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Exploring the Regulatory Challenges and Opportunities for *Echinacea purpurea* as a Food in the European Union

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INTRODUCTION

Following the two World Wars, several countries within European territory came together to establish the European Economic Community (EEC), at the time, now known as the European Union (EU), through economic integration. With the prospect of peace and a more united Europe, the EEC marked the first pro-European movement, which began with the founding of the Council of Europe in 1949 (S4D4C European Science Diplomacy), set to promote democracy, human rights, and the rule of law (Council of Europe). It was France and Germany who spearheaded the establishment of the economic alliance, leading to the formation of the European Coal and Steel Community in 1951, which comprised France, Germany, Italy, the Netherlands, Belgium, and Luxembourg (S4D4C European Science Diplomacy). Motivated by this achievement, these six countries sought to bring about economic integration among the Member States (MS) throughout different sectors, resulting in the signing of the Treaty of Rome in 1957 and the creation of the European Economic Community[1]. The EEC's objective was characterized to have a more political approach to European Integration: as stated in the Treaty of Rome (1957), members were "*determined to lay the foundations of an ever-closer union among the peoples of Europe*" choosing to establish a common market which would allow for economic policies to progressively come together as one (Sapir, 2011). This collaborative initiative resulted in Denmark, Ireland, and the United Kingdom joining the project in the 1970s, followed by Greece in 1981, and Spain and Portugal in 1986, marking the EEC's expansion into Southern Europe and catalyzing political stability and economic development in the Mediterranean region (S4D4C European Science Diplomacy).

By 1968 custom duties had disappeared with the removal of significant barriers to the free circulation of persons, services, and capital, plus the establishment of a customs union for goods. However, trade was not flowing freely across borders between the Member States, proving how the main obstacle was actually the differences in national regulations. Thus, by the early 1980s, the president of the European Commission, Jacques Delors, launched the single market program (SMP) with the promise to complete the single market[2] by December 31st, 1992, soughing to remove all remaining barriers to the free circulation within the EEC (Sapir, 2011) with the intention to uphold the strengthening of trade and economic relations between Member States in a continuous and balanced manner (EUR Lex). Ultimately, the European Union was shaped in 1992 with the signing of the Maastricht Treaty, establishing the single internal market as a pivotal milestone in the European

[1] In 1993 the EEC was incorporated and renamed the European Community (EC). Later the EC's institutions were absorbed into the EU's wider framework and the community ceased to exist (European Commission).

[2] The new name for the common market.

integration process (S4D4C European Science Diplomacy). Six years after being proposed, the single market is launched with the guarantee of "4 freedoms": free movement of people, goods, services, and capital. The agreement of hundreds of laws covering tax policy, business regulations, professional qualifications, and other barriers to open frontiers has been seen as one of the EU's greatest achievements (European Union). Within such agreements the interconnection through trade stood out as a strategy to raise the opportunity cost of war as much as possible (Vicard, 2012); through the elimination of all trade barriers among its Member States, the facilitation of movement across borders benefited everyone involved.

To this day, the European Union has the largest single market area of the world, with the support and defense it offers to its industry and business by constantly working on removing trade barriers so European exporters gain fair conditions and access to other markets. The EU has exclusive power to "*legislate on trade matters and to conclude international trade agreements* (EUR-Lex)" on behalf of its [current 27] Member States. Through the authorization of trade defense and market access instruments, the EU aims at protecting businesses from obstacles to trade by facilitating the import of raw materials to make their products, allowing them to expand their operations and grow (European Union).

Out of the four "freedoms" this research will focus on the free movement of goods, which includes foodstuffs. The European Commission oversees and guarantees that Member States act accordingly to Community law when controlling how easily goods may cross their borders. The hundreds of technical, legal and bureaucratical barriers abolished benefit the consumers equally as they can enjoy a wider choice of products often at lower prices as a cause of "*more choice means more competition to attract customers*" (European Commission, 2007, p. 1). This free movement of goods has created a healthy, yet large, competitive marketplace, which has fueled the growth of the European economy to this day.

Whilst ensuring the free movement of food and feed within the internal market, the European Commission has harmonized much of the legislation related to food safety standards which are aimed at guaranteeing a "*high level of protection of human life and health and the protection of consumers' interests* (Laaninen, 2017, p. 1)". According to the Food and Agriculture Organization (FAO), in all nations, food is governed by a complexity of laws and regulations aimed at laying out the government's requirements that must be met by food chain operators to ensure food safety and quality. Hence, the term "food law" refers to legislation which establishes how risks to food safety must be assessed, setting out animal welfare and environmental requirements for food production, trade, and handling (Lydgate and Anthony, 2022). Following the "farm-to-fork" strategy, food law applies and covers the regulation of food control, food safety, quality, and any relevant aspects of

food trade across the entire food chain (FAO), meaning from animal feed production, primary production, food processing, storage and transport, to retail sale (Laaninen, 2017, p.1). In the European Union, the founding act of current food and feed legislation lies within the General Food Law Regulation[3] as part of the European Commission's Better Regulation Agenda[4]. Developed in 2002, this legislation laid out a new legal and institutional framework in response to the World Trade Organization (WTO) Agreement on Sanitary and Phytosanitary Measures and the BSE (bovine spongiform encephalopathy) crisis[5] (Laaninen, 2017). Created with the intention to have an integrated and homogenous approach to food and feed safety, the General Food Law ensures an appropriate methodology to food crises and risks by establishing principles and rules to avoid Member States from creating obstacles in trade.

The general obligations for food trade are tackled in Articles 11 to 13 of the General Food Law Regulation, establishing how food and feed imported into the EU must comply with requirements of food law (Laaninen, 2017, p. 6). Additionally, Regulation (EU) No 2019/515 delignates the mutual recognition principle[6], a principle under EU law which prevents EU countries from banning the sale of goods on their territory when they are lawfully sold in another EU country (Eur-Lex). Derived from Articles 34-36 of the Treaty on the functioning of the European Union, this Regulation outlines the mutual recognition of goods which may not be fully subject to EU harmonization legislation (European Commission). The principle guarantees that any product that is legally sold in one EU country can be sold in another, even if it does not fully meet the technical standards of the receiving country. Nevertheless, there are exceptions in the case public safety, health, and environmental concerns come into place: if there exist valid public interest reasons to limit or deny market access, then the countries can justify their restrictions (European Commission).

According to Baldwin (2006), third country trade policy practitioners and non-trade EU professionals are often astounded by the inner workings of the EU trade policy process, known as

[3] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, OJ L 31, 1.2.2002, pp. 1-24.

[4] EC agenda aiming to establish a transparent and evidence-based approach to crating EU laws, considering the perspective of the individuals and groups who could potentially get affected by these laws, such as citizens and businesses (European Commission).

[5] Also called "mad cow disease", this BSE outbreak came about because of the utilization of meat and bone meal (made from carcasses of infected cattle) in cattle feed. It caused a new variant of Creutzfeldt-Jacob disease (a fatal neurodegenerative disorder in humans) to start spreading to humans via consumption of contaminated meat products.

