mL MIC = 200 μg/mL MIC = 200 μg/mL MIC = 100 μg/mL	[39]
Mentha longifolia	Agar diffusion method	*Escherichia coli* *Staphylococcus aureus* *Bacillus cereus* *Pseudomonas aeruginosa* *Bacillus subtilis*	- MIC = 0.070 mg/mL MIC = 0.095 mg/mL - MIC = 0.050 mg/mL	[29]
Scutellaria immaculata *Scutellaria ramosissima*	Diffusion method and microdilution method	*Staphylococcus aureus* *Streptococcus pyogenes* *Escherichia coli* *Pseudomonas aeruginosa*	MIC = 0 I. Z. Φ = 0.5 mm MMC > 0.5 MIC = 0 I. Z. Φ = 0.5 mm MMC > 0.5 MIC = 0 I. Z. Φ = 0.5 mm MMC > 0.5 MIC = 0	[32]

(*continued on next page*)

Table 3 (*continued*)

Origins	Methods used	Strains tested	Key results	References
			I. Z. Φ = 0.5 mm MMC > 0.5	
Soymida febrifug *Callus cultures*	Disc diffusion	*Klebsiella pneumonia* *Salmonella typhimurium* *Proteus vulgaris* *Pseudomonas aeruginosa* *Bacillus subtilis* *Escherichia coli* *Staphylococcus aureus*	I. Z. Φ (200 μg/disc) = 10.0 ± 0.16 mm I. Z. Φ (400 μg/disc) = 12.5 ± 0.67 mm I. Z. Φ (200 μg/disc) = 10.5 ± 0.50 mm I. Z. Φ (400 μg/disc) = 14.3 ± 0.00 mm I. Z. Φ (200 μg/disc) = 11.1 ± 0.36 mm I. Z. Φ (400 μg/disc) = 13.0 ± 0.25 mm I. Z. Φ (200 μg/disc) = no inhibition I. Z. Φ (400 μg/disc) = 11.3 ± 0.37 mm I. Z. Φ (200 μg/disc) = 10.4 ± 0.70 mm I. Z. Φ (400 μg/disc) = 11.6 ± 0.34 mm I. Z. Φ (200 μg/disc) = 11.6 ± 0.34 mm I. Z. Φ (400 μg/disc) = 11.0 ± 0.43 mm I. Z. Φ (200 μg/disc) = no inhibition I. Z. Φ (400 μg/disc) = 10.4 ± 0.52 mm	[30]
Lonicera japonica Thunb.	Disk diffusion assay	*Escherichia coli* *Staphylococcus aureus*	I. Z. Φ = 22.9 ± 0.2 mm I. Z. Φ = 27.4 ± 0.4 mm	[37]
Chimonanthus salicifolius S. Y.Hu. leaves	Broth microdilution method	*Escherichia coli* *Staphylococcus aureus* *Bacillus subtilis*	MIC = 2.8 μg/mL MBC > 2500 μg/mL MIC = 317.5 μg/mL MBC > 2500 μg/mL MIC = 1250 μg/mL MBC > 2500 μg/mL	[36]
Youngia japonica	Disk diffusion assay	*Vibrio cholera* and *Vibrio parahaemolyticus*	I. Z. Φ = 0.7 cm I. Z. Φ = 0.8 cm	[33]
Echium arenarium	Disk diffusion assay	*Listeria monocytogenes* *Staphylococcus aureus* *Methicillin-resistant Staphylococcus aureus* *Enterrococcus faecalis* *Bacillus cereus* *Pseudomonas aeruginosa* *Escherichia coli* *Klebsiella pneumonia*	MIC = 1000 μg/mL MIC = 62 μg/mL MIC = 62 μg/mL MIC = 125 μg/mL MIC = 500 μg/mL MIC = 500 μg/mL MIC > 1000 μg/mL MIC > 1000 μg/mL MIC > 1000 μg/mL	[31]
Veronica amygdalina	Agar-well diffusion method	*Staphylococcus aereus* *Bacillus cereus* *Shigella* spp.	No inhibition (at 10 mg/mL) I. Z. Φ = 0.69 mm (at 25 mg/mL) I. Z. Φ = 1.21 mm (at 50 mL/mL) I. Z. Φ = 0.4 mm (at 10 mg/mL) I. Z. Φ = 0.81 mm (at 25 mg/mL) I. Z. Φ = 1.32 mm (at 50 mL/mL) No inhibition (at 10 mg/mL) I. Z. Φ = 0.52 mm (at 25 mg/mL) I. Z. Φ = 0.82 mm (at 50 mL/mL)	[34]

Ooi et al. [33] examined the ethanolic extract of *Y. japonica* with a disc diffusion assay. This extract was then used to isolate and characterize three anti-fungal agents (3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, and luteolin-7-O-glucoside). The diameter of the inhibition zone induced by cynaroside's antifungal action against *B. cereus* was only 0.7 cm.Tables 4–6.

4.3.1. Antioxidant activity

Cynaroside has been investigated for its antioxidant effect by several studies [35,42–48]. Its protective activity against H_2O_2-induced apoptosis in H9c2 cardiomyoblasts will be demonstrated, Xiao et al. [47] examined the antioxidant effect of cynaroside on oxidative damage in cardiac myocytes. Cynaroside pretreatment for 4 h was applied to H9c2 cells, with addition of H_2O_2 (150 mM) for 6 h. Therefore, pretreatment with cynaroside showed promising results. Superoxide dismutase, glutathione peroxidase, and catalase are all endogenous antioxidant enzymes that act energetically to prevent ROS production in the cell. Cynaroside inhibited ROS production, which in turn reduced the damage to mitochondrial membrane potential caused by hydrogen peroxide. It also enhanced the expression of the anti-apoptotic protein Bcl-2 and lowered that of pro-apoptotic protein Bax. Cynaroside suppressed the upregulation of c-Jun N-terminal kinase (JNK) and p53 protein expression triggered by H_2O_2. Cynaroside was detected by Elansary et al. [42] when examining the polyphenol profiles of methanolic leaf extracts of *M. piperita* and *M. longifolia*. In addition, antioxidant activity was explored using β-carotene bleaching, FRAP (ferric reducing antioxidant power), and DPPH (2,2-Diphenyl-1-picrylhydrazyl) assays. Chromatographic analyses revealed an amount of cynaroside (162.8 mg/100 g DW) in *M. piperita* leaves. The IC_{50} values were 6.9 ± 0.1 μg/mL, 8.2 ± 0.1 mM TEAC/g Extract, and 6.3 ± 0.1 μg/mL for β-carotene bleaching, FRAP, and DPPH assays, respectively.

To demonstrate the antioxidant activity of cynaroside in protecting ARPE-19 cells against H_2O_2-induced oxidative stress, Yu et al. [48] used cynaroside (100 μL) which was added to ARPE-19 cells cutured in CO_2 with the positive control NAC. Intracellular ROS generation was measured, followed by intracellular activities of bicinchoninic acid-binding proteins (CAT, SOD, GSH, and MDA) detection and Western blot analysis. Very low concentrations of cynaroside (500 *vs.* 100 μM) revealed substantial antioxidant and anti-apoptotic effects. Cynaroside protected ARPE19 cells from apoptosis through down-regulation of caspase-3 protein activation, which was controlled by upstream proteins; Bcl2 and Bax. Cynaroside effectively inhibited oxidative stress-induced apoptosis in ARPE19 cells through the regulation of related enzymes activation and protein expression. Cynaroside was shown to increase antioxidant and antiapoptotic capacity of ARPE19 cells *via* increased pAkt expression. Kim et al. [43] isolated and characterized the antioxydante componds from the aerial parts of *A. keiskei*, the cynaroside was extracted with boiling water, the extracted

Table 4
Antifungal activity.

Origins	Methods Used	Strains tested	Key results	References
Bidens tripartita Fresh herb	Disc diffusion test And broth microdilution method	*Candida albicans* *Candida parapsilosis* *Aspergillus fumugatus* *Aspergillus terreus*	MIC > 100 mg/mL; (Water extract) I. Z. Φ = 0 mm; (Water extract) MIC > 100 mg/mL; (Methanol/Water extract) I. Z. Φ = 0 mm; (Methanol/Water extract) MIC > 100 mg/mL; (Acetone/Water extract) I. Z. Φ = 0 mm; (Acetone/Water extract) MIC > 100 mg/mL; (Water extract) I. Z. Φ = 0 mm; (Water extract) MIC > 100 mg/mL; (Methanol/Water extract) I. Z. Φ = 0 mm; (Methanol/Water extract) MIC > 100 mg/mL; (Acetone/Water extract) I. Z. Φ = 0 mm; (Acetone/Water extract) MIC > 100 mg/mL; (Water extract) I. Z. Φ = 0 mm; (Water extract) MIC > 100 mg/mL; (Methanol/Water	[40]
Anthriscus sylvestris (L.) Hoffm	Disc diffusion method	*Rhodotorula glutinis*	I. Z. Φ = 12 mm	[38]
Cynara scolymus L. Leaves	Disc diffusion method	*Candida albicans* *Saccharomyces cerevisiae* *Saccharomyces carlsbergensis* *Aspergillus niger* *Penicillum oxalicum* *Candida lusitaniae* *Mucor mucedo* *Cladosporium cucumerinum*	MIC = 50 μg/mL MIC = 50 μg/mL MIC = 200 μg/mL MIC = 100 μg/mL MIC = 50 μg/mL MIC = 50 μg/mL MIC = 50 μg/mL MIC = 50 μg/mL	[39]
Scutellaria immaculata *Scutellaria ramosissim*	Diffusion method and microdilution method	*Candida albicans* *Candida glabata*	MIC = not active I. Z. Φ = not active MMC = not active MIC = not	[32]

