Echinacea purpurea (L.) Moench

Subjects: Pharmacology & Pharmacy

Contributor: Cristina Burlou-Nagy, Annamaria Pallag, Florin Banica, Jurca Tunde, Laura Vicaș, Eleonora Marian, Mariana Eugenia Mureșan , Dr Bácskay Ildikó, Rita Kiss, Pálma Fehér

Echinacea purpurea (L.) Moench (EP)is a perennial herbaceous flowering plant, commonly known as purple coneflower and it belongs to the Asteraceae family. The Echinacea genus is originally from North America, in the United States, and its species are widely distributed throughout. There are nine different species of Echinacea, but only three of them are used as medicinal plants with wide therapeutic uses: *Echinacea purpurea* (L.) Moench, *Echinacea pallida* (Nutt.) Nutt. and *Echinacea angustifolia* DC. Several significant groups of bioactive compounds with pharmacological activities have been isolated from Echinacea species. Numerous beneficial effects have been demonstrated about these compounds.

Keywords: Echinacea purpurea (L.) Moench ; bioactive compounds ; immunomodulatory ; cannabinomimetic ; anti-inflammatory ; antiviral ; antimicrobial ; antioxidant effect

1. Introduction

Nature has always been a great source of therapeutic substances, providing us with various medicinal plants that produce valuable phytochemicals.

Medicinal plant use dates back to remote times and it is therefore believed to be the genesis of modern medicine. In addition, chemicals generated from plants are and will continue to be a valuable source of molecules for pharmaceuticals [1]. In the past, folk observations and experience were the guiding principles in the use of herbs, but today their active ingredients, their action mechanisms and their usage based on principles of evidence-based medicine have been discovered.

Phytotherapy is widely utilized in the treatment and prevention of a variety of medical conditions and is well-known among the general populace [2].

Plant-based pharmaceuticals now represent about 30% of the drugs market made up of necessary medications, while the remaining 11% is made up of non-essential drugs [3][4].

This evaluation's primary goal is the synthesis of the data from the specialized literature regarding the bioactive compounds, chemical composition, pharmacological and biological properties of *Echinacea purpurea* (L.) Moench to highlight the possibilities and perspectives for future studies, and to obtain safe and pharmacologically effective products.

The species of the genus Echinacea occupy an important place among medicinal plants, are native to North America and belong to the Asteraceae family. Echinacea comes in nine distinct species, but just three are utilized as medicinal herbs with wide therapeutic uses: *Echinacea purpurea* (L.) Moench, *Echinacea pallida* (Nutt.) Nutt. and *Echinacea angustifolia* DC [5][6].

A large number of species in the Asteraceae family have been utilized for therapeutic purposes in comparison to other plant families because of the availability of chemicals with a broad spectrum of therapeutic properties, as well as the fact that the Asteraceae family of plants is one of the most prominent and well-known [7][8].

Figure 1 shows the evolution over time of publications on the genus Echinacea and the species *Echinacea purpurea* (L.) Moench. There has been an increase in scientific research on these species over time until 2009, after which there was a slight decrease until 2015, followed by an increase again until today [9][10].

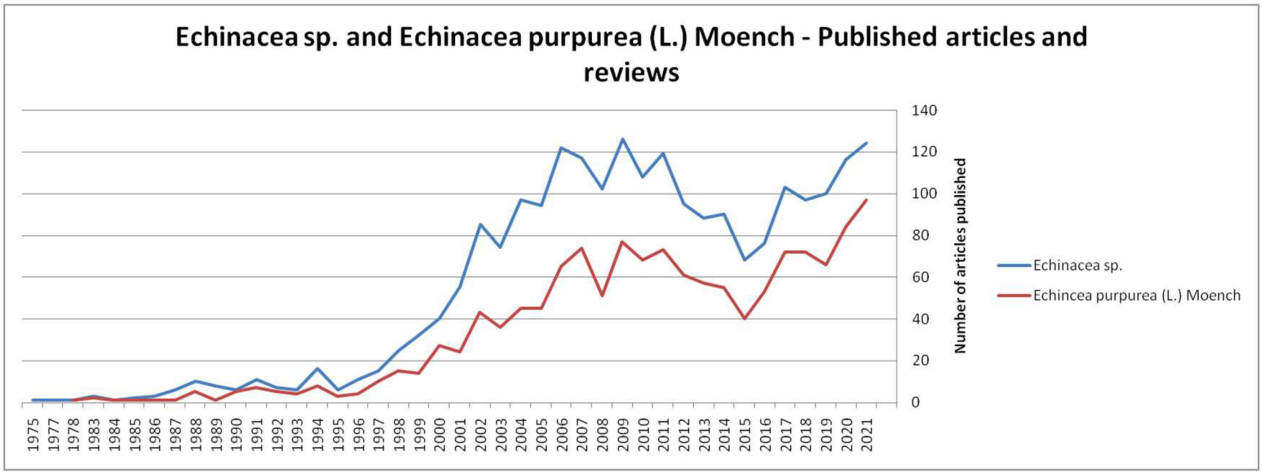

Figure 1. Evolution of the number of articles and reviews about Echinacea sp. and *Echinacea purpurea* (L.) Moench [9][10].

Echinacea purpurea (L.) Moench is a perennial plant, 100–150 cm tall, vigorous and herbaceous. The roots and rhizome are highly developed. *Echinacea purpurea* (L.) Moench is a perennial plant, vigorous, 100–150 cm tall and herbaceous. The roots are cylindrical, brownish-gray on the exterior and white on the interior. The aerial stem is branching and has rough hairs and reddish-brown patches, giving it the appearance of a bush. Linear-lanceolate leaves with three arching ribs and rough hairs are entire, 3–6 cm wide. It produces a rosette of leaves during the first year of cultivation and blooms only in the second year [11][12][13].

2. Bioactive Compounds of Echinacea purpurea (L.) Moench

Several significant groups of bioactive compounds, with pharmacological activities, have been isolated from Echinacea species. The most important components of *Echinacea purpurea* (L.) Moench are alkylamides, polysaccharides, glycoproteins, flavonoids and phenolic compounds, which include [14] derivates of caffeic acid, like caffeic acid, chicoric acid, caftaric acid, chlorogenic acid and echinacoside, **Figure 2**, [15][16], whose amounts vary based on the plant's sections. In addition to these components, the researchers also identified thatphylloxanthobilins, β-phellandrene, acetaldehyde, dimethyl sulfide, camphene, hexanal, α-pinene and limonene are present in all plant tissues, regardless of species. Fatty acids, aldehydes and terpenoidsare constituents whose presence depend on the parts of plants used [17][18][19][20][21][22][23][24][25][26][27][28][29][30].