[6] It is important to note that the mutual recognition principle should not be confused with mutual recognition agreements which enable market access between the EU and non-EU nations (European Commission).

authorizing environment; trade policy within the EU operates under a highly "federal" approach, predominantly relying on the "Community method". This entails the Commission formulating proposals, Member States making decisions, for then to the Commission to implement them: under Article 133 of the Treaty, the Commission assumes the role of negotiator on behalf of Member States when engaging with third countries, whether within the World Trade Organization or through bilateral/regional agreements (Baldwin, 2006). The Commission seeks a mandate, which can be granted through a qualified majority vote, ensuring that no individual MS can exercise a veto. Throughout the negotiation process, the Commission consults with Member States in the 133 Committee on a regular basis. If successful, the Commission returns to the MS at the conclusion of negotiations to seek approval, which again can be granted by a qualifies majority (Baldwin, 2006).

The comprehensive regulatory framework governing food trade in the European Union, encompassing obligations for imported food and feed as well as the mutual recognition principle, extends to the specific realm of food supplements. Euromonitor International, provider of market analyses, reported that the annual spending on food supplements in the EU was around 7 billion euros as of 2018 and how it is continuously increasing (Czepielewska *et al*., 2018). According to Czepielewska *et al*. (2018), this growth can be attributed to various factors, including the aging population's interest in maintaining a healthy lifestyle through self-medication, growing skepticism towards traditional medicine, and the rapid development of information technology making these products easily accessible. Food supplements are used by the general population for a range of purposes, such as balancing diets, maintaining health, preventing diseases, improving appearance and well-being, and enhancing sexual or athletic performance. These products are heavily marketed, often claiming effectiveness, availability without prescription, and being "natural" and "harmless" (Czepielewska *et al*., 2018). Consequently, the food supplements market is flourishing, with over half the population in some EU States consuming these products, according to Czepielewska *et al*. (2018): recent data from the PlantLIBRA project shows that nearly 19% of EU consumers use at least one plant food supplement, with Italy having the highest usage rate at approximately 23%. As for the marketing and legislation of food supplements, they are governed by Directive 2002/46/EC[7], commonly known as the Food Supplement Directive. To be marketed within the European Union, these supplements must adhere to the regulations outlined in this Directive. The primary aim of this Directive was to standardize rules regarding food supplements across Member States, however, it notoriously only covers substances such as vitamins and minerals (Vargas-Murga *et al*., 2011). Other

[7] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements (Text with EEA relevance), OJ L 183, 12.7.2002, p. 51–57.

substances like amino and fatty acids, fibers, plants, and plant extracts need to be regulated by individual national decrees.

Simultaneously, the use of herbal products, particularly plant food supplements and herbal medicine, is also gaining popularity in not only Europe, but in other parts of the world. There is an increasing trend of their usage among the general public as well as specific populations, including children, women, and individuals dealing with conditions like cancer (Vargas-Murga *et al*., 2011). Varga-Murga *et al*. (2011) note the European herbal market is expanding due to the growing interest in complementary and alternative healthcare therapies like acupuncture, ayurvedic medicine, chiropractic, homeopathy, naturopathy, traditional Chinese medicine, and yoga. Additionally, factors such as the increasing elderly population, emerging studies on the effectiveness of herbal plants – including their interaction and side effects, – and greater consumer awareness of general health and well-being contribute to this growth. A study conducted by the European Advisory Services (EAS) provided comprehensive data on the sales of herbal products in the four largest EU Member States, with Italy leading in sales, closely followed by Germany, the UK, and France (Vargas-Murga *et al*., 2011). Regarding herbal ingredients, the EAS report highlighted that gingko, followed by echinacea, garlic, and ginseng, were the four most commercially significant botanicals in the combined markets of 17 EU Member States. However, it is worth noting that echinacea and ginkgo are also included in products registered as medicinal drugs (Vargas-Murga *et al*., 2011).

Some factors impacting the growth of the market for food supplements containing other substances other than vitamins and minerals, whether in a positive or negative light, might be the compliance with national requirements for notification and authorization, restrictions on distribution channels, and the extent to which national authorities implement mutual recognition (Vargas-Murga *et al*., 2011). Among these "other substances" used in food supplements are botanical ingredients derived from plants, algae, fungi, or lichens, which have become widely accessible in the EU market, offering a variety of preparations that are classified differently (Bilia and do Ceú Costa, 2021). These classifications include food supplements, herbal medicinal products, cosmetics, and medical devices.

Remarkably, under the General Food Law Regulation (EC) 178/2002, food supplements are currently classified as food products. This Regulation defines food as any substance or product, whether processed or unprocessed, intended to be consumed by humans (Regulation No 178/2002, art. 2). It also specifies that products with medicinal characteristics, as defined by pharmaceutical legislation, cannot be classified as food supplements. As per Directive 2002/46/EC, the labeling, presentation, and advertising of food supplements must not attribute properties of preventing, treating, or curing human diseases. The Directive also introduced partial harmonization of the rules for marketing food supplements across Member States and provides a list of authorized mineral

compounds and vitamins. The classification of food supplements as food implies that manufacturing must comply not only with the above-mentioned GFL, but also Regulation (EC) no 852/2004, Hygiene Regulation, and Regulation (EU) 2023/915 in terms of acceptable levels of nitrates, aflatoxins, heavy metals, and dioxins, alongside the horizontal requirements laid down by the General Food Law Regulation (EC) 178/2002 and Regulation (EU) No 1169/2011 on food information to costumers. If a food supplement is claimed to reduce risk factors for specific diseases, it must also comply with the Nutrition and Health Claims Regulation (EC) 1924/2006.

The previously mentioned Echinacea refers to herbaceous flowering plants whose preparations are widely popular herbal immune boosters in North America and Europe (Bauer *et al*., 1996). These products are derived from three species: *Echinacea purpurea* (L.) Moench, *E. angustifolia* DC., and *E. pallida* (Nutt.) Nutt. In Europe, the primary products are made from the pressed juice of *Echinacea purpurea* aerial parts or hydroalcoholic extracts of *E. pallida* or *E. purpurea* roots (Bauer *et al*., 1996). The medicinal use of Echinacea dates to the Native American, who highly valued it as a remedy for treating wounds, snake bites, headaches, and the common cold. In mid 20th century, *Echinacea purpurea* was introduced to Europe as a medicinal plant and has since been used to combat infections and stimulate the body's immune response (Bauer *et al*., 1996). The present review aims at demonstrating how the current regulatory frameworks of the European Union allow *Echinacea purpurea* to be marketed as a food product, particularly as an herbal tea. By first exploring the so-called "purple coneflower's" botanical and pharmacological characteristics delving into the scientific evidence supporting its health properties, its position on the market will be better understood. In addition, an analysis of the intricate and evolving legislation of the EU concerning food ingredients and food supplements, viewed from the position of *E. purpurea*, will provide insights into the challenges and opportunities faced by business operators seeking to market Echinacea products. Ultimately, this review will propose alternative approaches, based on the existing legislations and scientific evidence, for the safe and compliant introduction of *E. purpurea* tea in the market of EU Member States. Specifically, by exploring the option of an herbal medicinal product application and a traditional food from Third Countries notification.