(*continued on next page*)

Table 4 (*continued*)

Origins	Methods Used	Strains tested	Key results	References
			active I. Z. Φ = not active MMC = not active	
Soymida febrifug cultures	Disc diffusion method	*Aspergillus fumigatus* *Aspergillus niger* *Alternaria alternata*	I. Z. Φ (200 µg/disc) = 10.2 ± 0.15 mm I. Z. Φ (400 µg/disc) = 17.5 ± 0.42 mm I. Z. Φ (200 µg/disc) = 11.7 ± 0.38 mm I. Z. Φ (400 µg/disc) = 14.6 ± 0.13 mm I. Z. Φ (200 µg/disc) = 15.2 ± 0.83 mm I. Z. Φ (400 µg/disc) = 18.2 ± 0.67 mm	[30]
Chimonanthus salicifolius S. Y.Hu. leaves	Broth microdilution method	*Saccharomyces cerevisiae* (CICC 1340) *Saccharomyces cerevisiae* (CICC 1540) *Penicillium digitatum* (AS3.5752) *Aspergillus niger* *Cephalckiscus Fiagans*	MIC = 156 µg/mL MBC = 317.5 µg/mL MIC = 156 µg/mL MBC = 317.5 µg/mL MIC = 156 µg/mL MBC = 156 µg/mL MIC = 156 µg/mL MBC = 1250 µg/mL	[36]
Youngia japonica	Disk diffusion assay	*Bacillus cereus*	I. Z. Φ = 0.7 cm	[33]

solution was partitioned with ethyl acetate, and the free radical scavenging activity showed 2.2 DPPH radical traped per 1.0 mol of α-tocopherol. In other trials, Ma et al. [45] evaluated the antioxidant activity of cynaroside by scavenging the stable DPPH free radicals. Cynaroside was isolated from the methanolic extract from *Lophatherum gracile* leaves. The authors recorded a value of 0.43 µM and also using the DPPH assay, Liu et al. [44] tested cynaroside extracted from *L. japonica* (IC_{50} = 0.334 g/L). In the same context of DPPH assay, Orhan et al. [46] investigated *Bidens tripartite* to extact cynaroside with 80% ethanol extract and then with ethyl acetate to obtain a sub-extract, with a cynaroside level 10.87%, the inhibition pourcentage was 62.86 ± .80% at 2 mg/mL of ethyl acetate extract. Testing *Salvia multicaulis* antioxidant capability Shojaeifard et al. [35] extracted cynaroside using methanol extract. Both the DPPH and FRAP assays were used to evaluate cynaroside activity. Therefore, the IC_{50} values were 2.42 µg/mL and 3.30 mg eq. FeSO4/1 g of plant extract for both tests, respectively.

4.4. Hepatoprotective effect

Park et al. [50] administered bromobenzene to rats to promote hepatic lipid peroxidation, and they examined the influence of cynaroside on hepatic lipid peroxide and the activities of free radical producing and scavenging enzymes. Additionally, methanol was used to isolate cynaroside from *A. keiskei*. Cynaroside (50 or 100 mg/kg) was administered intraperitoneally once daily to four groups of rats for one week; subsequently, the last two days of week 4, bromobenzene was injected. Lipid peroxidation was evaluated by measuring the amount of thiobarbituric acid reactive material in the liver after it was cleaned, minced, and centrifuged twice. Through spectrophotometric analysis, the rate of trans-stilbene oxide production was used to measure epoxide hydrolase activity. The findings demonstrate that cynaroside attenuates bromobenzene-induced hepatic lipid peroxidation by increasing epoxide hydrolase activity. Ethyl acetate extract from *Phillyrea latifolia* (L.) showed luteolin 7-*O*-glucoside to be the main extracted component [49]. A total of 24 6-week-old male Wistar albino rats were divided into four groups of six; (1) a control group fed standard pellets, (2) a group fed a high-energy diet for 15 weeks, (3) a group fed a standard pellet diet for 10 weeks, a group fed the aqueous extract of *P. latifolia* leaves for 5 weeks, and (4) a group fed a high-energy diet for 10 weeks which continued to receive aqueous extract of *P. latifolia*. At the end of the 15th week, haematoxylin-eosin (HE) staining was used to perform histological analyses on liver tissue samples. The structural integrity of liver tissue and leukocyte infiltration were both enhanced after treatment with *P. latifolia* aqueous extract. The high energy diet group had decreases in blood glucose, leptin, total cholesterol, and LDL after receiving *P. latifolia*.

4.5. Antidiabetic activity

Van et al. [51] investigated the flavonoid-rich fraction of *Merremia tridentate* dissolved in 100 mL of the methanol:water (1: 1) mixture.

Cynaroside showed the highest level with a pourcentage of 4.375% in the stem-ethanol extract and 58.430% in the flavonoid rich fraction. The test was performed on healthy adult Swiss albino mice. The animals were fasted overnight and then given an intraperitoneal injection of 200 mg/kg of alloxan dissolved in sterile water. After 72 h, blood glucose levels were tested and mice with levels above 250 mg/dL were maintained for further testing. Diabetic mice treated with a flavonoid-rich fraction (25, 50, and 75 mg/kg) had enhanced glycogen phosphorylase activity and reduced glycogen synthase activity. Compared to pretreatment levels, these enzymes returned to near normal levels. The flavonoid-rich fraction had an IC_{50} value for the α-glucosidase enzyme of 0.24 mg/mL. The flavonoid-rich fraction inhibited α-amylase with an IC_{50} of 1.72 mg/mL.

Orhan et al. [46] selected *B. tripartite* to extact the cynaroside with 80% ethanol extract and then with ethyl acetate to obtain a sub-extract. The cynaroside level was 10.87%. Diabetes was induced by streptozotocin (STZ, 60 mg/kg, intraperitoneally), and male Wistar Albino rats were used for glucose oxydase technique for blood level assessment and oral tolerance test. The ethanol extract and ethyl acetate sub-extract of *B. tripartite* were orally administered to diabetic rats for seven consecutive days to measure blood glucose levels, and *in vitro* experiments included α-amylase and α-glucosidase inhibitory activities assays were performed. The results showed a decrease in blood glucose levels of 11.5–25.8% in normoglycaemic and glucose-loaded rats, compared to healthy control rats, in a dose-dependent manner. In another study using

Table 5
Antioxidant activity of Cynaroside.

Origins	Extraction methods	Experimental approaches	Key results	References
Purchased	-	Hoechst 33342 staining Double fluorescence staining (Phosphatidylserine) Total intracellar reactive oxygen species (ROS) detection Mitochondrial transmembrane potential Fluorometric Assay to analyse the labeled cells with JC-1 Western blot analysis	Pretreatment with cyanoside significantly increased the endogenous anti-oxidative activity of superoxide dismutase, glutathione peroxidase, and catalase, and reduced ROS production inside the cell Reduced loss of mitochondrial membrane potential induced by H_2O_2 Increased Bcl-2 expression while decreasing Bax expression, and thus prevented cell apoptosis Inhibited c-Jun N-terminal kinase (JNK) induced by oxidative stress and P53 protein production	[47]
Mentha piperita *Mentha longifolia* Leaf extracts	Methanol extract	Evaluation of β-carotene bleaching Ferric reducing antioxidant power (FRAP) test Evaluation with 2,2-Diphenyl-1-picrylhydrazyl (2,2-DPPH)	β-carotene bleaching assay; $IC_{50} = 6.9 \pm 0.1$ μg/mL FRAP assay; $IC_{50} = 8.2 \pm 0.1$ mM TEAC/g Extract DPPH; $IC_{50} = 6.3 \pm 0.1$ μg/mL	[42]
Purchased	-	ROS level detection Bicinchoninic acid protein assay Intracellular activities (CAT, SOD, GSH, and MDA) detection Western blot analysis	After being pretreated with cynaroside, H2O2-treated ARPE-19 cells exhibited a dramatic increase in ROS Apoptosis of ARPE-19 cells generated by oxidative stress was successfully suppressed through modulation of associated enzyme activity and protein expression Inhibited the upstream proteins Bcl-2 and Bax from activating caspase-3, which protected ARPE-19 cells from apoptosis Increased the expression of pAkt, which increased the antioxidant and antiapoptotic capacity of ARPE19 cells	[48]
Lophatherum gracile	Methanol extract	DPPH scavenging	$IC_{50} = 0.43 \pm 0.00$ μM	[45]
Angelica keiskei	Boiling water and Ethyl acetate	DPPH radical scavenging	2.2-DPPH radical traped per 1.0 mol of α-tocopherol	[43]
Lonicera japonica	methanol extract	DPPH radical scavenging activity assay	$IC_{50} = 0.334$ g/L	[44]
Bidens tripartita	Ethyl acetate sub-extract	DPPH assay	62.86 ± 80% at 2 mg/mL of ethyl acetate extract	[46]
Salvia multicaulis Vahl	80% methanol	Detection of Reduced Phosphorus in Halothane FRAP test, or ferric reducing antioxidant power	$IC_{50} = 2.42$ ug/mL 3.30 mg eq. FeSO4/ 1 g plant extract	[35]

STZ-induced diabetic rats, the euglycemic index of *B. tripartita* ethanol extract ranged from 14.0% to 32.7%. The ethanol extract of *B. tripartite* (500 mg/kg) significantly lowered blood glucose levels from 24.3% to 32.7%, with moderate inhibitory activity against α-glucosidase. The ethyl acetate sub-extract exhibited the highest inhibitory activity against α-glucosidase (64.56% at 2 mg/mL ethyl acetate), while the ethanol extract was inactive against the enzyme α-amylase and its sub-extracts.