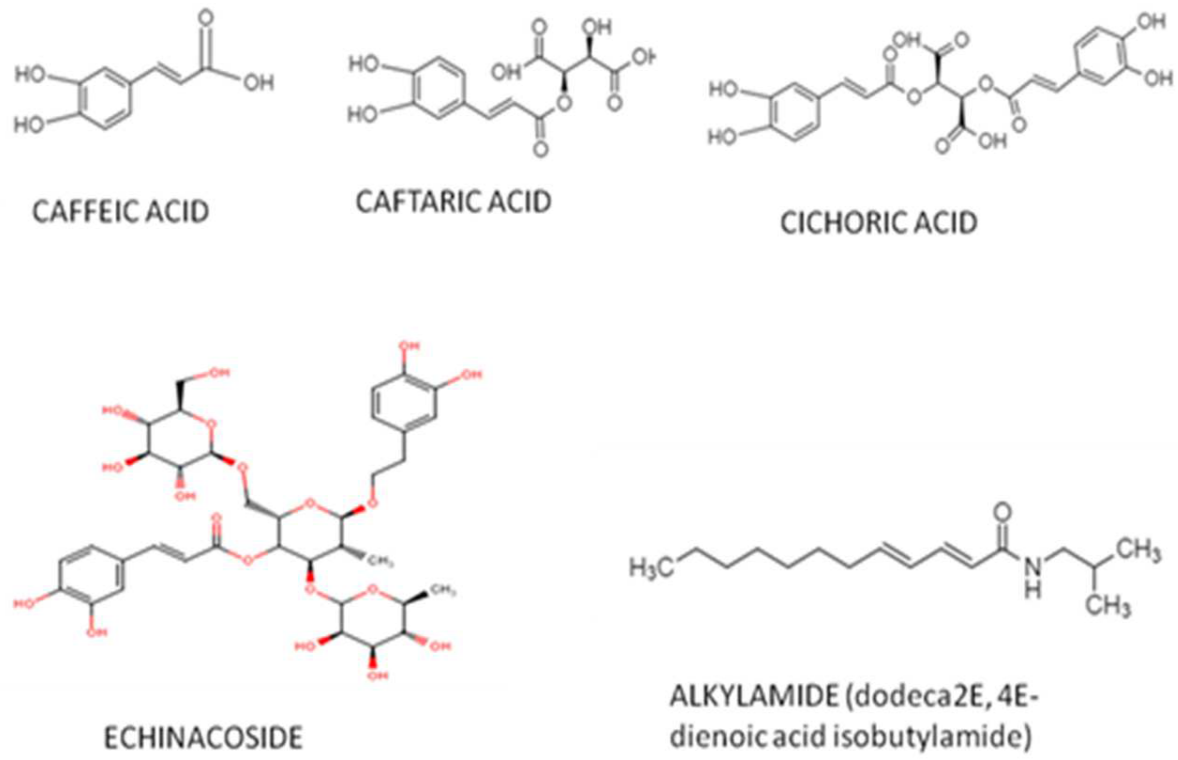

Figure 2. Structure of major compounds.

The chemical components responsible for the immunomodulatory activities of purple coneflower roots are glycoproteins, alkylamides and polysaccharides [31]. Glycoproteins are proteins and carbohydrate chains that have a role in a variety of physiological activities, including immunology. Alkylamides are a kind of chemical found in genus Echinacea (Asteraceae) that has been demonstrated to have high bioavailability and alsoimmunomodulatory properties. Structurally, they have a common feature of an amine bond and usually contained an aliphatic chain of polyunsaturated fatty acids connected to a short-chain amine. Polysaccharides are complex carbohydrate polymers made up of more than two monosaccharides. The Asteraceae family contains important polysaccharides, pectins, arabinogalactans and inulin. Bioactive polysaccharides may substantiate a part of the traditional uses of these species.

EP supplements are, in general, sold as encapsulated tablets containing aerial parts or dried roots or as tablets containing extruded material from pressed plants or ethanol extracts.

The above-ground parts of the plant contain smaller amounts of volatile oils and pyrolizid alkaloids such as tussilagin and isotussilagin than the root [32].

The most important derivative of caffeic acidof the *Echinacea purpurea* (L.) Moench species is considered to be chicoric acid, the most predominant phenolic component in the root and petiole [33][34][35][36][37]. Chicoric acid is the most abundant phenolic component in the root and petiole of *Echinacea purpurea* (L.) Moench. These antioxidant and antibacterial compounds can help the immunological system of the body to function better. However, caffeic acid derivative concentrations will vary according to EP species, organ type, growing conditions and environmental factors.

Using the HPLC method, some studies demonstrated the retention of caffeic acid derivatives in dried EP. It was reported that chicoric acid accounted for 63% and 67%, respectively, of the relative peak area for aerial sections. By using the HPLC method, caffeic acid cannot be detected in all dried flowers. In contrast, the caffeic acid content was 8–18% of the measured relative peak area [38][39][40]. Chicoric acid (71.45%) is the most predominant caffeic acid derivative in flowers, followed by caffeic acid (23.25%) [41].

Echinacoside was discovered to have a variety of pharmacologically important benefits on human health, particularly neuroprotective and cardiovascular effects [27][42]. Echinacosite is a caffeic acid derivative found in the flower at a concentration of 1.45% [40]. In addition to these substances, Echinacea species contain flavonoids, polyacetylenes and alkaloids [43][44].

The constituents that are also important, isolated from the extracts of *Echinacea purpurea* (L.) Moench leaves, are phylloxanthobilins. The breakdown of chlorophyll produces these natural tetrapyrrole compounds. Phylloxanthobilins were identified in the leaves of deciduous trees about 10years ago and are currently considered a compound class with great bioactivity potential, which has yet to be studied. However, there have been no reports of phylloxanthobines being found in sections of a medicinal plant utilized in pharmaceutical formulations until now [45][46].

β-phellandrene was discovered to be prominent in the roots of EP, but lacking in all tissues of *Echinacea pallida* Nutt, in one research study using gas chromatography/mass spectrometry. α-Myrcene was found in large concentrations in all three Echinacea species' flowers, leaves and stems, but was missing from the roots of *Echinaceae angustifolia* and *Echinacea purpurea* (L.) Moench and was only in small concentrations in the roots of *Echinacea pallida Nutt*. Acetaldehyde, dimethyl sulfide, camphene, hexanal, α-pinene and all plant tissues contain limonene, regardless of species. Dimethyl sulfide has been identified in trace amounts in all species' leaves, stems and flowers; nonetheless, it was the most abundant ingredient in *Echinacea pallida* roots and, second, was the most abundant component in *Echinacea angustifolia* and *Echinacea purpurea* (L.) Moench roots. Butanals and propanals, in particular, are aldehydes, comprising 41–57% of root tissue headspace and 19–29% of leaf tissue headspace, and just 6–14% of the headspace between the bloom and the stem tissue. Terpenoids such as α–myrcene, β– and α–pinene, ocimene, camphene, terpenene and limonene constitute between 82–91% of the headspace of stems and flowers, 46–58% of the leaf tissue's headspace and 6–21% of the roots. Furthermore, there are 14 hydrocarbons, 12 alcohols, 7 esters, 6 ketones and 7 other chemicals found [47][48][49]. In another study, the researchers identified compounds in an n-hexane extract of *Echinacea purpurea* (L.) Moench such as fatty acids comprising 9,12-octadecadienoic acid (linoleic acid), hexadecanoic acid (palmitic acid) and octadecanoic acid (stearic acid), accounting for 25.8% of the extract, and after that come the next long-chain hydrocarbons (14.6%) and sterols (13.9%) [50].