CHAPTER 1
ECHINACEA PURPUREA, BEYOND A BEAUTIFUL FLOWER

1.1 *Echinacea purpurea* in history

Long before Western society developed chemical, pharmacological, and toxicological methods to prepare effective and reasonably safe synthetic drugs, plants were the main sources of medicine (Lawson and Bauer, 1998). Notably, the majority of these new drugs were developed with the compounds discovered within plants. Unlike the United States, Europe persevered the use and study of medically used plants and herbs despite the development of modern synthetic drugs. Because of their continued used by physicians and the favorable government regulations encouraging research, Europe, and most specifically Germany, have led the research on this science of medicines of plant origin, also known as, phytomedicine.

Perhaps no other herb can rival *Echinacea* in terms of enduring popularity among the general population, having a track record of being the number one herbal supplement in terms of sales in the natural health market. Regardless of nomenclature issues, *Echinacea purpurea* (L.) Moench has shown to be the first plant noticed by physicians and medical botanists for its therapeutic properties throughout history (Flannery, 1999). Being cultivated broadly in the Unites States, Canada, and Europe – exclusively Germany – *E. purpurea* is known, not only for its beauty, but also its reported medical properties, which range from virucidal to antimicrobial activities. Despite reports dating back as early as 1762 and 1787, it wasn't until 1913 that it was documented to be used as an immunomodulator with the publishing of a medical practitioner in New York City, Dr. Victor von Unruh's report on increasing phagocytosis of tuberculosis bacteria (Sharifi-Rad *et al*, 2017). Flannery (1999) made the humorous remark highlighting how if the story of *Echinacea* had been left to its history in American soil, little would be known about the plant today.

1.2 Taxonomy and botany

Taxonomy, the science of classification and naming of organisms which best reflects the totality of their similarities and differences (Binns, 2002), enables the identification of a species through a unique Latin binomial name (*genus* and *species*) to said organism. The species within the *Echinacea* genus form a group of nine herbaceous and perennial plants that share comparable biological and ecological requirements. Kindscher and Wittenberg (2016) bring attention to how particularly confusing the genus *Echinacea* is, due to the fact it crossbreeds readily in the wild and has maintained different species names due to its long-established and prevalent use in the herbal

product sector. *Echinacea*'s taxonomy has undergone numerous changes since the 1700s because of the high morphological variability within the genus itself (Kindscher and Wittenberg, 2016), leading to the well-known confusion of various German researchers studying what they thought was *E. purpurea*, but was later reported to be *E. angustifolia*.

Within the plant family Asteraceae, also known as the daisy, aster, or sunflower family, lies the *Echinacea* genus, a group of native American wildflowers characterized by their cone-shaped capitulum inflorescent with spiny bracts (Kindscher and Wittenberg, 2016). Mainly found throughout the eastern and central United States territory and southern Canada, *Echinacea* is derived from the Greek word "*echinos*", which means hedgehog or sea urchin, in relation to the prickly spikes found in the flower head (Flannery, 1999; Hobbs, 1995, in Kindscher and Wittenberg, 2016), this elevated receptacle forms the cone-like shape that grants it its common English name, "purple coneflowers". The plants from this genus are herbaceous perennials, *E. purpurea* is characterized by its straight stem that can reach heights of 2 meters, with leaves arranged alternatively on extended stalks, covered in rough hairs and solitary prickles (Sharifi-Rad *et al*., 2018). Being members of the Asteraceae family, each "flower" or daisy-like head unit is a conglomeration of multiple tiny florets, with the inner ones, referred to as discending in spines, and the surrounding droopy florets, named ray, having teeth at their ends (Mistríková and Vaverková, 2007). The latter can be found in different colors, ranging from white, through pink to deep purple, whereas the disc may be brownish red to green (Mistríková and Vaverková, 2007).

1.3 Ethnobotany

According to the United States Department of Agriculture (n.d.), ethnobotany refers to the study of how people of a specific culture and region utilize the indigenous, native plants around them. With its rich cultural history, *Echinacea* was widely used by Native Americans in the Midwest and the Great Plains – between the Appalachian Mountains in the east and the Rocky Mountains in the west – in what is now the Unites States of America (Kindscher, 2016). The plant's use as an ailment was part of a complex healing system natives grounded in a religious or spiritual context, where the spiritual forces coming through the plant were the ones to provide the healing properties (Kindscher, 2016).

It is critical to make clear how the lack of interest and antagonism from European settlers towards Native Americans and their traditional practices has led to much information been lost (Kindscher, 2016). The cosmic approach medicinal plants were viewed and used with was foreign to Europeans, and it wasn't until a German patent medicine salesman by the name H.C.F. Mayer, in Pawnee City, Nebraska, learned of the value *Echinacea* as a "blood purifier" from the Indians and

then devised a patented herbal medicine made with it, that the coneflower was popularized for its health benefits (Kindscher, 2016). Described by Bauer (1998, p. 141) as a "quack" doctor, Meyer sold a tincture made from *E. angustifolia* roots, promoting it as a remedy for "*rheumatism, neuralgia, headache, erysipelas, dyspepsia, tumors and boils, open wounds, vertigo, scrofula and bag eyes, as well as "poisoning by herbs", and rattlesnake bites*".

The recorded uses among Indian tribes of *E. purpurea* are lesser compared to that of *Echinacea angustifolia*, with the first one in the Delaware tribe in Oklahoma, for example, only dating back to 1942 (Kindscher, 2016). Tantaquidgeon (1942, in Kindscher, 2016) reported the tribe's elder called the plant "horse-hobble weed", and how when combined with *Rhus typhina* – common name staghorn sumac – it was used as a remedy for venereal disease, known today as sexually transmitted infections (STIs). She also reported that a tea made from *E. purpurea* alone would cure an "*advanced case of venereal disease in 7 days*", giving it the name Yuchi[8] gonorrhea medicine (Kindscher, 2016). Gideon Lincecum, a self-taught physician, and trading-post operator, documented the use of *E. purpurea* in the Choctaw tribe to treat a cough by chewing on the root of the plant as follows:

> "*The tincture of the roots of this plant has been used with success in bad cough, and dyspepsia attended with a bad cough… The Choctaws use it for the above purposes, by chewing and swallowing the saliva. They keep a small piece of the root in the mouth nearly all the time, continuing its use for a long time*" (Campbell, 1951 in Kindscher, 2016).

Moreover, native Americans also deemed *E. purpurea* as an aphrodisiac and analgesic, believed to enhance courage, stamina, and pain tolerance, using the fresh leaves to bind wounds (Dweck, 1997). When illnesses or injuries related to the skin occurred, like mumps, measles, smallpox, wounds, or snakebites, Plain Indians would suck on the root (Dweck, 1997). In general, the *Echinacea* plants were used therapeutically in otorhinolaryngological treatments, in the likes of ear remedy, eye medicine, nose medicine, oral aid, throat aid, and toothache remedy (Daley, 2019, p. 3).