Wei et al. [52] carried out a test on STZ-induced diabetic mice. They were fasted for 12 h before oral administration of *Stigma Maydis* powder extracted with 75% ethanol. The amount of cynaroside administered was equivalent to 24.5 mg/kg. Blood samples were collected before and after oral administration and then centrifuged. A non-compartmental analysis of plasma concentration. Kim et al. [53] tested the inhibition of α-glucosidase and α-amylase by luteolin 7-*O*-glucoside extracted from *Salix gracilistyla,* the compond was resolved in dimethylsulfoxide (5 mg/mL) and used as a test solution. The α-glucosidase and porcine pancreatic α-amylase inhibitory assays were carried out by the chromogenic method. Inhibitory activity was expressed as the relative absorbance difference. The results were: α-glucosidase $IC_{50} > 50$ ug/mL and α-amylase $IC_{50} > 100$ μg/mL. In order to assess the hypoglycemic activity of cynaroside from *C. citratus* by α-glucosidase inhibition, Borges et al. [70] used the oil-free infusion prepared from the dried leaves of *C. citratus*, the chemical composition was evaluated by HPLC-PDA-ESI/MSn, and the flavonoid showed an IC_{50} value of 21.01 μM for the α-glucosidase inhibition test (*in vivo*).

4.6. Anti-inflammatory activities of Cynaroside

As a natural molecule, cynaroside was investigated by numerous scientists for its anti-inflammatory effects (Table 7). Szekalska and colleagues reported that 10% of cynaroside isolated from *B. tripartita* aerial parts suppress the release of some anti-inflammatory mediators. Besides, this bioactive molecule (2 and 20 mg) reduced the oxazolone-induced ear swelling in male C57BL6/cmdb outbred mice. Histopathological examination revealed a marked reduction in inflammation of the paw skin and ear tissue in the animal model. These findings suggest that topical use of cynaroside expressively decreases T cells, mast cells and histiocytes in mouse skin with inflammation [54]. Another study examined the anti-inflammatory effect of cynaroside extracted from *E. bodinieri* (*in vitro* and *in vivo*). Cynaroside was found to regress nitrite oxide (NO) and ROS levels in lipopolysaccharide (LPS)-stimulated RAW264.7 cells and considerably reduced inflammation in the mouse model [55]. Similarly, Lee et al. [135] analyzed the protective effect of this substance on human periodontal ligament (hPDL) cells against lipopolysaccharide-induced damage and inflammation. NO and prostaglandin E_2 (PGE_2) were measured to assess the inflammatory response. Therefore, cynaroside inhibited the expression of inducible nitric oxide synthase (*iNOS*), a key nitric oxide-generating enzyme, and cyclooxygenase-2 (COX-2) which is implicated in the inflammatory response. Some cytokines implicated in chronic inflammation were also repressed, namely tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), in LPS-stimulated hPDL and RAW264.7 cells, without any cytotoxicity. Additionally, cynaroside significantly inhibited the expression of matrix metalloproteinase 3 and prevented nuclear factor κB (NF-κB) p65 subunit translocation to the cell nucleus. This bioactive compound exerts these effects through inhibition of IκB-α phosphorylation and degradation [135]. Moreover, another experiment revealed that cynaroside stimulates macrophage phenotypic transition from pro-inflammatory M1 to anti-inflammatory M2, and reduces inflammatory liver damage associated with sepsis. The mechanism of action

Table 6
Antidiabetic activity of Cynaroside.

Origins	Models used	Experimental approaches	Key results	References
Merremia tridentate	Alloxan-induced diabetic mice	Mice were fasted overnight and then received an intraperitoneal injection of 200 mg/kg of alloxan dissolved in sterile water. Blood glucose levels were monitored in mice for a total of 72 h	The flavonoid-rich fraction (58.430%) had the highest cynaroside concentration In diabetic mice, treatment with a flavonoid-rich fraction (25, 50, and 75 mg/kg) stimulated glycogen phosphorylase activity while decreasing glycogen synthase activity IC_{50} = 0.24 mg/mL against the enzyme α-glucosidase IC_{50} = 1.72 mg/mL against α-amylase enzyme	[51]
Bidens tripartita	Ethanol extract Ethyl acetate sub-extract	*In vitro* enzyme inhibitory assay by glucose oxidase method STZ-induced diabetic rats *In vitro* α-amylase and α-glucosidase inhibitory activities	Reduced blood sugar levels by 11.5–25.8% Reduced blood glucose levels by 14.0–32.7% in STZ-induced diabetic rats Induced a statistically significant antidiabetic effect of the extract at 500 mg/kg (24.3–32.7%)	[46]
Maydis stigma	Methanol And 0.1% formic acid water	STZ-induced diabetic rats	Cynaroside coul have a potential role in in type 2 diabetes. Mice diabetes group showed better absorption for cynaroside than normal group The area under the curve was (AUC0-t)= 3072 ± 675.7 ugh/L, AUC0-∞ = 3074 ± 676.2 ugh/l; Mean residence time (MRT) = 4.53 ± 0.15 h Terminal half-life (T1/2) = 3.26 ± 0.22 h	[52]
Salix gracilistyla	Not mentionned	*In vivo* α-glucosidase inhibitory assay Porcine pancreatic α-amylase	Time to maximum concentration (Tmax) = 1.25 ± 0.27 h Maximum concentration (Cmax) = 769.3 ± 111.2 ug/L and clearance (CLz/F) = 8.323 ± 1.966 (L/Kg/h) IC_{50} > 50 μg/mL IC_{50} > 100 μg/mL	[53]
Cymbopogon citratus Stapf.	Oil-free infusion	*In vivo* α-glucosidase inhibition assay	IC_{50} = 21.01 μM	[70]

was explained by the fact that cynaroside inhibits the binding of pyruvate kinase M2 (PKM2), a potential target for controlling the inflammatory response, to hypoxia-inducible factor-1α (HIF-1α) which is considered an essential regulator of transcription. This is due to prevention of PKM2 translocation to the nucleus and suppression of PKM2 phosphorylation [56,135]. Furthermore, Odontuya et al. [57] estimated the ability of cynaroside derived from luteolin to inhibit enzymes responsible for the synthesis of thromboxane B2 (TXB2) and leukotriene B4 (LTB4) involved in the pain and inflammatory response. The phenolic compound was found to possess a moderate inhibitory effect on both enzyme synthesis pathways. This activity was dose dependent and the inhibition values ranged from 0% to 42.23% and 21.68–57.68% for TXB2 and LTB4, respectively. More interestingly, Feng et al. [58] studied the protective effect of cynaroside against sepsis and its mechanism on cecal ligation puncture (CLP) and sham surgery in mouse model. At concentrations of 5 and 10 mg/kg, cynaroside has been observed to regulate serum levels of inflammatory factors, including IL-1β and TNF-α. Thus, some tissue damage markers such as creatinine, creatine kinase-MB and lactate dehydrogenase were significantly decreased at the serum level compared with the sepsis mice. It was also observed that the biomarker of pro-inflammatory macrophage M1 phenotype (iNOS+) was suppressed and the anti-inflammatory M2 polarization (CD206 +) was promoted in injured organs of septic mice. Mechanistic research has established that cynaroside inhibits LPS-induced polarization of macrophage into M1 phenotype, which can be highly blocked by Nrf2 inhibitor, and expected that Nrf2 and its downstream (Heme oxygenase-1 (HO-1)) was adjusted in injured organs after treatment with cynaroside. Another work was carried out by Lee et al. in order to determine the chondroprotective effect of cynaroside as well as its mechanism of action by measuring the protein levels of catabolic and anabolic factors. The results of this work revealed that cynaroside inhibits the expression of catabolic factors (nitrite, iNOS, ROS, PGE_2, Cox-2, MMP-1, MMP-3, and MMP-13), and regresses the degradation of anabolic factors (type II collagen and aggrecan). This substance has also been reported to limit the phosphorylation of MAPKs and NF-κB into the nucleus, playing a central role in inflammation [59]. Other important studies have specified that cynaroside extremely inhibits the phosphorylation of IκB kinase (IKK)β, an enzyme complex involved in the propagation of the cellular response to inflammation, *via* the NF-κB signaling pathway. It has also been cited that this molecule inhibits the activation of the inflammasome and the secretion of

Table 7
Anti-inflammatory activities of cynaroside.

Origins	Doses	Study types	Methods used	Key results	References
Bidens tripartita	2 – 20 mg	*In vivo*	Carrageenan-induced mouse paw oedema inflammation model	Reduced T cells, mast cells and histiocytes in mouse skin with inflammation or atopic dermatitis	[54]
Elsholtiza bodinieri	5–300 μg/mL	*In vitro* and *in vivo*	NO and ROS production in LPS-stimulated RAW264.7 cells xylene-induced auricular swelling mice model	Inhibited NO and ROS production in LPS-stimulated RAW264.7 cells Reduced inflammation in the mouse model	[55]
Purchased	5–20 μM	*In vitro*	Measurement of NO and prostaglandin E_2 (PGE_2)	Inhibited iNOS, COX-2, TNF-α, and IL-6 production in LPS-stimulated hPDL and RAW264.7 cells	[135]
Purchased	5 mg/kg	*In vivo*	Analysis of pyruvate kinase activity of PKM2	Prevented macrophage polarization into pro-inflammatory phenotype and relief of cecal ligation and puncture-induced liver injury by targeting PKM2/HIF-1α axis	[56]
Oxalis corniculata	25–100 μg/mL	*in vitro*	Thromboxane B2 and leukotriene B4 scavenging activity	Inhibited 42.23% of TXB2 and 57.68% of LTB4	[57]
Lonicera spp. (honeysuckel)	5–10 mg/kg	*in vivo* and *in vitro* models	Sepsis mouse model by cecal ligation and puncture (CLP) surgery in mice C57BL/6 miceSerum cytokine measurement and hematoxylin-eosin (HE) staining	Improved systematic inflammation and multi-organ injury dependent on Nrf2/HO-1 pathway in septic mice	[58]
Anthriscus sylvestris	160 μM	*In vitro* and *in vivo*	Measurement of nitrite, PGE_2, type II collagen, aggrecan, and ROS production Measurement of iNOS, Cox-2, MMP-1, MMP-3, MMP-13, ADAMTS-4, MAPKs, and the NF-κB p65 subunit	Inhibited IL-1β-induced inflammatory factors (NO, ROS, PGE_2, iNOS, Cox-2, and TNF-α) and cartilage-degrading enzymes (MMP-1, MMP-3, MMP-13, and ADAMTS-4) Protected type II collagen and aggrecan from degradation by IL-1β treatment	[59]

Table 8
Anticancer activities of cynaroside.