EP has also been prepared for use as a topical treatment for skin and wound inflammation. In addition, Echinacea products are licensed in Europe to heal infections of the upper respiratory tract and wound healing [51][52][53][54].

Many bioactivities of EP have been discovered in modern pharmacological investigations, including immunomodulatory, anti-inflammatory, antioxidant, antiviral and antifungal activities [55][56].

Chronic arthritis, cancer, antimicrobial action, persistent fatigue syndrome, HIV infection, a range of skin ailments, wounds and chronic pelvic infections were all mentioned as potential therapeutic uses for EP [57].

Preparations containing EP are among the best-selling herbal medications in Europe and the United States [52][58]. EP supplementation may decrease the severity and duration of acute respiratory tract infections, according to current research; however, no studies have been identified using Echinacea to prevent or treat the SARS-CoV virus infection [59].

The immunomodulatory effects of Echinacea species are of primary concern for research, especially those related to upper respiratory tract infections. Discoveries made recently have also shown that certain standardized preparations of Echinacea have strong antiviral, antifungal, antimicrobial, anti-inflammatory, antioxidant and psychoactive activities. Given the available data, preparations obtained from Echinacea are well-tolerated by the human organism [60]. Therefore, further investigations are needed to ensure the quality and safety of the various preparations of Echinacea sp. [61]. Echinacea sp. can cause minor side effects; it should be considered if the patient who is receiving Echinacea sp. preparations is allergic to *Ambrosia artemisifolia L.* or other species of the Asteraceae family. *Echinacea* sp., like many other Asteraceae plants, includes phototoxic polyacetylene compounds that can be inactivated with minimal processing [62][63].

It is important to note that during preservation, enzymatic processes have the potential to degrade bioactive substances as a result of long-term storage from collection to marketing, leading in compositional changes.

Stuart and Wills (2000) studied the alkylamide and chicoric acid content of ground and dried *Echinacea purpurea* (L.) Moench roots for 60 days, **Table 1** [63][64].

Table 1. Correlation between the storage condition and bioactive compounds concentration.

Storage Condition	Storage Temperature	Alchylamides Concentration	Chicoric Acid Concentration	Ref.
60 days in the dark	5 °C	unchanged	70% decrease	[63][64]
60 days in the light	20 °C	65% decrease	unchanged	[63][64]

3. Biological and Pharmacological Effects of Echinacea purpurea (L.) Moench

Currently, the number of herbs that are subject to scientific studies is increasing. The well-known medicinal plants are intensively studied to obtain the most accurate data about the chemical composition, the pharmacological effects and the safety of use in therapy [65].

Table 2 summarizes the most important components identified in *Echinacea purpurea* (L.) Moench and the scientifically proven biological and pharmacological effects, according to the literature. It can be seen that most of the demonstrated effects are common to several compounds, such as the immunomodulatory, antioxidant or antimicrobial effects.

Table 2. Biological and pharmacological effects of the bioactive compounds of *Echinacea purpurea* (L.) Moench.

Bioactive Compounds	Biological and Pharmacological Effects	References
Alkylamides	Anti-inflammatory Immunomodulatory Modulation of macrophages Reduction of NO and tumor necrosis factor -α Mediators of antiviral immunity Cannabinoid receptor type 2 Antitumoral Antioxidant Antimicrobial Antifungal Antiviral	[66][67][68][69][70][71][72][73]
Polysaccharides	Immunomodulatory Hypoglycemic Hepatoprotective Gastrointestinal-protective Antidiabetic	[74][75][76][77][78][79][80][81][82][83][84][85][86][87][88][89][90]
Glycoproteins	Immunomodulatory Antioxidant activity	[91][92][93][94][95]
Flavonoids	Anti-inflammatory Anti-ulcer activity Antiallergic Antiviral	[96][97][98][99][100][101]

Bioactive Compounds	Biological and Pharmacological Effects	References
Caffeic acid derivatives	Antioxidant activity	[102][103][104][105][106][107][108][109][110][111][112][113][114][115][116][117][118]
	Antiosteoporotic activity	
	Anti-inflammatory	
	Antimicrobial	
	Anti-tumoral	
	Neuroprotective action	

Following the study of the literature, the researchers identified a large number of scientifically proven therapeutic properties for *Echinacea purpurea (L.) Moench* (**Figure 3**).

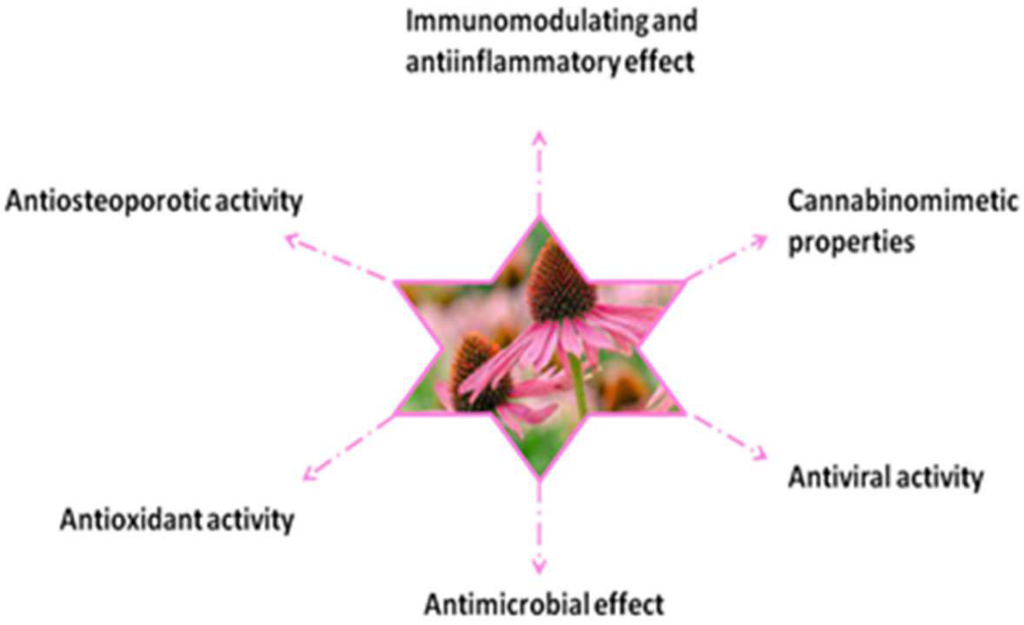

Figure 3. Properties of *Echinacea purpurea (L.) Moench*.