Despite the scarcity of knowledge there is on the correct gathering, preparation, and usage of native medicinal plants, due to the concern the Native American people have about this information being publishing, enough interest has been generated among the medical community to study and research the bioactive compounds found within *E. purpurea* and other species that contribute to the health properties which long predate European contact (Kindscher, 2016).

[8] Indigenous people of Oklahoma

1.4 Pharmacology and phytomedicine

Anton and Kuballa highlight how plants have given rise to a large number of preparations used by humans as remedies since ancient times; nowadays, plants can be classified into three groups, those safe for human consumption, the ones recognized for their toxic properties but have pharmaceutical applications, and lastly, those used in therapy (1998, p. 13). The latter classification has two types of raw materials which have been developed from them; the industrial extraction of pure active compound used to treat severe illnesses – in the likes of morphine –, and secondly, crude herbs and extracts found in healthcare products, over-the-counter products, and phytomedicines, used to treat minor pathologies and/or to maintain general health (Anton and Kuballa, 1998).

Phytomedicine refers to medical products based on standardized active ingredients within an herbal base (European Environmental Agency), also known a phytochemicals found in plants. It represents a collection of therapeutic knowledge developed through many successive generations within various cultures, serving as the foundation for early versions of pharmacopoeias. These pharmacopoeias were heavily based on natural products derived from sources like botanicals, animals, fungi, and minerals (Li *et al*., 2021). Existing prior to the emergence of synthetic medicine, the demand phytomedicine has been on a continuous rise with Europe taking the largest share of the pie in the market (Li *et al*., 2021).

In the early 20th century, the use of these unique flowers was introduced in Europe, and since then, the most common medicinal products come in the form of expressed juice preparations or alcoholic tinctures, as well as capsules for herbal supplements (Bauer, 1998). The main species used for such products are *E. purpurea*, *E. angustifolia*, and *E. pallida* (Cao and Kindscher, 2016); in the case of products using *E. purpurea*, these are made with either the aerial – meaning the stems, leaves, and flowers – or the underground parts of the plant, whilst the roots of *E. angustifolia*, and *E. pallida* are preferred *pallida* (Cao and Kindscher, 2016). In recent times, *Echinacea*-based medical products have become increasingly popular and globally available, marketed, and utilized as nonspecific immunostimulants to treat and prevent conditions such as the common cold, influenza, and upper respiratory tract infections (Dasgupta, 2019). In 2001, Binns described the species *Echinacea* Moench as leading sources of modern medical plants, providing a universal remedy of what once was used by Native Americans to treat a variety of ailments, from toothache to wounds, and from colds to systemic infections as described before (Foster, 1991).

As early as 1915, studies on *Echinacea* demonstrated how the beneficial effects of the perennial were not primarily due to its antimicrobial properties, but rather came from its ability to nonspecifically stimulate the human immune system (Sharifi-Rad, 2018). All nine recognized species have been subject of significant scientific interest, with around half the records being about *Echinacea*

purpurea (Cao and Kindscher, 2016). The genus has been found to contain various chemical constituents fundamental for product standardization, including alkylamides, derivatives of caffeic acid, glycoproteins and polysaccharides, polyacetylenes and polyenes, flavonoids, and terpenoids (Cao and Kindscher, 2016, pg. 128). However, the specific compounds responsible for *Echinacea*'s property to stimulate the immune system are assumed to be the alkylamides, caffeic acid derivates (CADs), glycoproteins, and polysaccharides, as they have shown bioactivity against both plant and human pathogens (Daley, 2019). This is backed up by Wills and Stuart (1999, in Daley, 2019), who clarify that not only do CADs and alkylamides constitute the species' dominant phytochemistry, but they are also believed to play a significant role in the plant's pharmacological properties.

Daley (2019) describes how the phytochemical division throughout the plant is often complemented by its bioactivity; for example, antimicrobial inhibition is distributed between the roots, leaves, flowers, and stems, with the roots showing a more prominent inhibition. There have been significant studies related to the differentiated phytochemicals in *Echinacea*, for example, the roots of the plant are the most active inhibiting pathogens that affect Cystic Fibrosis patients (Chielliniet *et al*., 2017, in Daley, 2019). However, aerials parts of the plant have also being shown to have important antimicrobial properties (Vimalanathan *et al*., 2005). Even though *Echinacea* has been used as a remedy for the common cold, some studies have shown contradicting results, whilst others have demonstrated a significant reduction in symptoms (Daley, 2019). Meta-analysis of 14 studies by Shah *et al*. (2007, in Daley, 2019) showed evidence of the benefits of *Echinacea* in decreasing the development and longevity of the common cold. In addition to its effects on the common cold and influenza, *Echinacea* has been reported to have virucidal effects against other viruses and inhibits microbial growth (Daley, 2019). Because of this, dose levels for *E. purpurea* are important to consider when wanting to have influence in immune stimulation (Drisko and Kindscher, 2016). A handful of pharmacological studies on the flower's polysaccharide constituents indicated how a high oral dose, meaning 10 mg/kg daily, administered over a ten-day period is effective as an immunostimulant (Wagner and Proksch 1985; Wagner *et al*. 1985, in Drisko and Kindscher, 2016). However, when the daily dose was increased, it resulted in a reduction in pharmacological activity, this phenomenon is known as hormesis.

Although polysaccharides and glycoproteins have been linked to the immune-stimulating effects of the plant, studies indicate that *E. purpurea*'s antimicrobial properties mainly come from alkylamides and caffeic acid derivatives (CADs) (Tsai *et al*., 2012, in Daley, 2019). All three groups will be explored in a detailed and elucidatorily manner in the subsequent section.

1.4.1 Alkylamides

Alkylamides, also known as alkamides, represent a group of lipophilic compounds which contain a carbonyl connected to an alkyl group, plus a nitrogen atom (Cao and Kindscher, 2016). In the core of *Echinacea*'s phytochemistry lie the main alkamides found within the species; a polyunsaturated fatty acid with acetylenic bonds and an isobutylamide moiety (Boonen *et al*., 2015; Romero *et al*., 2009, in Daley, 2019). The alkamides found in *Echinacea* are responsible for the pungent taste and tongue-tingling feeling associated with consuming the roots of the plant (Cao and Kindscher, 2016). The irregular distribution of the compound is noticeable throughout *Echinacea*'s major organs, the roots showing the highest concentration with around 70% of the plants total alkylamides, followed by the flowers, stems, and leaves, containing 20%, 10% and 1%, respectively (Stuart and Wills, 2000, in Daley, 2019, p. 13).