Origins	Doses	Cell lines/ Animal models	Key results	References
Purchased	0, 25, 50, 75, and 100 μM	Gastric cancer cell lines (HGC27, MKN45, and SGC7901)	Reduced gastric cancer cell self-renewal ability Inhibited tumorigenesis ability *in vivo* Inhibited the activation of the MET/AKT/mTOR axis	[62]
Lonicera japonica	10, 20, 40, and 80 μM 10 mg/kg, i.p., once daily for 3 days	Human kidney proximal tubule cell (HK-2 cells) Male BALB/c mice	Reduced cell death, DNA fragmentation, apoptosis and mitochondrial dysfunction Decreased nephrotoxicity *in vivo*	[63]
Lonicera japonica	80 μM	HK-2 cells	Ameliorated doxorubicin-induced necrosis in HK-2 cells	[64]

inflammatory factors, and it that is able to reduce retinal damage after exposure to blue light by inhibiting the nuclear translocation of NF-κB and activating autophagy [60], [130].

4.7. Anticancer activities of cynaroside

Some scientific reports have shown that cynaroside has important anticancer properties on different tumor cell lines (Table 8) [61]. Ji et al. [62] investigated the antitumor effect of cynaroside using many assays to assess cell viability and proliferation and to perceive cell cycle and apoptosis (MTT assay, BrdU staining, plate colony formation, flow cytometry, and western blotting). Data obtained in this work showed that cynaroside induces cell cycle arrest at S phase and inhibits proliferation migration and invasion of gastric cancer cells. This substance was also able to activate the apoptosis and suppress the tumorigenic capacity of gastric cancer cells *in vivo* and *in vitro*. Mechanistic analysis has established that cynaroside can block an intracellular signaling pathway, MET/AKT/mTOR axis, having a pivotal role in cell cycle control [62]. Nho and colleagues investigated the effect of cynaroside on the caspase-3/MST-1 signaling pathway in cisplatin-induced nephrotoxicity using a human proximal tubule cell line (HK-2 cells). On the other hand, they tested the protective effect of this compound on cisplatin-induced nephrotoxicity in male BALB/c mice. The results indicated that 10 μM cynaroside regresses cisplatin-induced apoptosis and suppresses mitochondrial dysfunction and caspase-3 activation. Cynaroside treatment decreased caspase-3/MST-1 pathway upregulation in HK-2 cells. Additionally, 10 mg/kg cynaroside, i.p., once daily for 3 days, reduced renal dysfunction, tubular damage, and neutrophilia induced by cisplatin injection in mice. These results showed that this compound can attenuate cisplatin-induced side effects [63]. The same research team evaluated the protective effect of cynaroside against doxorubicin-induced necrosis in HK-2 cells. They revealed that pre-treatment with 80 μM cynaroside attenuates DNA fragmentation, caspase-3 activity, and mitochondrial hyperactivation induced by 10 μM doxorubicin in HK-2 cells [64]. It was also found that cynaroside isolated from *A. sylvestris* exerts a significant antimutagenic effect against two carcinogenic and mutagenic food additives; 2-nitrofluorene (2NF) and 3-(5- nitro-2-furyl)acrylic acid (NFAA) [38].

5. Conclusion and perspectives

Here, we report the natural sources and biological properties of cynaroside. It has been revealed that this bioactive compound is synthetized by different natural sources, incldluing medicinal plants. With its particular chemical structure, cynaroside exhibits stocastic pharmacological actions such as ani-inflammatory, anti-microbial, and anti-cancer activities. *In vitro* investigations highlighed certain cellular and molecular mechanisms of this molecule. However, further mechanistic investigations should be carried out eventually to determine precisely its diffent mechanisms with all the versatil stochasticity. Moreover, other investigations concerning pharmacokinetic and toxicological studies should also be carried out to determine the absorption, availability, and metabolism of cynaroside, as well as to validate its safety.

Funding

The authors would like to thank the Deanship of Scientific Research at Umm Al-Qura University for supporting this work by Grant Code: (22UQU4331128DSR18).

CRediT authorship contribution statement

Conceptualization, A.B, L.C.M., C.A., C.S.T., ; methodology, A.B., S. B., G.Z., C.A., N.E.O. and N.E.H.; software, A.B.; validation, A.B., D.T., T. B., Y.B., A.K.; A.N.A.; formal analysis, A.B; investigation, C.A., N.S. and A.B.; resources, S.B., A.K.; A.N.A.; data curation, N.S.; writing – original draft preparation, D.T., T.B., L.C.M., A.B. and N.E.H.; writing – review and editing, C.A., A.B.,N.E.O. and C.S.T.; visualization, A.B., N.E.O. ; supervision, A.B. and L.C.M.; project administration, A.B. All authors have read and agreed to the published version of the manuscript.

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

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments

The authors would like to thank the Deanship of Scientific Research at Umm Al-Qura University for supporting this work by Grant Code: (22UQU4331128DSR77).

References

[1] S.A. Rajput, C. Zhang, Y. Feng, X.T. Wei, M.M. Khalil, I.R. Rajput, D.M. Baloch, A. Shaukat, N. Rajput, H. Qamar, Proanthocyanidins Alleviates AflatoxinB1-Induced Oxidative Stress and Apoptosis through Mitochondrial Pathway in the Bursa of Fabricius of Broilers, Toxins 11 (2019) 157.

[2] K.M. Anusmitha, M. Aruna, J.T. Job, A. Narayanankutty, P.B. Benil, R. Rajagopal, A. Alfarhan, D. Barcelo, Phytochemical Analysis, Antioxidant, Anti-Inflammatory, Anti-Genotoxic, and Anticancer Activities of Different Ocimum Plant Extracts Prepared by Ultrasound-Assisted Method, Physiol. Mol. Plant Pathol. 117 (2022), 101746.

[3] Z. Barmoudeh, M.T. Ardakani, A.H. Doustimotlagh, H. Bardania, Evaluation of the Antioxidant and Anticancer Activities of Hydroalcoholic Extracts of Thymus Daenensis Čelak and Stachys Pilifera Benth, J. Toxicol. (2022) *2022*.

[4] T. Benali, K. Habbadi, A. Bouyahya, A. Khabbach, I. Marmouzi, T. Aanniz, H. Chtibi, H.N. Mrabti, E.H. Achbani, K. Hammani, Phytochemical Analysis and Study of Antioxidant, Anticandidal, and Antibacterial Activities of Teucrium Polium Subsp. Polium and Micromeria Graeca (Lamiaceae) Essential Oils from Northern Morocco, Evid. -Based Complement. Altern. Med. (2021) *2021*.

[5] T. Benali, K. Habbadi, A. Khabbach, I. Marmouzi, G. Zengin, A. Bouyahya, I. Chamkhi, H. Chtibi, T. Aanniz, E.H. Achbani, GC–MS Analysis, Antioxidant and Antimicrobial Activities of Achillea odorata Subsp. Pectinata and Ruta Montana Essential Oils and Their Potential Use as Food Preservatives, Foods 9 (2020) 668.

[6] M.R. Kachmar, A.P. Oliveira, P. Valentão, A. Gil-Izquierdo, R. Domínguez-Perles, A. Ouahbi, El Badaoui, K.; Andrade, P.B.; Ferreres, F. HPLC-DAD-ESI/MSn Phenolic Profile and in Vitro Biological Potential of Centaurium erythraea Rafn Aqueous Extract, Food Chem. 278 (2019) 424–433.

[7] H.N. Mrabti, A. Bouyahya, A. Ed-Dra, M.R. Kachmar, N.N. Mrabti, T. Benali, M. A. Shariati, A. Ouahbi, L. Doudach, M.E.A. Faouzi, Polyphenolic Profile and Biological Properties of Arbutus unedo Root Extracts, in: European Journal of Integrative Medicine, 42, 2021, 101266.

[8] A. Nieto-Maldonado, S. Bustos-Guadarrama, H. Espinoza-Gomez, L.Z. Flores-López, K. Ramirez-Acosta, G. Alonso-Nuñez, R.D. Cadena-Nava, Green Synthesis of Copper Nanoparticles Using Different Plant Extracts and Their Antibacterial Activity, J. Environ. Chem. Eng. 10 (2022), 107130.

[9] M. Oves, M.A. Rauf, M. Aslam, H.A. Qari, H. Sonbol, I. Ahmad, G.S. Zaman, M. Saeed, Green Synthesis of Silver Nanoparticles by Conocarpus Lancifolius Plant Extract and Their Antimicrobial and Anticancer Activities, Saudi J. Biol. Sci. 29 (2022) 460–471.