References

1. Salmeron-Manzano, E.; Garrido-Cardenas, J.A.; Manzano-Agugliaro, F. Worldwide Research Trends on Medicinal Plants. Int. J. Environ. Res. Public Health 2020, 17, 3376.
2. Pazyar, N.; Yaghoobi, R.; Rafiee, E.; Mehrabian, A.; Feily, A. Skin Wound Healing and Phytomedicine: A Review. Ski. Pharmacol. Physiol. 2014, 27, 303–310.
3. Hegedűs, C.; Muresan, M.; Badale, A.; Bombicz, M.; Varga, B.; Szilágyi, A.; Sinka, D.; Bácskay, I.; Popoviciu, M.; Magyar, I.; et al. SIRT1 Activation by Equisetum arvense L. (Horsetail) Modulates Insulin Sensitivity in Streptozotocin Induced Diabetic Rats. Molecules 2020, 25, 2541.
4. Stanisavljević, I.; Stojičević, S.; Veličković, D.; Veljković, V.; Lazic, M. Antioxidant and Antimicrobial Activities of Echinacea (Echinacea purpurea L.) Extracts Obtained by Classical and Ultrasound Extraction. Chin. J. Chem. Eng. 2009, 17, 478–483.
5. Kaya, M.; Merdivan, M.; Tashakkori, P.; Erdem, P.; Anderson, J.L. Analysis of Echinacea flower volatile constituents by HS-SPME-GC/MS using laboratory-prepared and commercial SPME fibers. J. Essent. Oil Res. 2018, 31, 91–98.

6. Lekar', A.V.; Borisenko, S.N.; Filonova, O.V.; Vetrova, E.V.; Maksimenko, E.V.; Borisenko, N.I.; Minkin, V.I. Extraction of caftaric and cichoric acids from Echinacea purpurea L. in subcritical water. Russ. J. Phys. Chem. B 2013, 7, 968–975.
7. Nadaf, M.; Joharchi, M.R.; Amiri, M.S. Ethnomedicinal uses of plants for the treatment of nervous disorders at the herbal markets of Bojnord, North Khorasan Province, Iran. J. Phytomedicine 2018, 9, 153–163.
8. Cao, C.; Kindscher, K. The Medicinal Chemistry of Echinacea Species. Echinacea 2016, 127–145.
9. Scopus Database. Available online: https://www-scopus-com.am.e-nformation.ro/results/results.uri?sort=plf-f&src=s&st1=Echinacea&sid=1265d6dbcfd9127a51f79e0747ea36dd&sot=b&sdt=b&sl=24&s=TITLE-ABS-KEY%28Echinacea%29&origin=searchbasic&editSaveSearch=&yearFrom=Before+1960&yearTo=Present (accessed on 9 March 2022).
10. Web of Science Database. Available online: https://www-webofscience-com.am.e-nformation.ro/wos/woscc/summary/cc619678-4982-4090-8c17-ca37d828cff1-3348de15/relevance/1 (accessed on 10 March 2022).
11. Mistríková, I.; Vaverková, Š. Morphology and anatomy of Echinacea purpurea, E. angustifolia, E. pallida and Parthenium integrifolium. Biologia 2007, 62, 2–5.
12. Awang, D.V.C.; Kindack, D.G. Herbal medicine: Echinacea. Can. Pharm. J. 1991, 124, 512–516.
13. McGregor, R. The taxonomy of the genus Echinacea (Compositae). University of Kansas. Sci. Bull. 1968, 48, 113–142.
14. Harborne, J.B.; Williams, C.A. Phytochemistry of the Genus Echinacea, Echinacea; CRC Press: Boca Raton, FL, USA, 2004; pp. 71–88.
15. Attarzadeh, M.; Balouchi, H.; Rajaie, M.; Dehnavi, M.M.; Salehi, A. Improving growth and phenolic compounds of Echinacea purpurea root by integrating biological and chemical resources of phosphorus under water deficit stress. Ind. Crop. Prod. 2020, 154, 112763.
16. Bruni, R.; Brighenti, V.; Caesar, L.K.; Bertelli, D.; Cech, N.B.; Pellati, F. Analytical methods for the study of bioactive compounds from medicinally used Echinacea species. J. Pharm. Biomed. Anal. 2018, 160, 443–477.
17. Pallag, A.; Bungau, S.; Tit, M.D.; Jurca, T.M.; Sirbu, V.; Honiges, A.; Horhogea, C. Comparative Study of Polyphenols, Flavonoids and Chlorophylls in Equisetum arvense L. Populations. Revista Chimie 2016, 67, 350–353.
18. Banica, F.; Bungau, S.; Tit, D.M.; Behl, T.; Otrisal, P.; Nechifor, A.C.; Gitea, D.; Pavel, F.-M.; Nemeth, S. Determination of the Total Polyphenols Content and Antioxidant Activity of Echinacea Purpurea Extracts Using Newly Manufactured Glassy Carbon Electrodes Modified with Carbon Nanotubes. Processes 2020, 8, 833.
19. Bauer, R.; Wagner, H.; Hikano, H.; Farnsworth, N.R. Echinacea species as potential immunostimulatory drugs. Econ. Med. Plant Res. 1991, 5, 253–321.
20. Abdelmohsen, M.M.; Nafiz, N.M.; Seif el Nasr, M.M. Microwave assisted extraction of bio-active compounds (phenolics and alkamides) from Echinacea purpurea. Int. J. Pharma Pharma Sci. 2014, 6, 265–268.
21. Barnes, J.; Anderson, L.A.; Gibbons, S.; Phillipson, J.D. Echinacea species (Echinacea angustifolia (DC.) Hell., Echinacea pallida (Nutt.) Nutt., Echinacea purpurea (L.) Moench): A review of their chemistry, pharmacology and clinical properties. J. Pharm. Pharmacol. 2005, 57, 929–954.
22. de Oliveira, B.G.; Santos, L.F.F.; Pianetti, G.A.; César, I.C. A Rapid UPLC Method for the Simultaneous Quantitation of Caffeic Acid Derivatives in Dried Extracts of Echinacea Purpurea. J. Chromatogr. Sci. 2021, 59, 439–444.
23. Vendramin, V.; Viel, A.; Vincenzi, S. Caftaric Acid Isolation from Unripe Grape: A "Green" Alternative for Hydroxycinnamic Acids Recovery. Molecules 2021, 26, 1148.
24. Ramezannezhad, R.; Aghdasi, M.; Fatemi, M. Enhanced production of cichoric acid in cell suspension culture of Echinacea purpurea by silver nanoparticle elicitation. Plant Cell Tissue Organ Cult. (PCTOC) 2019, 139, 261–273.
25. Attarzadeh, M.; Balouchi, H.; Rajaie, M.; Dehnavi, M.M.; Salehi, A. Growth and nutrient content of Echinacea purpurea as affected by the combination of phosphorus with arbuscular mycorrhizal fungus and Pseudomonas florescent bacterium under different irrigation regimes. J. Environ. Manag. 2018, 231, 182–188.
26. Maggini, V.; De Leo, M.; Granchi, C.; Tuccinardi, T.; Mengoni, A.; Gallo, E.R.; Biffi, S.; Fani, R.; Pistelli, L.; Firenzuoli, F.; et al. The influence of Echinacea purpurea leaf microbiota on chicoric acid level. Sci. Rep. 2019, 9, 1–11.
27. Tabar, R.S.; Moieni, A.; Monfared, S.R. Improving biomass and chicoric acid content in hairy roots of Echinacea purpurea L. Biologia 2019, 74, 941–951.
28. Dalby-Brown, L.; Barsett, H.; Landbo, A.-K.R.; Meyer, A.A.S.; Mølgaard, P. Synergistic Antioxidative Effects of Alkamides, Caffeic Acid Derivatives, and Polysaccharide Fractions from Echinacea purpurea on in Vitro Oxidation of Human Low-Density Lipoproteins. J. Agric. Food Chem. 2005, 53, 9413–9423.