E. purpurea is mainly consumed in the form of an ethanol tincture which has been shown to be rich in alkamides with demonstrated antifungal properties due to its anti-inflammatory activity carried out by the inhibition of 5-lipoxygenase (5-LOX) enzyme of the arachidonic acid pathway (Merali *et al*., 2003). The metabolism of arachidonic acid mediates an inflammatory response through the 5-LOX pathway, which is responsible for leukotriene synthesis or the cyclooxygenase pathway, both resulting in the production of various prostaglandins (Merali *et al*., 2003). For their part, leukotrienes are responsible for conditions like bronchoconstriction, eosinophil activation, and mucus production (Merali *et al*., 2008). Compared to other constituents in *Echinacea*, alkylamides have a higher bioavailability, and therefore, may be responsible for the pharmacological effects reported in ethanol extracts (Mir-Rashed *et al*., 2010). Studies have evaluated the ability of *Echinacea* to prevent fungal growth and have identified it can alleviate symptoms of athlete's foot, a common fungal infection affecting the feet (Navabi and Silva, 2018). Mir-Radesh *et at.* (2010) observed how *Echinacea* extracts disrupted the fungal cell wall integrity by having a negative effect on functions that may indirectly cause alterations in the cell wall synthesis pathways, making these coneflowers desirable for the development of antifungal drugs.

1.4.2 Caffeic Acid Derivates

The secondary group of phytochemicals that contribute to *Echinacea*'s pharmacological properties are caffeic acid derivates, or CADs, a group of phenolics known for their antioxidant activity (Daley, 2019). Aside from being present in *Echinacea*, caffeic acid's high abundance in nature has displayed pharmacological effects *in vitro* and *in vivo*, namely as anti-inflammatory, anti-cancer and, antiviral activities (Yu *et al*., 2013). CADs not only play a role in plant defense with their anti-herbivory and interspecies properties but are also linked to the immunostimulant and antioxidant

effects given to the *Echinacea* species (Bergeron *et al*., 2002; Thygesen *et al*., 2007; Dias *et al*., 2012, in Daley, 2019). In respect to *E. purpurea*, the most prominent polyphenols are caftaric acid and cichoric acid; the extracts made from the aerial parts have been shown to contain many distinct antiviral activities against diverse viruses, from respiratory to herpes, linked to the phenolic compounds listed above (Daley, 2019).

One popular product in the market is Echinaforce®, a standardized preparation extracted from *E. purpurea* plants with a 65% alcoholic solution (Signer *et al*., 2020). Its prevention and treatment of respiratory tract infections is achieved through the interaction with both the entire virions and the viral envelope proteins to inhibit the infectivity of enveloped respiratory viruses, such as influenza A and B, respiratory syncytial virus (RSV), and parainfluenza virus (Signer *et al*., 2020). Signer *et al*.'s study concluded four human coronaviruses –HCoV-229E, MERS-CoV, SARS-CoV1 and SARS-CoV2 – can be inactivated by Echinaforce® *in vitro*, making the product an optimal prophylactic treatment against a vast array of respiratory viruses which can result in severe pulmonary disease or mild common cold symptoms. Additionally, the extract exhibited adaptive properties which modulate the immune system *in vivo* by decreasing the inflammatory cytokines TNF-α and IL-1β, whilst increasing the anti-inflammatory cytokine IL-10 (Kolev *et al*., 2022).

Alongside *Echinacea*'s direct inactivation of viral particles, it interferes with cytokine secretion triggered by viruses during infection, which are linked to various cold-associated symptoms, like a runny nose, coughing, sneezing et cetera (Signer *et al*., 2020). The reduced release of pro-inflammatory cytokines could potentially alleviate such symptoms (Signer *et al*., 2020). When going through a viral infection the boost of the immune system contributes to the destruction of the respiratory epithelium, in this sense, the inhibition of cytokine production by Echinaforce® has a beneficial influence in how it reduces the damage done to the respiratory epithelium by the immune system (Kolev *et al*., 2022).

Different studies have culminated *Echinacea* products are not effective at preventing rhinovirus infection, leading to the conclusion that indirect antiviral properties from the medicinal plant, such as its immunomodulating activities, may be responsible for ameliorating rhinovirus symptoms (Vimalanathan *et al*., 2005). Kolev *et al*. (2022) concluded in their study that instead of immune stimulation, using immune modulation can enable Echinaforce® to be used preventively in a prolonged manner, allowing for the potential to reduce viral loads to be fully utilized.

Vimalanathan *et al*.'s research (2005) proved the ability of various fractions and subfractions to inactivate herpes simplex virus (HSV) and influenza virus (FV). The fact both viruses have similar membrane structures suggests a possible membrane target for the antiviral components of *E. purpurea*'s aerial parts, with cichoric acid and at least one other caffeic acid derivative contributing

to some of the moderate antiviral activity against HSV. Vimalanathan *et al*. suggest several phenolic compounds may be acting synergistically to provide the genus with potent anti-HSV and anti-FV properties.

Furthermore, the cichoric acid found in *E. purpurea*'s roots and aerial parts was found to be a selective inhibitor of integrase (IN), one of the three viral enzymes produced by the human immunodeficiency viruses (HIV) with a promising target role for chemotherapeutic intervention of the infection (Bailly *et al.*, 2005). These derivates target various stages of HIV replication and can help reduce chronic oxidative stress in HIV-infected patients (Bailly *et al.*, 2005). The review from Bailly *et al.*'s (2005), demonstrated caffeic acid derivates' promising outcome as an affordable and safe candidate for an anti-HIV treatment that must be further studied to determine its effectiveness, including their impact on HIV viral and how a diet containing CADs can play a role in their effectiveness.

E. purpurea's second major phenolic compound, caftaric acid, is often overlooked due to the extended interest and research on cichoric acid, yet it plays a supporting role in preventing the production of free radicals and lipid peroxidation, both which are associated with inflammation development (Stanisavljević *et al*., 2009; Speroni *et al*., 2002, in Daley, 2019). Although all the previously described health attributes linked to *E. purpurea*'s CADs are used to evaluate its effectiveness, several studies (Matthias *et al.* 2004; Zolgharnein *et al*., 2010, in Daley, 2019) have shown oral administration lacks overall bioavailability and caffeic acid abortion into the bloodstream. Bioavailability refers to the fraction of a compound's given dose which reaches the circulation as an intact compound; therefore, doubts have been raised about *Echinacea*'s effects on human health or at least limited to the gut (Daley, 2019).

1.4.3 Polysaccharides and Glycoproteins

The two main components also considered responsible for the immunostimulatory effects of the genus are glycoproteins and polysaccharides, both of which were first observed in *Echinacea purpurea*'s aerial parts (Wagner *et al*., 1998, in Lim, 2014). The polysaccharide fraction of *Echinacea* has shown to stimulate macrophage activity and several functions related to cytokine production (Vimalanathan *et at*., 2005). Wacker and Hilbig (1987) point out how a product sold in Germany containing the juice of the fresh aerial parts of the purple coneflower was found to make the cells of mice become 50-80% more resilient to influenza, herpes, and vesicular stomatitis viruses. But perhaps the most interesting finding of the same study lies in the discovery of highly active polysaccharide molecules, in *E. purpurea* allowing it to possess immunostimulant properties *in vitro* and *in vivo*.

A third polysaccharide found in the perennial is fucogalactoxyloglucan, which helps enhance phagocytosis in cell cultures and in living organisms, while another polysaccharide named arabinogalactan stimulated macrophages to release tumor necrosis factor (TNF), a major regulator of the inflammatory response (Wagner *et al*., 1998, in Cao and Kindscher, 2016). Wagner *et al*.'s (1988) study denoted how these two compounds increase the process of engulfing and destruction of intercellular particulate matter carried out by immune cells.