[10] E. Souri, G. Amin, H. Farsam, H. Jalalizadeh, S. Barezi, Screening of Thirteen Medicinal Plant Extracts for Antioxidant Activity, Iran. J. Pharm. Res. 7 (2022) 149–154.

[11] S. Aboulaghras, N. Sahib, S. Bakrim, T. Benali, S. Charfi, F.-E. Guaouguaou, N. E. Omari, M. Gallo, D. Montesano, G. Zengin, Health Benefits and Pharmacological Aspects of Chrysoeriol, Pharmaceuticals 15 (2022) 973.

[12] K.K. Aggarwal, S.P.S. Khanuja, A. Ahmad, Santha Kumar, T.R.; Gupta, V.K.; Kumar, S. Antimicrobial Activity Profiles of the Two Enantiomers of Limonene and Carvone Isolated from the Oils of Mentha spicata and Anethum Sowa, Flavour Fragr. J. 17 (2002) 59–63.

[13] S. Bakrim, H. Machate, T. Benali, N. Sahib, I. Jaouadi, N.E. Omari, S. Aboulaghras, S.P. Bangar, J.M. Lorenzo, G. Zengin, Natural Sources and Pharmacological Properties of Pinosylvin, Plants 11 (2022) 1541.

[14] N.A. Elkanzi, H. Hrichi, R.A. Alolayan, W. Derafa, F.M. Zahou, R.B. Bakr, Synthesis of Chalcones Derivatives and Their Biological Activities: A Review, ACS Omega (2022).

[15] M. Friedman, P.R. Henika, R.E. Mandrell, Bactericidal Activities of Plant Essential Oils and Some of Their Isolated Constituents against Campylobacter Jejuni, Escherichia coli, Listeria Monocytogenes, and Salmonella Enterica, J. Food Prot. 65 (2002) 1545–1560.

[16] H. Hwang-Bo, W.S. Lee, A. Nagappan, H.J. Kim, R. Panchanathan, C. Park, S.-H. Chang, N.D. Kim, S.-H. Leem, Y.-C. Chang, Morin Enhances Auranofin Anticancer Activity by Up-Regulation of DR4 and DR5 and Modulation of Bcl-2 through Reactive Oxygen Species Generation in Hep3B Human Hepatocellular Carcinoma Cells, Phytother. Res. 33 (2019) 1384–1393.

[17] A.K. Jangid, H. Agraval, N. Gupta, P. Jain, U.C. Yadav, D. Pooja, H. Kulhari, Amorphous Nano Morin Outperforms Native Molecule in Anticancer Activity and Oral Bioavailability, Drug Dev. Ind. Pharm. 46 (2020) 1123–1132.

[18] N. Karaca, B. Demirci, F. Demirci, Evaluation of Lavandula stoechas L. Subsp. Stoechas L., Mentha spicata L. Subsp. Spicata L. Essential Oils and Their Main Components against Sinusitis Pathogens, Z. für Naturforsch. C. 73 (2018) 353–360.

[19] E. Królicka, K. Kieć-Kononowicz, D. Lażewska, Chalcones as Potential Ligands for the Treatment of Parkinson's Disease, Pharmaceuticals 15 (2022) 847.

[20] R. Naigre, P. Kalck, C. Roques, I. Roux, G. Michel, Comparison of Antimicrobial Properties of Monoterpenes and Their Carbonylated Products, Planta Med. 62 (1996) 275–277.

[21] A. Rauf, M. Akram, H. Anwar, M. Daniyal, N. Munir, S. Bawazeer, S. Bawazeer, M. Rebezov, A. Bouyahya, M.A. Shariati, Therapeutic Potential of Herbal Medicine for the Management of Hyperlipidemia: Latest Updates, Environ. Sci. Pollut. Res. (2022) 1–21.

[22] B. Salehi, D. Mnayer, B. Özçelik, G. Altin, K.N. Kasapoğlu, C. Daskaya-Dikmen, M. Sharifi-Rad, Z. Selamoglu, K. Acharya, S. Sen, Plants of the Genus Lavandula: From Farm to Pharmacy, Nat. Prod. Commun. 13 (2018), 1934578X1801301037.

[23] E. Schmidt, L. Jirovetz, G. Buchbauer, Z. Denkova, A. Stoyanova, I. Murgov, M. Geissler, Antimicrobial Testings and Gas Chromatographic Analyses of Aroma Chemicals, J. Essent. oil Bear. Plants 8 (2005) 99–106.

[24] I. Trendafilova, J. Mihály, D. Momekova, R. Chimshirova, H. Lazarova, G. Momekov, M. Popova, Antioxidant Activity and Modified Release Profiles of Morin and Hesperetin Flavonoids Loaded in Mg-or Ag-Modified SBA-16 Carriers, Mater. Today Commun. 24 (2020), 101198.

[25] M. D'hooghe, B. Willekens, V. Delvaux, M. D'haeseleer, D. Guillaume, G. Laureys, G. Nagels, P. Vanderdonckt, Van Pesch, V.; Popescu, V. Sativex®(Nabiximols) Cannabinoid Oromucosal Spray in Patients with Resistant Multiple Sclerosis Spasticity: The Belgian Experience, BMC Neurol. 21 (2021) 1–9.

[26] J.W.-H. Li, J.C. Vederas, Drug Discovery and Natural Products: End of an Era or an Endless Frontier? Science 325 (2009) 161–165.

[27] I. Urits, K. Gress, K. Charipova, K. Habib, D. Lee, C. Lee, J.W. Jung, H. Kassem, E. Cornett, A. Paladini, Use of Cannabidiol (CBD) for the Treatment of Chronic Pain, Best. Pract. Res. Clin. Anaesthesiol. 34 (2020) 463–477.

[28] L. Zhu, L. Chen, Progress in Research on Paclitaxel and Tumor Immunotherapy, Cell. Mol. Biol. Lett. 24 (2019) 1–11.

[29] S. Akroum, D. Bendjeddou, D. Satta, K. Lalaoui, Antibacterial Activity and Acute Toxicity Effect of Flavonoids Extracted from Mentha Longifolia, Am. -Eurasia J. Sci. Res. 4 (2009) 93–96.

[30] K.K. Chiruvella, A. Mohammed, G. Dampuri, R.G. Ghanta, S.C. Raghavan, Phytochemical and Antimicrobial Studies of Methyl Angolensate and Luteolin-7-O-Glucoside Isolated from Callus Cultures of Soymida Febrifuga, Int. J. Biomed. Sci.: IJBS 3 (2007) 269.

[31] S. Kefi, R. Essid, K. Mkadmini, A. Kefi, F.M. Haddada, O. Tabbene, F. Limam, Phytochemical Investigation and Biological Activities of Echium Arenarium (Guss) Extracts, Microb. Pathog. 118 (2018) 202–210.

[32] N.Z. Mamadalieva, F. Herrmann, M.Z. El-Readi, A. Tahrani, R. Hamoud, D. R. Egamberdieva, S.S. Azimova, M. Wink, Flavonoids in Scutellaria Immaculata and S. Ramosissima (Lamiaceae) and Their Biological Activity, J. Pharm. Pharmacol. 63 (2011) 1346–1357.

[33] L.S. Ooi, H. Wang, Z. He, V.E. Ooi, Antiviral Activities of Purified Compounds from Youngia japonica (L.) DC (Asteraceae, Compositae), J. Ethnopharmacol. 106 (2006) 187–191.

[34] Salawu, S.O.; Ogundare, A.O.; Ola-Salawu, B.B.; Akindahunsi, A.A. Antimicrobial Activities of Phenolic Containing Extracts of Some Tropical Vegetables. 2011.

[35] Z. Shojaeifard, B. Hemmateenejad, A.R. Jassbi, Chemometrics-Based LC-UV-ESIMS Analyses of 50 Salvia Species for Detecting Their Antioxidant Constituents, J. Pharm. Biomed. Anal. 193 (2021), 113745.

[36] N. Wang, H. Chen, L. Xiong, X. Liu, X. Li, Q. An, X. Ye, W. Wang, Phytochemical Profile of Ethanolic Extracts of Chimonanthus Salicifolius SY Hu. Leaves and Its Antimicrobial and Antibiotic-Mediating Activity, Ind. Crops Prod. 125 (2018) 328–334.

[37] J. Xiong, S. Li, W. Wang, Y. Hong, K. Tang, Q. Luo, Screening and Identification of the Antibacterial Bioactive Compounds from Lonicera japonica Thunb. Leaves, Food Chem. 138 (2013) 327–333.

[38] L. Žemlička, P. Fodran, V. Lukeš, A. Vagánek, M. Slováková, A. Staško, T. Dubaj, T. Liptaj, M. Karabín, L. Birošová, Physicochemical and Biological Properties of Luteolin-7-O-β-d-Glucoside (Cynaroside) Isolated from Anthriscus sylvestris (L.) Hoffm, Mon. für Chem. -Chem. Mon. 145 (2014) 1307–1318.

[39] X. Zhu, H. Zhang, R. Lo, Phenolic Compounds from the Leaf Extract of Artichoke (Cynara scolymus L.) and Their Antimicrobial Activities, J. Agric. Food Chem. 52 (2004) 7272–7278.

[40] M. Tomczykowa, M. Tomczyk, P. Jakoniuk, E. Tryniszewska, Antimicrobial and Antifungal Activities of the Extracts and Essential Oils of Bidens tripartita, Folia Histochem. Et. Cytobiol. 46 (2008) 389–393.

[41] S. Tabrez, F. Rahman, R. Ali, A.S. Alouffi, S.K. Akand, B.M. Alshehri, F. A. Alshammari, A. Alam, M.A. Alaidarous, S. Banawas, Cynaroside Inhibits Leishmania Donovani UDP-Galactopyranose Mutase and Induces Reactive Oxygen Species to Exert Antileishmanial Response, Biosci. Rep. (2021) *41*.