29. Kakimov, A.; Muratbayev, A.; Zharykbasova, K.; Amanzholov, S.; Mirasheva, G.; Kassymov, S.; Utegenova, A.; Jumazhanova, M.; Shariati, M.A. Heavy metals analysis, GCMS-QP quantification of flavonoids, amino acids and saponins, analysis of tannins and organoleptic properties of powder and tincture of Echinacea purpurea (L.) and Rhapónticum carthamoídes. Potravinarstvo Slovak J. Food Sci. 2021, 15, 330–339.

30. Nyalambisa, M.; Oyemitan, I.; Matewu, R.; Oyedeji, O.; Oluwafemi, O.; Songca, S.P.; Nkeh-Chungag, B.N. Volatile constituents and biological activities of the leaf and root of Echinacea species from South Africa. Saudi Pharm. J. 2016, 25, 381–386.

31. Balciunaite, G.; Haimi, P.-J.; Mikniene, Z.; Savickas, G.; Ragazinskiene, O.; Juodziukyniene, N.; Baniulis, D.; Pangonyte, D. Identification of Echinacea Purpurea (L.) Moench Root LysM Lectin with Nephrotoxic Properties. Toxins 2020, 12, 88.

32. Kumar, K.M.; Ramaiah, S. Pharmacological importance of Echinacea purpurea. Int. J. Pharm. Biol. Sci. 2011, 2, 305–314.

33. Liu, C.-Z.; Abbasi, B.H.; Gao, M.; Murch, A.S.J.; Saxena, P.K. Caffeic Acid Derivatives Production by Hairy Root Cultures of Echinacea purpurea. J. Agric. Food Chem. 2006, 54, 8456–8460.

34. Erkoyuncu, M.T.; Yorgancilar, M. Optimization of callus cultures at Echinacea purpurea L. for the amount of caffeic acid derivatives. Electron. J. Biotechnol. 2021, 51, 17–27.

35. Pellati, F.; Benvenuti, S.; Magro, L.; Melegari, M.; Soragni, F. Analysis of phenolic compounds and radical scavenging activity of Echinacea spp. J. Pharm. Biomed. Anal. 2004, 35, 289–301.

36. Thygesen, L.; Thulin, J.; Mortensen, A.; Skibsted, L.H.; Molgaard, P. Antioxidant activity of cichoric acid and alkamides from Echinacea purpurea, alone and in combination. Food Chem. 2007, 101, 74–81.

37. Jukić, H.; Habeš, S.; Aldžić, A.; Durgo, K.; Kosalec, I. Antioxidant and prooxidant activities of phenolic compounds of the extracts of Echinacea purpurea (L.). Bull. Chem. Technol. Bosnia Herzeg. 2015, 44, 43–52.

38. Kim, H.-O.; Durance, T.D.; Scaman, C.H.; Kitts, D.D. Retention of Caffeic Acid Derivatives in Dried Echinacea purpurea. J. Agric. Food Chem. 2000, 48, 4182–4186.

39. Bergeron, C.; Livesey, J.F.; Awang, D.V.C.; Arnason, J.T.; Rana, J.; Baum, B.R.; Letchamo, W. A quantitative HPLC method for the quality assurance of Echinacea Products on the North American market. Phytochem. Anal. 2000, 11, 207–215.

40. Brown, P.N.; Chan, M.; Betz, J.M. Optimization and single-laboratory validation study of a high-performance liquid chromatography (HPLC) method for the determination of phenolic Echinacea constituents. Anal. Bioanal. Chem. 2010, 397, 1883–1892.

41. Chiou, S.-Y.; Sung, J.-M.; Huang, P.-W.; Lin, S.-D. Antioxidant, Antidiabetic, and Antihypertensive Properties of Echinacea purpurea Flower Extract and Caffeic Acid Derivatives Using In Vitro Models. J. Med. Food 2017, 20, 171–179.

42. Geng, X.; Tian, X.; Tu, P.; Pu, X. Neuroprotective effects of echinacoside in the mouse MPTP model of Parkinson's disease. Eur. J. Pharmacol. 2007, 564, 66–74.

43. Bauer, R. . Z. fur arztliche Fortbild. 1996, 90.

44. Hou, R.; Xu, T.; Li, Q.; Yang, F.; Wang, C.; Huang, T.; Hao, Z. Polysaccharide from Echinacea purpurea reduce the oxidant stress in vitro and in vivo. Int. J. Biol. Macromol. 2020, 149, 41–50.

45. Karg, C.A.; Wang, P.; Vollmar, A.M.; Moser, S. Re-opening the stage for Echinacea research—Characterization of phylloxanthobilins as a novel anti-oxidative compound class in Echinacea purpurea. Phytomedicine 2019, 60, 152969.

46. Karg, C.A.; Wang, P.; Kluibenschedl, F.; Müller, A.P.D.T.; Allmendinger, L.; Vollmar, A.M.; Moser, S. Phylloxanthobilins are Abundant Linear Tetrapyrroles from Chlorophyll Breakdown with Activities Against Cancer Cells. Eur. J. Org. Chem. 2020, 2020, 4499–4509.

47. Mazza, G.; Cottrell, T. Volatile Components of Roots, Stems, Leaves, and Flowers of Echinacea Species. J. Agric. Food Chem. 1999, 47, 3081–3085.