Moring (1984, in Kindscher, 1989) describes that by binding to carbohydrate receptors on the cell surfaces of T-lymphocytes, *Echinacea* stimulates the immune system as it induces the cells' nonspecific transformation, production of interferon[9], and secretion of other lymphokines. What follows is the activation of phagocytic macrophages and natural killer (NK) cells, triggered by the lymphocytes, responsible for the destruction of bacteria and tumor cells respectively (Moring, 1984, in Kindscher, 1989). In this way, the antiviral activity of *Echinacea* is attributed to T-cell transformation resulting in the increase of cytotoxic killing of virus infected cells.

E. purpurea teas or other water extraction-based products meant for oral consumption are enriched in polysaccharide and glycoproteins since these molecules are readily extracted in hot water (Arnason *et al*., 2002). Apart from its support of the immune system, *Echinacea* extracts have been traditionally used in wound healing, the effect being attributed to the perennial's polysaccharide fraction, specifically echinacin B (Newall, 1996, in Sharifi-Rad *et al*., 2017). The fraction produces a hyaluronic acid-polysaccharide complex which stimulates wound healing and subsequently inhibits hyaluronidase and promotes fibroblast growth (Newall *et al*. in Sharifi-Rad *et al*., 2017).

1.5 *Echinacea* in the market

In Europe, there is a growing trend towards the use of botanical products by consumers who wish to incorporate them into their diets to promote their health (Trovato and Ballabio, 2018). These products are available in various forms, such as teas, juices, herbal medicines, and plant food supplements (PFS) (Garcia-Alvarez *et al*., 2014). The European Food Safety Authority (EFSA) defines "botanicals" as all the following materials: whole, fragmented or cut plants, plant parts, algae, fungi, and lichens, therefore "botanical preparations" means all preparations derived from botanicals through different techniques. These techniques include extraction, pressing, fractioning, squeezing, distillation, drying, fermentation, and concentration (EFSA, 2009).

[9] Interferons are proteins produced by diverse cells during an inflammatory response, they bind to cell surfaces and stimulate the synthesis of intracellular proteins, blocking the transcription of viral RNA, and in turn prevent viral infection (Lim, 2014).

Botanicals has become an umbrella term for all "medical, aromatic and cosmetic plants" that can be used to make infusion and decoctions, as cooking spices, or as ingredients of food in processed form, food supplements, cosmetics, medicines, medical devices, animal feed, and husbandry products (Trovato and Ballabio, 2018, p. 4). Each of them falling under different specific regulatory frameworks. Trovato and Ballabio (2018) indicate how at present, the term "botanicals" is being used to describe plant materials used in food and food supplements, by these means distinguishing them from plant materials used in herbal medicines, which are commonly referred to as "herbs". Regardless, many plants have a dual purpose, in the likes of chamomile (*Matricaria chamomilla* L.) or *Echinacea*, known for their herbal medicines and their infusions/teas (Trovato and Ballabio, 2018).

The EU has introduced regulation in recent times to govern products of plant origin to establish control in a market that has expanded in disorderly, without direction (Trovato and Ballabio, 2018). Despite the lack of a centralized authorization process for the use of botanical and related substances in food, the European Union demands the compliance of general requirements in accordance with Regulation (EC) No 178/2002 (General Food Law). Thus, the responsibility to ensure product safety lies on the business operators themselves.

Botanical extracts and related products, such as those obtained through water or alcohol, can serve as active ingredients for medical products and as an ingredient in dietary supplements (Trovato and Ballabio, 2018). The benefit of herbal medicines in dose forms (i.e., capsules, tablets, pills, and pastilles) is its convenience for the consumer who is guaranteed a dietary supplement with no presence of potentially harmful substances, the ideal concentration of the beneficial components the plant is sought out for, plus a more shelf-stable product, all these factors thanks to the manufacturing processes plants go through commercially (Trovato and Ballabio, 2018). Recorded to be one of the top ten herbs sold in 2013, grossing $16.6 million in annual sales by 2011 in the United States alone (Blumenthal *et al*., 2012 in Riggs and Kindscher, 2016), *Echinacea* is commercially sold as either a tinctures (also called liquid extracts), capsules, tablets, syrups, pastilles, or by following into the footsteps of Native Americans, using dried *E. purpurea* to make into an herbal tea. Extraction is the ideal technology to recover bioactive compounds from any herb yet drying of the plant allows for an extended shelf-life, plus teas and tinctures can be prepared easily at any time (Senica *et al*., 2018). Senica *et al*. (2018) established the leaves of the plant are better suited to prepare a water-based infusion or extract with to ensure the highest levels of caftaric acid and other phenolic compounds found in *E. purpurea*.

Global Market Insights lists the leading suppliers of *Echinacea* products to be Nature's Bounty (Bountiful Co), Now Foods, and Solgar Inc. in the USA, besides Bioforce AG, A. Vogel (Switzerland), Arkopharma (France), Dr. Theiss Naturwaren GmbH (Germany), and Nature's Plus

(UK) in Europe. In November of 2020, A. Vogal and Spiez Laboratory published a study demonstrating the natural health properties of the previously mentioned product, Echinaforce®. According to the team, the drug effectively destroyed coronaviruses *in vitro*, upon direct contact in suspension (Signer *et al*., 2020).

Riggs and Kindscher (2016) point out *Echinacea*'s fantastic publicity within the media, being featured on Time Magazine's cover on November 23, 1998, showing a beautiful *E. purpurea* shot alongside the phrase "The Herbal Medicine Boom". The authors highlight the importance of successful clinical trials with positive results to increase the plant's attractiveness and consequently increase its demand and price for producers. In Europe, *Echinacea* was acknowledged as one of the four most significant herbal products in the market, as stated by the European Advisory Services survey in 2007. According to Verified Market Research, the global *Echinacea* market was valued at 1.47 billion USD by 2019. The increasing interest in natural and organic ingredients that act on the human immune system is helping boost the growth of the plant's market globally (Global Market Insights). The recent COVID-19 pandemic has further accelerated *Echinacea*-based preparations due to its historical use as a common cold treatment, together with other ailments. The demand for an herbal product that could help prevent or treat coronaviruses, as well as relieve mental conditions like stress and anxiety caused by the related lifestyle changes, impacted the *Echinacea* market share positively (Global Market Insights).

Despite there been over 800 products on the market made from purple coneflower in Germany alone, there is little evidence suggesting *Echinacea purpurea* has been used in culinary arts (Lekar *et al*., 2011). However, author T.K. Lim (2014) presented some dishes that include *Echinacea*'s edible petals between its ingredients, like pane bagno, or bathed bread, which uses fresh petals and a single wedge of lemon as decoration. Lim (2014) also mentions American Indian savory *Echinacea* spread, *Echinacea* and melon fruit salad, fried petals with watercress, onion, and mustard leaves to be spread over sweet potatoes. While some other sources support the leaves and flowers may be edible and have a slightly sweet taste, they are not commonly used and consumed as a common food. In fact, the plant is generally considered to be ornamental rather than edible.