[42] H.O. Elansary, A. Szopa, P. Kubica, H. Ekiert, M. Klimek-Szczykutowicz, D.O. El-Ansary, E.A. Mahmoud, Polyphenol Profile and Antimicrobial and Cytotoxic Activities of Natural Mentha$\times$ Piperita and Mentha Longifolia Populations in Northern Saudi Arabia, Processes 8 (2020) 479.

[43] S.-J. Kim, J.-Y. Cho, J.-H. Wee, M.-Y. Jang, C. Kim, Y.-S. Rim, S.-C. Shin, S.-J. Ma, J.-H. Moon, K.-H. Park, Isolation and Characterization of Antioxidative Compounds from the Aerial Parts of Angelica Keiskei, Food Sci. Biotechnol. 14 (2005) 58–63.

[44] H. Liu, S. Zhu, Q. Liu, Y. Zhang, Spectrum–Effect Relationship Study between HPLC Fingerprints and Antioxidant of Honeysuckle Extract, Biomed. Chromatogr. 33 (2019), e4583.

[45] N.-H. Ma, J. Guo, S.-H. Xu Chen, X.-R. Yuan, T. Zhang, Y. Ding, Antioxidant and Compositional HPLC Analysis of Three Common Bamboo Leaves, Molecules 25 (2020) 409.

[46] N. Orhan, Ü.G. İçöz, L. Altun, M. Aslan, Anti-Hyperglycaemic and Antioxidant Effects of Bidens tripartita and Quantitative Analysis on Its Active Principles, Iran. J. Basic Med. Sci. 19 (2016) 1114.

[47] X. Sun, G. Sun, M. Wang, J. Xiao, X. Sun, Protective Effects of Cynaroside against H2O2-Induced Apoptosis in H9c2 Cardiomyoblasts, J. Cell. Biochem. 112 (2011) 2019–2029.

[48] H. Yu, J. Li, X. Hu, J. Feng, H. Wang, F. Xiong, Protective Effects of Cynaroside on Oxidative Stress in Retinal Pigment Epithelial Cells, J. Biochem. Mol. Toxicol. 33 (2019), e22352.

[49] S. Yazici-Tutunis, E. Gurel-Gurevin, S. Ustunova, C. Demirci-Tansel, F. Mericli, Possible Effects of Phillyrea Latifolia on Weight Loss in Rats Fed a High-Energy Diet, Pharm. Biol. 54 (2016) 1991–1997.

[50] J.C. Park, J.G. Park, H.J. Kim, J.M. Hur, J.H. Lee, N.J. Sung, S.K. Chung, J. W. Choi, Effects of Extract from Angelica Keiskei and Its Component, Cynaroside, on the Hepatic Bromobenzene-Metabolizing Enzyme System in Rats, Phytother. Res. 16 (2002) 24–27.

[51] L.V. Van, E.C. Pham, C.V. Nguyen, N.T.N. Duong, T.V. Le Thi, T.N. Truong, In Vitro and in Vivo Antidiabetic Activity, Isolation of Flavonoids, and in Silico Molecular Docking of Stem Extract of Merremia Tridentata (L.), Biomed. Pharmacother. 146 (2022), 112611.

[52] B.-B. Wei, Z.-X. Chen, M.-Y. Liu, M.-J. Wei, Development of a UPLC-MS/MS Method for Simultaneous Determination of Six Flavonoids in Rat Plasma after Administration of Maydis Stigma Extract and Its Application to a Comparative Pharmacokinetic Study in Normal and Diabetic Rats, Molecules 22 (2017) 1267.

[53] J.-S. Kim, C.-S. Kwon, K.H. Son, Inhibition of Alpha-Glucosidase and Amylase by Luteolin, a Flavonoid, Biosci., Biotechnol., Biochem. 64 (2000) 2458–2461.

[54] M. Szekalska, K. Sosnowska, M. Tomczykowa, K. Winnicka, I. Kasacka, M. Tomczyk, In Vivo Anti-Inflammatory and Anti-Allergic Activities of Cynaroside Evaluated by Using Hydrogel Formulations, Biomed. Pharmacother. 121 (2020), 109681.

[55] Y. Zou, M. Zhang, T. Zhang, J. Wu, J. Wang, K. Liu, N. Zhan, Antioxidant and Anti-Inflammatory Activities of Cynaroside from Elsholtiza Bodinieri, Nat. Prod. Commun. 13 (2018), 1934578X1801301122.

[56] L. Pei, Y. Le, H. Chen, J. Feng, Z. Liu, J. Zhu, C. Wang, L. Chen, X. Dou, D. Lu, Cynaroside Prevents Macrophage Polarization into Pro-Inflammatory Phenotype and Alleviates Cecal Ligation and Puncture-Induced Liver Injury by Targeting PKM2/HIF-1α Axis, Fitoterapia 152 (2021), 104922.

[57] Odontuya, G.; Hoult, J.R.S.; Houghton, P.J. Structure-activity Relationship for Antiinflammatory Effect of Luteolin and Its Derived Glycosides. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives 2005, 19, 782–786.

[58] J. Feng, Z. Liu, H. Chen, M. Zhang, X. Ma, Q. Han, D. Lu, C. Wang, Protective Effect of Cynaroside on Sepsis-Induced Multiple Organ Injury through Nrf2/HO-1-Dependent Macrophage Polarization, Eur. J. Pharmacol. 911 (2021), 174522.

[59] S.A. Lee, B.-R. Park, S.-M. Moon, J.H. Hong, D.K. Kim, C.S. Kim, Chondroprotective Effect of Cynaroside in IL-1β-Induced Primary Rat Chondrocytes and Organ Explants via NF-KB and MAPK Signaling Inhibition, Oxid. Med. Cell. Longev. 2020 (2020).

[60] W. Wei, H. Ping, J. XiaoMing, Anti-Inflammatory and Antioxidant Effects of Luteolin and Its Flavone Glycosides, Shipin Kexue/Food Sci. 41 (2020) 208–215.

[61] B.T. Phuong Thuy, N.T. Ai Nhung, T. Duong, P.Van Trung, N.M. Quang, H.T. Kim Dung, P. Tat, Van Prediction of Anticancer Activities of Cynaroside and Quercetin in Leaf of Plants Cynara scolymus L and Artocarpus Incisa L Using Structure–Activity Relationship, Cogent Chem. 2 (2016) 1212452.

[62] J. Ji, Z. Wang, W. Sun, Z. Li, H. Cai, E. Zhao, H. Cui, Effects of Cynaroside on Cell Proliferation, Apoptosis, Migration and Invasion Though the MET/AKT/MTOR Axis in Gastric Cancer, Int. J. Mol. Sci. 22 (2021) 12125.

[63] J.-H. Nho, H.-K. Jung, M.-J. Lee, J.-H. Jang, M.-O. Sim, D.-E. Jeong, H.-W. Cho, J.-C. Kim, Beneficial Effects of Cynaroside on Cisplatin-Induced Kidney Injury in Vitro and in Vivo, Toxicol. Res. 34 (2018) 133–141.

[64] J.H. Nho, H.K. Jung, M.J. Lee, J.H. Jang, M.O. Sim, J.K. Jung, D.E. Jung, B.K. An, H.W. Cho, Inhibitory Effect of Cynaroside Isolated from Lonicera Japonia Thunb on Doxorubicin-Induced Necrosis in Human Renal Proximal Tubular HK-2 Cells. *Korean*, J. Med. Crop Sci. 25 (2017) 322–327.

[65] Sa, R.; Daofu, A.; Sa, C. Identification of Chemical Constituents in Rat Serum and Brain Tissue of Cumin (Cuminum cyminum L.) Aqueous Extract by UPLC-Q-TOF-MS. Cuminum cyminum 2022.

[66] R. Saif, G. Ali, K. Ashfaq, S. Zia, A.R. Qureshi, Computational Prediction of Olea europaea Compounds as Inhibitor of Main-Peptidase of SARS-CoV2, Adv. Life Sci. 8 (2021) 133–136.

[67] Hong, J.H.; Lee, M.J.; Jo, Y.I.; Moon, S.M.; Lee, S.A.; Kim, C.S. Analytical Method Validation of Cynaroside in Domestic Anthriscus sylvestris (L.) Hoffm. Leaves Extract for Standardization as a Functional Ingredient Using RP-HPLC. 2021.

[68] T.X.T. Nguyen, D.L. Dang, V.Q. Ngo, T.C. Trinh, Q.N. Trinh, T.D. Do, T.T. T. Thanh, Anti-Inflammatory Activity of a New Compound from Vernonia Amygdalina, Nat. Prod. Res. 35 (2021) 5160–5165.

[69] Y. Dong, C. Chen, C. Zhang, L. Zhang, Y. Zhang, Y. Li, Z. Dong, Stigmasterol Inhibits the Progression of Lung Cancer by Regulating Retinoic Acid-Related Orphan Receptor C, Histol. Histopathol. (2021), 18388–18388.

[70] P.H. Borges, S. Pedreiro, S.J. Baptista, C.F. Geraldes, M.T. Batista, M.M. Silva, A. Figueirinha, Inhibition of α-Glucosidase by Flavonoids of Cymbopogon citratus (DC) Stapf, J. Ethnopharmacol. 280 (2021), 114470.

[71] A. Aras, F. Türkan, U. Yildiko, M.N. Atalar, Ö. Kılıç, M.H. Alma, E. Bursal, Biochemical Constituent, Enzyme Inhibitory Activity, and Molecular Docking Analysis of an Endemic Plant Species, Thymus Migricus, Chem. Pap. 75 (2021) 1133–1146.