48. Luo, X.-B.; Chen, B.; Yao, S.-Z.; Zeng, J.-G. Simultaneous analysis of caffeic acid derivatives and alkamides in roots and extracts of Echinacea purpurea by high-performance liquid chromatography–photodiode array detection–electrospray mass spectrometry. J. Chromatogr. A 2002, 986, 73–81.

49. Thomsen, M.O.; Fretté, X.C.; Christensen, K.B.; Christensen, L.P.; Grevsen, K. Seasonal Variations in the Concentrations of Lipophilic Compounds and Phenolic Acids in the Roots of Echinacea purpurea and Echinacea pallida. J. Agric. Food Chem. 2012, 60, 12131–12141.

50. Coelho, J.; Barros, L.; Dias, M.I.; Finimundy, T.C.; Amaral, J.S.; Alves, M.J.; Calhelha, R.C.; Santos, P.F.; Ferreira, I.C. Echinacea purpurea (L.) Moench: Chemical Characterization and Bioactivity of Its Extracts and Fractions. Pharmaceuticals 2020, 13, 125.

51. Meyer, S.A. Echinacea. Elsevier 2005, 2, 116.

52. Billah, M.; Hosen, B.; Khan, F.; Niaz, K. Echinacea Book: Nonvitamin and Nonmineral Nutritional Supplements, 1st ed.; Academic Press: Cambridge, MA, USA, 2019; pp. 205–210.

53. Birt, D.F.; Widrlechner, M.P.; Lalone, C.; Wu, L.; Bae, J.; Solco, A.K.; Kraus, G.; Murphy, P.; Wurtele, E.; Leng, Q.; et al. Echinacea in infection. Am. J. Clin. Nutr. 2008, 87, 488S–492S.

54. Rahman, A.N.A.; Khalil, A.A.; Abdallah, H.; ElHady, M. The effects of the dietary supplementation of Echinacea purpurea extract and/or vitamin C on the intestinal histomorphology, phagocytic activity, and gene expression of the Nile tilapia. Fish Shellfish Immunol. 2018, 82, 312–318.

55. Barrett, B. Medicinal properties of Echinacea: A critical review. Phytomedicine 2003, 10, 66–86.

56. Senchina, D.S.; Martin, A.E.; Buss, J.E.; Kohut, M.L. Effects of Echinacea extracts on macrophage antiviral activities. Phytotherapy Res. 2009, 24, 810–816.

57. Soon, S.L.; Crawford, R.I. Recurrent erythema nodosum associated with echinacea herbal therapy. J. Am. Acad. Dermatol. 2001, 44, 298–299.

58. Cupp, M.J.; Davis, J. Toxicology and Clinical Pharmacology of Herbal Products; Humana Press: Totowa, NJ, SUA, 2000; pp. 85–93.

59. Aucoin, M.; Cooley, K.; Saunders, P.R.; Carè, J.; Anheyer, D.; Medina, D.N.; Cardozo, V.; Remy, D.; Hannan, N.; Garber, A. The effect of Echinacea spp. on the prevention or treatment of COVID-19 and other respiratory tract infections in humans: A rapid review. Adv. Integr. Med. 2020, 7, 203–217.

60. Weishaupt, R.; Bächler, A.; Feldhaus, S.; Lang, G.; Klein, P.; Schoop, R. Safety and Dose-Dependent Effects of Echinacea for the Treatment of Acute Cold Episodes in Children: A Multicenter, Randomized, Open-Label Clinical Trial. Children 2020, 7, 292.

61. Elek, F.; Eszter, D.; Rebeka, K.; Szende, V.; Melinda, U.; Eszter, L.-Z. Mapping of Echinacea-based food supplements on the Romania market and qualitative evaluation of the most commonly used products. Bull. Med Sci. 2020, 93, 111–123.

62. Chen, X.-L.; Zhang, J.-J.; Chen, R.; Li, Q.-L.; Yang, Y.-S.; Wu, H. An Uncommon Plant Growth Regulator, Diethyl Aminoethyl Hexanoate, Is Highly Effective in Tissue Cultures of the Important Medicinal Plant Purple Coneflower (Echinacea purpurea L.). BioMed Res. Int. 2013, 2013, 1–12.

63. Stuart, D.L.; Wills, R.B.H. Alkylamide and Cichoric Acid Levels inEchinacea purpureaTissues During Plant Growth. J. Herbs Spices Med. Plants 2000, 7, 91–101.

64. Thomas, A. Regulatory Aspects of Herbal Medicine; Academic Press: Cambridge, MA, USA, 2017; pp. 165–178.

65. Waidyanatha, S.; Pierfelice, J.; Cristy, T.; Mutlu, E.; Burback, B.; Rider, C.V.; Ryan, K. A strategy for test article selection and phytochemical characterization of Echinacea purpurea extract for safety testing. Food Chem. Toxicol. 2020, 137, 111125.

66. Rios, M.Y.; Olivo, H.F. Natural and Synthetic Alkamides. Stud. Nat. Prod. Chem. 2014, 43, 79–121.

67. Woelkart, K.; Koidl, C.; Grisold, A.; Gangemi, J.D.; Turner, R.B.; Marth, E.; Bauer, R. Bioavailability and Pharmacokinetics of Alkamides From the Roots of Echinacea angustifolia in Humans. J. Clin. Pharmacol. 2005, 45, 683–689.

68. Woelkart, K.; Dittrich, P.; Beubler, E.; Pinl, F.; Schoop, R.; Suter, A.; Bauer, R. Pharmacokinetics of the Main Alkamides after Administration of three Different Echinacea purpurea Preparations in Humans. Planta Medica 2008, 74, 651–656.

69. Saeidnia, S.; Manayi, A.; Vazirian, M. Echinacea purpurea: Pharmacology, phytochemistry and analysis methods. Pharmacogn. Rev. 2015, 9, 63–72.

70. Matthias, A.; Banbury, L.; Stevenson, L.M.; Bone, K.M.; Leach, D.N.; Lehmann, R.P. Alkylamides from Echinacea Modulate Induced Immune Responses in Macrophages. Immunol. Investig. 2007, 36, 117–130.

71. Mudge, E.; Lopes-Lutz, D.; Brown, P.; Schieber, A. Analysis of Alkylamides in Echinacea Plant Materials and Dietary Supplements by Ultrafast Liquid Chromatography with Diode Array and Mass Spectrometric Detection. J. Agric. Food Chem. 2011, 59, 8086–8094.

72. Cech, N.B.; Kandhi, V.; Davis, J.M.; Hamilton, A.; Eads, D.; Laster, S.M. Echinacea and its alkylamides: Effects on the influenza A-induced secretion of cytokines, chemokines, and PGE2 from RAW 264.7 macrophage-like cells. Int. Immunopharmacol. 2010, 10, 1268–1278.