CHAPTER 2
THE WORLD OF FOOD SUPPLEMENTS IN THE EUROPEAN UNION

2.1 Common foods in the EU

Regulation (EC) No 178/2002, or the General Food Law Regulation, lays down the foundation for the current food and feed legislation in the European Union by pronouncing the "*general principles, requirements and procedures related to decision making in food and feed safety*". It defines food or foodstuff as "*any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by human* (Regulation 178/2002, article 2)". This definition of food comprises drinks (including water), chewing gum, and any substance deliberately added to food during its production, preparation, or processing. The Regulation covers all stages connected to the food chain, starting from production and processing, all the way though transportation and distribution[10]. It aims at guiding all actors engaged in the food chain at guaranteeing a high level of human health protection and the efficient operation of the internal market, the latter by ensuring the free movement of food and feed and facilitating global trade (Laaninen, 2017).

Due to the nature of the Regulation's objectives, food law must revolve around risk analysis, which by itself shall be based on the available scientific evidence (Laaninen, 2017). The process of risk analysis, according to article 6, has three interconnected components; (1) risk assessment, being the EFSA's duty, consists of four steps, hazard identification, hazard characterization, exposure assessment, and risk characterization; (2) risk management, falls in the hands of the EU Commission, European Parliament, and Member States; (3) and lastly, risk communication which lies in the hands of all subjects of the food chain and the competent authorities (Regulation 178/2002). Moreover, article 18 discusses the importance of traceability in helping to solve food and feed safety problems by facilitating authorities and business operators to withdraw or recall these products, hence why food business operators (FBOs) must apply it at every stage of the food supply chain (Regulation 178/2002).

The GFL's pursue of consumers' interest protection is interpreted through the establishment of a foundation for consumers to make well-informed decisions, and for the prevention of deceitful activities such as food adulteration and other misleading practices that might misguide consumers

[10] Also cover feed produced for, or fed to, food-producing animals (Laaninen, 2017).

(Regulation 178/2002, article 8). Pertaining to article 8, article 9 and 10 of the Regulation describe the principle of transparency as the need for open public consultation, meaning when there is a possible risk to human health, public authorities are called to inform people.

Responsibility to guarantee that products meet safety standards and adhere to food regulations relays on food and feed business operators (FBO) according to the GFL Regulation (178/2002). Operators are held accountable for the safety of the food and feed they produce, transport, store, or sell (Laaninen, 2017, pg. 6). However, Member States are also responsible for monitoring and verifying that FBOs comply with the requirements of food law at every stage of the supply chain. In the case a food or feed is identified as unsafe, business operators are obliged to remove it from the market or retrieve it from consumers (Laaninen, 2017). Additionally, they must inform the relevant national authorities of the measures taken and cooperate with them to mitigate risks to the final consumers.

2.2 Food supplements in the EU

Said common foods encompass a wide variety of products that reflect the diverse cultural heritage and gastronomic traditions of the European Union. However, alongside these rich culinary offerings, EU citizens have also embraced the use of food supplements to enhance their overall well-being. These supplements, which include amongst many, vitamins, minerals, herbal extracts, and amino acids, have gained popularity as individuals seek to complement their diets to meet specific nutritional needs. The regulations governing both common foods and food supplements in the EU aim to ensure consumer safety, promote transparency, besides establishing guidelines for labeling and advertising. By adhering to these regulations, both food business operators and consumers can make informed choices about the foods they consume and the supplements they use.

Directive 2002/46/EC remarked the increase of products in the Community marketed as "*foods containing concentrated sources of nutrients*", aimed at supplementing nutrient intake from the normal diet. In the effort to prevent unequal conditions of competition between Member States that could affect the functioning of the internal market, rules had to be adopted on these products (Directive 2002/46/EC whereas 1 and 2). Despite the fact a balanced and diverse diet, under normal circumstances, does have the potential to administer all essential nutrients humans need to properly grow and maintain a healthy life – in the amounts that align with the establish and recommended levels supported by widely accepted scientific evidence –, surveys indicate how this ideal scenario is not actually being attained for every nutrient and for all demographic groups within the Community (Directive 2002/46/EC, whereas 3).

Since consumers may decide to support their nutrient intake using food supplements, products on the market to fulfil this purpose must be both safe and have the adequate and appropriate labelling to guarantee a high level of consumer protection whilst also simplifying their decision-making process (Directive 2002/46/EC, whereas 5). This is where Directive 2002/46/EC of the European Parliament and of the Council comes into place, laying the ground on the interpretation of regulations in the Member States concerning food supplements "marketed as foodstuffs and presented as such". Article 2 of the Directive defines food supplements as "*foodstuffs the purpose of which is to supplement the normal diets and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities* (2002/46/EC)". Here, "nutrients" refer to vitamins and minerals exclusively, listed in Annex I, food supplements must come in the forms listed in Annex II (Directive 2002/46/EC, art. 2). In the moment of the publishing of the Directive, various vitamin and mineral substances present in the food supplement market of some Member States had not been evaluated by the Scientific Committee on Food, thus were not included in the "positive list" or Annex I and were asked to summit to the European Food Safety Authority for evaluation (2002/46/EC, whereas 10)[11].

Despite the lack of clarification in terms of what is covered within "*other substance with a nutritional or physiological effect*" in the Directive, it has been generally understood as substances such as enzymes, amino acids, essential fatty acids, pre- and probiotics, and botanicals and botanical extracts (Silano *et al*., 2011). However, there are no specific regulations at the EU level for all the substances previously mentioned, and the existing laws within Member States vary significantly (Silano *et al*., 2011). Silano *et al*. (2011) also point out the absence of a definition for the term "*nutritional and physiological effect*" inside Directive 2002/46/EC, nor is there elucidation of the botanical species and their varieties that may be used in plant food supplements. Hence, why at that time the Directive was first published, the need for sufficient scientific data to establish precise regulations on nutrients and other substances with nutritional or physiological effects was highlighted (Directive 2002/46/EC, whereas 8). Member States can apply their own regulations concerning these

[11] At the time the Directive was in force, Member States had until December 31st, 2009, to allow the use of vitamins and minerals not present in Annex I to be sold within their territory. This only if (a) the substance in question were sold in one or more products in the Community on the Directive's date of entry into force, and (b) the ESFA had not given the substance's use an unfavorable opinion (Directive 2002/46/EC, art. 4, par. 6).

other nutritional substances used in food supplements in the case no EU specific rules have been established (Directive 2002/46/EC, whereas 8).

The Directive further emphasizes that, in addition to ensuring safety for human consumption, food supplements shall also exhibit bioavailability, meaning the substances' ability to be absorbed by the body (Directive 2002/46/EC, whereas 11). In terms of dosage, excess intake of vitamins or minerals can have an adverse effect on human health, therefore it is important to establish maximum safe levels of these substances which would ensure the food supplements are safe for consumption when used under the instructions provided by the manufacturer (Directive 2002/46/EC, whereas 13 and 14). According to the Directive, the quantity per daily serving of these vitamins and minerals, as recommended by the manufacturer, must be establish while considering the following factors: (a) the upper safe levels (UL) of these nutrients based on the scientific risk assessment of widely accepted scientific data, taking into consideration the varying sensitivity levels among different population group; and (b) nutrient intake from a normal diet (Directive 2002/46/EC, art. 5, par. 1). Concurrently, minimum level per daily dose, also as recommended by the manufacturer, must be set.