[72] O.Y. Adeniran, D.S. Metibemu, E.O. Akinsiku, O.A. Akinloye, R.N. Ugbaja, A. J. Akamo, A.O. Metibemu, A.O. Olusola, I.O. Omotuyi, Homo Sapien Bcr-Abl-Interacting Scaffolds from Bryophyllum Pinnatum and Cantharanthus Roseus: Computational Studies. *NISEB*, Journal (2021) *19*.

[73] A. Akbari-Ahangar, M.-R. Delnavazi, Flavone Glycosides from the Aerial Parts of Stachys Lavandulifolia Vahl, Pharm. Sci. 26 (2020) 198–202.

[74] E. Bimenyindavyi, O.A. Timofeeva, Phenolics and Ascorbic Contents in Two Sage (Salvia Sps. l) Species, J. Exp. Biol. Agric. Sci. 8 (2020) S286–S291.

[75] M.R. Chowdhury, K.H. Chowdhury, N.B. Hanif, M.A. Sayeed, J. Mouah, I. Mahmud, A.M. Kamal, M.N.U. Chy, M. Adnan, An Integrated Exploration of Pharmacological Potencies of Bischofia javanica (Blume) Leaves through Experimental and Computational Modeling, Heliyon 6 (2020), e04895.

[76] J. Ellenberger, N. Siefen, P. Krefting, Schulze Lutum, J.-B.; Pfarr, D.; Remmel, M.; Schröder, L.; Röhlen-Schmittgen, S. Effect of UV Radiation and Salt Stress on the Accumulation of Economically Relevant Secondary Metabolites in Bell Pepper Plants, Agronomy 10 (2020) 142.

[77] F. Emad, A.K. Khalafalah, M.A. El Sayed, A.-E.H. Mohamed, M. Stadler, S. E. Helaly, Three New Polyacetylene Glycosides (PAGs) from the Aerial Part of Launaea Capitata (Asteraceae) with anti-biofilm activity against staphylococcus aureus, Fitoterapia 143 (2020), 104548.

[78] S.H. Ghoran, O. Firuzi, A.R. Jassbi, Phytoconstituents from the Aerial Parts of Salvia Dracocephaloides Boiss. and Their Biological Activities, J. Environ. Treat. Tech. 8 (2020) 1274–1278.

[79] R. Mogana, A. Adhikari, M.N. Tzar, R. Ramliza, C. Wiart, Antibacterial Activities of the Extracts, Fractions and Isolated Compounds from Canarium Patentinervium Miq. against Bacterial Clinical Isolates, BMC Comp. Med. Therapies 20 (2020) 1–11.

[80] N.-T. Nguyen, T.-H. Nguyen, T.-H. Tran, T.-H.M. Thi, N.-T.N. Thi, X.-H. Tang, V.-H. Ha, G.-B. Tran, D.-T. Tran, Chemical constituents from the seeds of Alpinia Blepharocalyx K. Schum in Vietnam and their bioactives, Pharmacophore (2020) *11*.

[81] M.G. Suh, H.-S. Choi, K. Cho, S.S. Park, W.J. Kim, H.J. Suh, H. Kim, Anti-Inflammatory Action of Herbal Medicine Comprised of Scutellaria Baicalensis and Chrysanthemum morifolium, Biosci., Biotechnol., Biochem. 84 (2020) 1799–1809.

[82] K. Patonay, O. Szabó-Hudák, H. Szalontai, M. Jánószky, E. Kónya, É. Németh, Extraction and Identification of Major Polyphenol Constituents of Northern Hungarian Horsemint (Mentha Longifolia L.(L.)), Acta Biol. Plant. Agriensis 8 (2020) 53–68.

[83] Patonay, K.; Szalontai, H.; Jánószky, M.; Lovas, M.; Pénzesné, E. Main Phenolic Constituents of Mentha Longifolia (L.) L. Samples from Northern Hungary–Extractability, Variability and Contribution to Some in Vitro Antioxidant Properties of the Plant. 2019.

[84] L. Celaya, C. Viturro, L.R. Silva, Acantholippia Salsoloides: Phytochemical Composition and Biological Potential of a Thujonic Population, Nat. Prod. Commun. 14 (2019), 1934578X19858542.

[85] F. Genzel, M.D. Dicke, L.V. Junker-Frohn, A. Neuwohner, B. Thiele, A. Putz, B. Usadel, A. Wormit, A. Wiese-Klinkenberg, Impact of Moderate Cold and Salt Stress on the Accumulation of Antioxidant Flavonoids in the Leaves of Two Capsicum Cultivars, J. Agric. Food Chem. 69 (2021) 6431–6443.

[86] I.K. Karabagias, V.K. Karabagias, K.A. Riganakos, Physico-Chemical Parameters, Phenolic Profile, in Vitro Antioxidant Activity and Volatile Compounds of Ladastacho (Lavandula stoechas) from the Region of Saidona, Antioxidants 8 (2019) 80.

[87] H. Liu, S. Zhu, Q. Liu, Y. Zhang, Spectrum–Effect Relationship Study between HPLC Fingerprints and Antioxidant of Honeysuckle Extract, Biomed. Chromatogr. 33 (2019), e4583.

[88] A. Szopa, A. Starzec, H. Ekiert, The Importance of Monochromatic Lights in the Production of Phenolic Acids and Flavonoids in Shoot Cultures of Aronia melanocarpa, Aronia arbutifolia and Aronia$\times$ Prunifolia, J. Photochem. Photobiol. B: Biol. 179 (2018) 91–97.

[89] S.-H. Lee, H.-W. Kim, M.-K. Lee, Y.J. Kim, G. Asamenew, Y.-S. Cha, J.-B. Kim, Phenolic Profiling and Quantitative Determination of Common Sage (Salvia Plebeia R. Br.) by UPLC-DAD-QTOF/MS, Eur. Food Res. Technol. 244 (2018) 1637–1646.

[90] J.-H. Nho, H.-K. Jung, M.-J. Lee, J.-H. Jang, M.-O. Sim, D.-E. Jeong, H.-W. Cho, J.-C. Kim, Beneficial Effects of Cynaroside on Cisplatin-Induced Kidney Injury in Vitro and in Vivo, Toxicol. Res. 34 (2018) 133–141.

[91] J.H. Nho, H.K. Jung, M.J. Lee, J.H. Jang, M.O. Sim, J.K. Jung, D.E. Jung, B.K. An, H.W. Cho, Inhibitory Effect of Cynaroside Isolated from Lonicera Japonia Thunb on Doxorubicin-Induced Necrosis in Human Renal Proximal Tubular HK-2 Cells. *Korean*, J. Med. Crop Sci. 25 (2017) 322–327.

[92] E. Chuluunbaatar, P. Sodnomtseren, C. Chimedtseren, G. Batsuren, B. Dulamjav, Isolation of Two Flavonoids and Mannitol from Lagotis Integrifolia (Willd.) Schischk (Scrophulariaceae). *Central Asian*, J. Med. Sci. 3 (2017) 167–172.

[93] A. Korga, A. Józefczyk, G. Zgórka, M. Homa, M. Ostrowska, F. Burdan, J. Dudka, Evaluation of the Phytochemical Composition and Protective Activities of Methanolic Extracts of Centaurea Borysthenica and Centaurea Daghestanica (Lipsky) Wagenitz on Cardiomyocytes Treated with Doxorubicin, Food Nutr. Res 61 (2017) 1344077, https://doi.org/10.1080/16546628.2017.1344077.

[94] D.N. Olennikov, N.K. Chirikova, C. Vennos, Chemical Composition, Antioxidant and Anticholinesterase Activities of Gentianella Azurea from Russian Federation, Nat. Prod. Commun. 12 (2017), 1934578X1701200115.

[95] R. Dobrucka, Synthesis and Structural Characteristic of Platinum Nanoparticles Using Herbal Bidens Tripartitus Extract, J. Inorg. Organomet. Polym. Mater. 26 (2016) 219–225.

[96] M. Wolniak, M. Tomczykowa, M. Tomczyk, J. Gudej, I. Wawer, Antioxidant Activity of Extracts and Flavonoids from Bidens tripartita, Acta Pol. Pharm. 64 (2007) 441–447.

[97] G. Costa, J.P. Ferreira, C. Vitorino, M.E. Pina, J.J. Sousa, I.V. Figueiredo, M. T. Batista, Polyphenols from Cymbopogon citratus Leaves as Topical Anti-Inflammatory Agents, J. Ethnopharmacol. 178 (2016) 222–228.

[98] L. Lei, Y. Bin, Z. Wenxue, R. Guangyue, D. Xu, K. Xinyan, Degradation Kinetics of Functional Components of Honeysuckle Flowers during Controlled-Atmosphere Heat Pump Drying, Int. J. Agric. Biol. Eng. 9 (2016) 159–168.

[99] H.U. Wen, G.U.O. Ting, W.-J. Jiang, D. Guang-Li, C. Da-Wei, Y. Shi-Lin, L.I. He-Ran, Effects of Ultrahigh Pressure Extraction on Yield and Antioxidant Activity of Chlorogenic Acid and Cynaroside Extracted from Flower Buds of Lonicera japonica, Chin. J. Nat. Med. 13 (2015) 445–453.

[100] O.T. Olaru, G.M. Nițulescu, A. Orțan, C.E. Dinu-Pîrvu, Ethnomedicinal, Phytochemical and Pharmacological Profile of Anthriscus sylvestris as an Alternative Source for Anticancer Lignans, Molecules 20 (2015) 15003–15022.