73. Schumacher, A.; Friedberg, K. Untersuchungen zur Wirkung von Echinacea angustifolia auf die unspezifische zelluläre Immunantwort der Maus . Arzneimittel-Forschung 1991, 41, 141–147.

74. Shariatinia, Z. Natural Polysaccharides in Drug Delivery and Biomedical Applications; Academic Press: London, UK, 2019; Chapter 2; pp. 15–57.

75. Balciunaite, G.; Juodsnukyte, J.; Savickas, A.; Ragazinskiene, O.; Siatkute, L.; Zvirblyte, G.; Mistiniene, E.; Savickiene, N. Fractionation and evaluation of proteins in roots of Echinacea purpurea (L.) Moench. Acta Pharm. 2015, 65, 473–479.

76. Cai, C.; Chen, Y.; Zhong, S.; Ji, B.; Wang, J.; Bai, X.; Shi, G. Anti-Inflammatory Activity of N-Butanol Extract from Ipomoea stolonifera In Vivo and In Vitro. PLoS ONE 2014, 9, e95931.

77. Stimpel, M.; Proksch, A.; Wagner, H.; Lohmann-Matthes, M.L. Macrophage activation and induction of macrophage cytotoxicity by purified polysaccharide fractions from the plant Echinacea purpurea. Infect. Immun. 1984, 46, 845–849.

78. Sharma, S.; Anderson, M.; Schoop, S.; Hudson, J. Bactericidal and anti-inflammatory properties of a standardized Echinacea extract (Echinaforce®): Dual actions against respiratory bacteria. Phytomedicine 2010, 17, 563–568.

79. Vazirian, M.; Dianat, S.; Manayi, A.; Ziari, R.; Mousazadeh, A.; Habibi, E.; Saeidnia, S.; Amanzadeh, Y. Anti-inflammatory effect, total polysaccharide, total phenolics content and antioxidant activity of the aqueous extract of three basidiomycetes. Res. J. Pharmacogn. 2014, 1, 15–21.

80. Mazzio, E.A.; Soliman, K.F.A. In vitro screening for the tumoricidal properties of international medicinal herbs. Phytotherapy Res. 2008, 23, 385–398.

81. Vickers, A. Botanical Medicines for the Treatment of Cancer: Rationale, Overview of Current Data, and Methodological Considerations for Phase I and II Trials. Cancer Investig. 2002, 20, 1069–1079.

82. Voaden, D.J.; Jacobson, M. Tumor inhibitors. 3. Identification and synthesis of a oncolytic hydrocarbon from American coneflower roots. J. Med. Chem. 1972, 15, 619–623.

83. Yang, G.; Li, K.; Liu, C.; Peng, P.; Bai, M.; Sun, J.; Li, Q.; Yang, Z.; Yang, Y.; Wu, H. A Comparison of the Immunostimulatory Effects of Polysaccharides from Tetraploid and Diploid Echinacea purpurea. BioMed Res. Int. 2018, 2018, 1–12.

84. Yao, L.; Bai, L.; Tan, Y.; Sun, J.; Qu, Q.; Shi, D.; Guo, S.; Liu, C. The immunoregulatory effect of sulfated Echinacea purpurea polysaccharide on chicken bone marrow-derived dendritic cells. Int. J. Biol. Macromol. 2019, 139, 1123–1132.

85. Tsai, Y.-L.; Chiu, C.-C.; Chen, J.Y.-F.; Chan, K.-C.; Lin, S.-D. Cytotoxic effects of Echinacea purpurea flower extracts and cichoric acid on human colon cancer cells through induction of apoptosis. J. Ethnopharmacol. 2012, 143, 914–919.

86. Abreu, R.M.; Ferreira, I.; Calhelha, R.C.; Lima, R.T.; Vasconcelos, M.H.; Adega, F.; Chaves, R.; Queiroz, M.-J.R. Anti-hepatocellular carcinoma activity using human HepG2 cells and hepatotoxicity of 6-substituted methyl 3-aminothienopyridine-2-carboxylate derivatives: In vitro evaluation, cell cycle analysis and QSAR studies. Eur. J. Med. Chem. 2011, 46, 5800–5806.

87. Luettig, B.; Steinmüller, C.; Gifford, G.E.; Wagner, H.; Lohmann-Matthes, M.-L. Macrophage Activation by the Polysaccharide Arabinogalactan Isolated From Plant Cell Cultures of Echinacea purpurea. JNCI: J. Natl. Cancer Inst. 1989, 81, 669–675.

88. Sharif, K.O.M.; Tufekci, E.F.; Ustaoglu, B.; Altunoglu, Y.C.; Zengin, G.; Llorent-Martínez, E.; Guney, K.; Baloglu, M.C. Anticancer and biological properties of leaf and flower extracts of Echinacea purpurea (L.) Moench. Food Biosci. 2021, 41, 101005.

89. Jiang, W.; Zhu, H.; Xu, W.; Liu, C.; Hu, B.; Guo, Y.; Cheng, Y.; Qian, H. Echinacea purpurea polysaccharide prepared by fractional precipitation prevents alcoholic liver injury in mice by protecting the intestinal barrier and regulating liver-related pathways. Int. J. Biol. Macromol. 2021, 187, 143–156.

90. Xu, W.; Hu, B.; Cheng, Y.; Guo, Y.; Yao, W.; Qian, H. Echinacea purpurea suppresses the cell survival and metastasis of hepatocellular carcinoma through regulating the PI3K/Akt pathway. Int. J. Biochem. Cell Biol. 2021, 142, 106115.

91. Guiotto, P.; Woelkart, K.; Grabnar, I.; Voinovich, D.; Perissutti, B.; Invernizzi, S.; Granzotto, M.; Bauer, R. Pharmacokinetics and immunomodulatory effects of phytotherapeutic lozenges (bonbons) with Echinacea purpurea extract. Phytomedicine 2008, 15, 547–554.

92. Del-Río-Navarro, B.E.; Espinosa-Rosales, F.J.; Flenady, V.; Sienra-Monge, J.J. Immunostimulants for preventing respiratory tract infection in children. Cochrane Database Syst. Rev. 2006, CD004974.

93. Kim, H.-R.; Oh, S.-K.; Lim, W.; Lee, H.K.; Moon, B.-I.; Seoh, J.-Y. Immune Enhancing Effects of Echinacea purpurea Root Extract by Reducing Regulatory T Cell Number and Function. Nat. Prod. Commun. 2014, 9, 511–514.

94. Bodinet, C.; Beuscher, N. Antiviral and Immunological Activity of Glycoproteins from Echinacea purpurea Radix. Planta Medica 1991, 57, A33–A34.

95. Bergeron, C.; Gafner, S. Quantitative Analysis of the Polysaccharide and Glycoprotein Fractions in Echinacea purpurea. And Echinacea angustifolia. by HPLC-ELSD for Quality Control of Raw Material. Pharm. Biol. 2007, 45, 98–105.

96. Kurkin, V.A.; Akushskaya, A.S.; Avdeeva, E.V.; Velmyaikina, E.I.; Daeva, E.D.; Kadentsev, V.I. Flavonoids from Echinacea purpurea. Russ. J. Bioorganic Chem. 2011, 37, 905–906.

97. Agrawal, A.D. Pharmacological Activities of Flavonoids: A Review. Int. J. Pharm. Sci. Nanotechnol. 2011, 4, 1394–1398.

98. Maleki, S.J.; Crespo, J.F.; Cabanillas, B. Anti-inflammatory effects of flavonoids. Food Chem. 2019, 299, 125124.

99. Dogan, Z.; Ergul, B.; Sarikaya, M.; Filik, L.; Gonultaş, M.A.; Hucumenoglu, S.; Can, M. The protective effect of Echinacea spp. (Echinacea angustifolia and Echinacea purpurea) in a rat colitis model induced by acetic acid. Pak. J. Pharm Sci. 2014, 27, 1827–1835.

100. Lee, T.T.; Huang, C.C.; Shieh, X.H.; Chen, C.L.; Chen, L.J.; Yu, B. Flavonoid, Phenol and Polysaccharide Contents of Echinacea Purpurea, L. and Its Immunostimulant Capacity In Vitro. Int. J. Environ. Sci. Dev. 2010, 1.

101. Speroni, E.; Govoni, P.; Guizzardi, S.; Renzulli, C.; Guerra, M. Anti-inflammatory and cicatrizing activity of Echinacea pallida Nutt. root extract. J. Ethnopharmacol. 2001, 79, 265–272.

102. Ekeuku, S.O.; Pang, K.-L.; Chin, K.-Y. Effects of Caffeic Acid and Its Derivatives on Bone: A Systematic Review. Drug Des. Devel Ther. 2021, 15, 259–275.

103. Zhang, P.; Tang, Y.; Li, N.-G.; Zhu, Y.; Duan, J.-A. Bioactivity and Chemical Synthesis of Caffeic Acid Phenethyl Ester and Its Derivatives. Molecules 2014, 19, 16458–16476.

104. Yeğin, M.E.; Bilkay, U.; Tiftikçioğlu, Y.; Uyanikgil, Y.; Çavuşoğlu, T.; Ercan, G.; Gürdal, M. Altering effects of caffeic acid phenethyl ester (CAPE) and ischemia/reperfusion injury: An experimental study in a rat TRAM flap model. Eur. J. Plast. Surg. 2020, 43, 527–534.

105. Wu, S.; Zhang, K.; Qin, H.; Niu, M.; Zhao, W.; Ye, M.; Zou, H.; Yang, Y. Caffeic acid phenethyl ester (CAPE) revisited: Covalent modulation of XPO1/CRM1 activities and implication for its mechanism of action. Chem. Biol. Drug Des. 2016, 89, 655–662.

106. Wang, F.; Yang, J. A comparative study of caffeic acid and a novel caffeic acid conjugate SMND-309 on antioxidant properties in vitro. LWT 2012, 46, 239–244.

107. Silva, T.; Oliveira, C.; Borges, F. Caffeic acid derivatives, analogs and applications: A patent review (2009–2013). Expert Opin. Ther. Patents 2014, 24, 1257–1270.

108. Chicca, A.; Adinolfi, B.; Martinotti, E.; Fogli, S.; Breschi, M.; Pellati, F.; Benvenuti, S.; Nieri, P. Cytotoxic effects of Echinacea root hexanic extracts on human cancer cell lines. J. Ethnopharmacol. 2007, 110, 148–153.

109. Senica, M.; Mlinsek, G.; Veberic, R.; Mikulic-Petkovsek, M. Which Plant Part of Purple Coneflower (Echinacea purpurea (L.) Moench) Should be Used for Tea and Which for Tincture? J. Med. Food 2019, 22, 102–108.

110. Wu, C.-H.; Murthy, H.N.; Hahn, E.-J.; Paek, K.-Y. Enhanced production of caftaric acid, chlorogenic acid and cichoric acid in suspension cultures of Echinacea purpurea by the manipulation of incubation temperature and photoperiod. Biochem. Eng. J. 2007, 36, 301–303.

111. Chiellini, C.; Maida, I.; Maggini, V.; Bosi, E.; Mocali, S.; Emiliani, G.; Perrin, E.; Firenzuoli, F.; Mengoni, A.; Fani, R. Preliminary data on antibacterial activity of Echinacea purpurea-associated bacterial communities against Burkholderia cepacia complex strains, opportunistic pathogens of Cystic Fibrosis patients. Microbiol. Res. 2017, 196, 34–43.

112. Tsai, Y.-L.; Chiou, S.-Y.; Chan, K.-C.; Sung, J.-M.; Lin, S.-D. Caffeic acid derivatives, total phenols, antioxidant and antimutagenic activities of Echinacea purpurea flower extracts. LWT 2012, 46, 169–176.

113. Jiang, Z.; Wang, J.; Li, X.; Zhang, X. Echinacoside and Cistanche tubulosa (Schenk) R. wight ameliorate bisphenol A-induced testicular and sperm damage in rats through gonad axis regulated steroidogenic enzymes. J. Ethnopharmacol. 2016, 193, 321–328.

114. Xing, X.X.; Liu, Z.J.; Han, B. Effects of Acteoside and Echinacoside on the Expression of the BMP2 in Rat Osteoblast. Prog. Vet. Med. 2011, 32, 45–48.

115. Liu, J.; Yang, L.; Dong, Y.; Zhang, B.; Ma, X. Echinacoside, an Inestimable Natural Product in Treatment of Neurological and other Disorders. Molecules 2018, 23, 1213.

116. Jia, C.; Shi, H.; Jin, W.; Zhang, K.; Jiang, Y.; Zhao, M.; Tu, P. Metabolism of Echinacoside, a Good Antioxidant, in Rats: Isolation and Identification of Its Biliary Metabolites. Drug Metab. Dispos. 2008, 37, 431–438.

117. Pires, C.; Martins, N.; Carvalho, A.M.; Barros, L.; Ferreira, I.C. Phytopharmacologic preparations as predictors of plant bioactivity: A particular approach to Echinacea purpurea (L.) Moench antioxidant properties. Nutrition 2016, 32, 834–839.
118. Zou, Z.; Dong, L.; Wang, H.; Niu, J.; Zou, M.; Wu, N.; Yu, D.; Wang, Y. Echinacoside induces apoptotic cancer cell death by inhibiting the nucleotide pool sanitizing enzyme MTH1. OncoTargets Ther. 2015, 8, 3649–3664.