[101] V.A.Saffloroside Kurkin, a New Flavonoid from Flowers of Carthamus tinctorius L, J. Pharmacogn. Phytochem. (2015) 4.

[102] M.R. Delnavazi, M. Shahabi, N. Yassa, Flavonoids Leaves Iran. Linden; Tilia Rubra Subsp. Caucasica. *Res. J. Pharmacogn.* 2 (2015) 17–22.

[103] Ahmed, S.A.; Kamel, E.M. Cytotoxic Activities of Flavonoids from Centaurea Scoparia. The Scientific world journal 2014, 2014.

[104] Y. Huang, H. Chen, F. He, Z.-R. Zhang, L. Zheng, Y. Liu, Y.-Y. Lan, S.-G. Liao, Y.-J. Li, Y.-L. Wang, Simultaneous Determination of Human Plasma Protein Binding of Bioactive Flavonoids in Polygonum Orientale by Equilibrium Dialysis Combined with UPLC–MS/MS, J. Pharm. Anal. 3 (2013) 376–381.

[105] Y. Huang, P. Zhang, F. He, L. Zheng, Y. Wang, J. Wu, Simultaneous Determination of Four Bioactive Flavonoids from Polygonum Orientale L. in Dog Plasma by UPLC–ESI-MS/MS and Application of the Technique to Pharmacokinetic Studies, J. Chromatogr. B 957 (2014) 96–104.

[106] Osmachko, A.P.; Kovaleva, A.M.; Ochkur, O.V.; Sydora, N.V. Morphological, Anatomical and Phytochemical Research of Veronica longifolia L. Herb. 2013.

[107] D.N. Olennikov, N.K. Chirikova, Z.M. Okhlopkova, I.S. Zulfugarov, Chemical Composition and Antioxidant Activity of Tánara Ótó (Dracocephalum Palmatum Stephan), a Medicinal Plant Used by the North-Yakutian Nomads, Molecules 18 (2013) 14105–14121.

[108] D.N. Olennikov, L.M. Tankhaeva, N.A. Pankrushina, D.V. Sandanov, Phenolic Compounds of Sophora flavescens Soland. of Russian Origin, Russ. J. Bioorg. Chem. 39 (2013) 755–760.

[109] A. Nugroho, M.-H. Kim, J. Choi, N.-I. Baek, H.-J. Park, In Vivo Sedative and Gastroprotective Activities of Salvia Plebeia Extract and Its Composition of Polyphenols, Arch. pharmacal Res. 35 (2012) 1403–1411.

[110] A.V. Kurkina, A Method for the Assay of Total Flavonoids in Common Agrimony Herb, Pharm. Chem. J. 45 (2011) 43–46.

[111] A.R. Gohari, S. Saeidnia, K. Mollazadeh, N. Yassa, M. Malmir, A.R. Shahverdi, Isolation of a New Quinic Acid Derivative and Its Antibacterial Modulating Activity. *Daru: Journal of Faculty of Pharmacy*, Tehran Univ. Med. Sci. 18 (2010) 69.

[112] K.-S. Lee, G.-H. Kim, H.-H. Kim, E.-S. Kim, H.-M. Park, M.-J. Oh, Quality Characteristics of Tea Thermally Processed from Dried Ixeris Dentata Root, Korean J. Food Preserv. 15 (2008) 524–531.

[113] S.K. Sadhu, F. Ahmed, T. Ohtsuki, M. Ishibashi, Flavonoids from Sonneratia Caseolaris, J. Nat. Med. 60 (2006) 264–265.

[114] S. Bolkent, R. Yanardag, O. Karabulut-Bulan, B. Yesilyaprak, Protective Role of Melissa officinalis L. Extract on Liver of Hyperlipidemic Rats: A Morphological and Biochemical Study, J. Ethnopharmacol. 99 (2005) 391–398.

[115] Z.A. Khushbaktova, S.K. Faizieva, V.N. Syrov, M.P. Yuldashev, E.K. Batirov, A. U. Mamatkhanov, Isolation, Chemical Analysis, and Study of the Hypolipidemic Activity of the Total Flavonoid Extract from Thermopsis Altherniaflora, Pharm. Chem. J. 35 (2001) 155–158.

[116] P. Marques, J. Marto, L.M. Gonçalves, R. Pacheco, M. Fitas, P. Pinto, M.L. M. Serralheiro, H. Ribeiro, Cynara scolymus L.: A Promising Mediterranean Extract for Topical Anti-Aging Prevention, Ind. Crops Prod. 109 (2017) 699–706.

[117] A.S. El Senousy, M.A. Farag, D.A. Al-Mahdy, L.A. Wessjohann, Developmental Changes in Leaf Phenolics Composition from Three Artichoke Cvs.(Cynara scolymus) as Determined via UHPLC–MS and Chemometrics, Phytochemistry 108 (2014) 67–76.

[118] M.I. Nassar, T.K. Mohamed, A.I. Elshamy, S.A. El-Toumy, A.M.A. Lateef, A.-R. H. Farrag, Chemical Constituents and Anti-Ulcerogenic Potential of the Scales of Cynara scolymus (Artichoke) Heads, J. Sci. Food Agric. 93 (2013) 2494–2501.

[119] E. Georgieva, Y. Karamalakova, G. Nikolova, B. Grigorov, D. Pavlov, V. Gadjeva, A. Zheleva, Radical Scavenging Capacity of Seeds and Leaves Ethanol Extracts of Cynara scolymus L.—A Comparative Study, Biotechnol. Biotechnol. Equip. 26 (2012) 151–155.

[120] A. Romani, P. Pinelli, C. Cantini, A. Cimato, D. Heimler, Characterization of Violetto Di Toscana, a Typical Italian Variety of Artichoke (Cynara scolymus L.), Food Chem. 95 (2006) 221–225.

[121] F. Emendörfer, F. Emendörfer, F. Bellato, V.F. Noldin, V. Cechinel-Filho, R. A. Yunes, Delle Monache, F.; Cardozo, A.M. Antispasmodic Activity of Fractions and Cynaropicrin from Cynara scolymus on Guinea-Pig Ileum, Biol. Pharm. Bull. 28 (2005) 902–904.

[122] H. Li, N. Xia, I. Brausch, Y. Yao, U. Förstermann, Flavonoids from Artichoke (Cynara scolymus L.) up-Regulate Endothelial-Type Nitric-Oxide Synthase Gene Expression in Human Endothelial Cells, J. Pharmacol. Exp. Ther. 310 (2004) 926–932.

[123] M. Wang, J.E. Simon, I.F. Aviles, K. He, Q.-Y. Zheng, Y. Tadmor, Analysis of Antioxidative Phenolic Compounds in Artichoke (Cynara scolymus L.), J. Agric. Food Chem. 51 (2003) 601–608.

[124] M. Häusler, M. Ganzera, G. Abel, M. Popp, H. Stuppner, Determination of Caffeoylquinic Acids and Flavonoids InCynara scolymus L. by High Performance Liquid Chromatography, Chromatographia 56 (2002) 407–411.

[125] Nüβlein, B.; Kreis, W. Purification and Characterization of a Cynaroside 7-O-β-d-Glucosidase from Cynarae Scolymi Folium. In Proceedings of the IV International Congress on Artichoke 681; 2000; pp. 413–420.

[126] F.M. Hammouda, Seif El-Nasr, M.M. Shahat, A.A, Flavonoids OfCynara scolymus L. Cultivated in Egypt, Plant Foods Hum. Nutr. 44 (1993) 163–169.

[127] V. Lattanzio, I. Morone, Variations of the Orthodiphenol Content OfCynara scolymus L. during the Plant Growing Seasons, Experientia 35 (1979) 993–994.

[128] L.N. Gvazava, Cynaroside from the Leaves OfDigitalis Ciliata, Chem. Nat. Compd. 12 (1976) 737–738.

[129] S.F. Dzhumyrko, Flavonoids of Plants of the Genus Symphyandra, Chem. Nat. Compd. 11 (1975), 537–537.

[130] N.K. Vavilova, É. Gella, Homoorientin from Phlomis tuberosa, Chem. Nat. Compd. 9 (1973), 282–282.

[131] M. Tomczykowa, M. Tomczyk, K. Leszczyńska, D. Kalemba, Flavonoids and Essential Oil of Bidens cernua of Polish Origin and in Vitro Antimicrobial Activity of the Oil, Rec. Nat. Prod. 11 (2017) 468–473.

[132] H.O. Elansary, A. Szopa, P. Kubica, H. Ekiert, M. Klimek-Szczykutowicz, D.O. El-Ansary, E.A. Mahmoud, Polyphenol Profile and Antimicrobial and Cytotoxic Activities of Natural Mentha$\times$ Piperita and Mentha Longifolia Populations in Northern Saudi Arabia, Processes 8 (2020) 479.

[133] Z.S. Ahmed, S.S. Abozed, M.S. Negm, Nutritional Value and Sensory Profile of Gluten-Free Tiger Nut Enriched Biscuit, World J. Dairy Food Sci. 9 (2014) 127–134.

[134] H.-C. Huang, D. Tang, K. Xu, Z.-F. Jiang, Curcumin Attenuates Amyloid-β-Induced Tau Hyperphosphorylation in Human Neuroblastoma SH-SY5Y Cells Involving PTEN/Akt/GSK-3β Signaling Pathway, J. Recept. Signal Transduct. 34 (2014) 26–37.

[135] S.A. Lee, B.-R. Park, S.-M. Moon, S.H. Shin, J.-S. Kim, D.K. Kim, C.S. Kim, Cynaroside Protects Human Periodontal Ligament Cells from Lipopolysaccharide-Induced Damage and Inflammation through Suppression of NF-KB Activation, Arch. Oral. Biol. 120 (2020), 104944.