Furthermore, because of their classification as food, food supplement manufacturing must be carried out under Regulation (EC) No 852/2004, Hygiene Regulation, and Regulation (EU) No 2023/915[12] in terms of acceptable levels of nitrates, aflatoxins, heavy metals and dioxins, alongside the horizontal requirements laid down by the General Food Law Regulation (EC) 178/2002 and Regulation (EU) No 1169/2011[13] about general food labelling (Silano *et al*., 2011). Through the scientific risk assessment EFSA carries out, the Commission can see whether to prohibit the use of said food component or submit its use to different conditions (Silano *et al*. 2011).

Article 6 of the Directive touches on the labelling, presentation, and advertising of food supplements in the EU[14]: as per Directive 2000/13/EC[15], products falling under this scope should be referred to as "food supplements" and be sold as such (Directive 2002/46/EC, art. 6, par. 1). Noteworthily, the labels, presentation, and advertising of these products shall not make claims that they prevent, treat, or cure human diseases, unlike medicinal products intended for human use and

[12] Previously Regulation (EC) No 1881/2006

[13] Previously Directive 2003/13/EC.

[14] Council Directive 90/469/EEC on nutrition labelling for foodstuffs does not apply to food supplements.

[15] Repealed on October 25, 2011, by Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004.

covered by Directive 2001/83/EC[16]. In addition to complying with Regulation (EU) No 1169/2011, the labelling of food supplements should include the following information: (a) name of the categories or an indication of the nature of the nutrients or substances; (b) the product's portion which is recommended for daily consumption; (c) a warning not to exceed said dose; (d) a statement indicating that food supplements do not replace a balanced and varied diet; (e) a statement specifying to keep product of reach form young children (Directive 2002/46/EC, art. 6, par. 3). The label must also include, in numerical form, the amount of nutrients or substances with a nutritional or physiological effect. Regarding voluntary nutritional and health claims, food supplements, as any other food, are governed by Regulation (EC) No 1924/2006 and its subsequent amendments and additions (Silano *et al*., 2011).

Member States must ensure food business operators market food supplements within the European Union only if they comply with the information stated previously as per the Directive, thus allowing consumers who wish to purchase them to not only make an informed choice, but one that involves proper and safe use of the product (Regulation (EU) 1169/2011, art. 3, par. 1). As per procedure, once Directive 2002/46/EC entered into force, every Member State was responsible to enforce the corresponsive laws, regulations and, administrative provisions to implement it, as to permit and/or prohibit the trade of products which complied[17] or not[18] with the Directive (Directive 2002/46/EC, art. 15). Silano *et al*. (2011) highlighted how limits that exist at EU level in terms of harmonization result in precise national regulations from Member States being applied, in addition to the mutual recognition agreement which allows food supplement products to be marketed in EU countries different from those of origin.

However, the Directive did not come about without some challenges, being appealed by different parties before the Court of Justice of the European Union (CJEU), its legal basis, i.e., Article 95 of the EU Treaty, was not considered appropriate for the harmonization of national regulations on food supplements at public health level (Silano *et al*., 2011). These appeals were emphasized in the combined Court Cases C-154/04 and C-155/04[19], which were brought against the parties responsible for enacting and implementing the regulation at issue, meaning the Secretary of State for Health in

[16] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p. 67–128.

[17] From August 1st, 2003, at the latest.

[18] From August 1st, 2005, at the latest.

[19] Judgment of the Court (Grand Chamber) of 12 July 2005, The Queen, on the application of Alliance for Natural Health and Nutri-Link Ltd v Secretary of State for Health (C-154/04) and The Queen, on the application of National Association of Health Stores and Health Food Manufacturers Ltd v Secretary of State for Health and National Assembly for Wales (C-155/04), Joined cases C-154/04 and C-155/04, ECR, 2005 I-06451, ECLI identifier: ECLI:EU:C:2005:449.

the United Kingdom and the National Assembly for Wales by the Alliance for Natural Health, along with others. The latter challenged certain provisions of the UK's regulations which implemented Directive 2002/46/EC, arguing that these provisions were unlawful and infringed upon their rights (Joined Cases C-154/04 and C-155/04). The key question before the Court was to determine whether the UK regulations were compatible with EU law and had correctly transposed the requirements of the Directive into national legislation. The Court's judgment ultimately clarified the legality of the UK regulations in the implementation and dismissed the challenge brought about by these parties (Joined Cases C-154/04 and C-155/04). Overall, the judgment provided clarity and confirmation that the directive was valid and had legal force within the European Union. It affirmed the obligation of Member States, including the United Kingdom, to properly transpose and implement the requirements of the Directive into their domestic legislation to ensure compliance with EU law (Joined Cases C-154/04 and C-155/04).

2.3 Case study: Food supplements and botanicals in Spain and the United Kingdom

Food supplements play a significant role in supporting nutrition and well-being, offering consumers the option to complement their diet with additional vitamins, minerals, and other beneficial substances. However, the regulations surrounding food supplements do vary across Member States, therefore, this subsection explores the contrasting approaches to regulating food supplements in the European Union, focusing on the specific case of Spain and the United Kingdom, which has now left the EU. Whilst in Spain, food supplements must undergo a mandatory notification process, requiring companies to obtain registration or authorization from competent authorities, in the UK there is no prerequisite for registration or authorization, even though certain regulations and guidelines govern the usage of vitamins, minerals, and related substances. Understanding the divergent regulatory frameworks between Spain and the UK provides insights into the complexities of ensuring consumer protection and market competitiveness even among geographical areas which were subject to the same provisions, until a few years ago. Additionally, this subsection examines the specific regulations and considerations related to the use of plants and botanicals in food supplements in these two countries. These distinct approaches can provide valuable insights into the regulatory landscape for food supplements in the EU, as the UK's legislation continues to be significantly influenced by EU regulations even after Brexit.

In many EU Member States, including Spain, food supplements must undergo a mandatory notification process before they can be made available for sale (Trovato and Ballabio, 2018). Consequently, the person accountable for initially introducing a food supplement to the market is required to notify the competent authorities through the submission of a copy of the product's label.

In contrast, in the United Kingdom[20] there is no prerequisite for food supplements to undergo registration or obtain authorization prior to being sold (Trovato and Ballabio, 2018). Additionally, in Spain, it is mandatory for companies involved in the production, packaging, and distribution of food supplements within its market to obtain a registration, authorization, or approval from the competent national authorities (Trovato and Ballabio, 2018).

In Spain, the legal rule overseen food supplements is the Royal Decree 1487/2009 (Real Decreto 1487/2009[21]) which was modified on March 16, 2018, under the Royal Decree 130/2018 (Real Decreto 130/2018[22]). The Ministry of the Presidency and for the Territorial Administrations in the State Official Gazette (Boletín Oficial del Estado or BOE) points out how Directive 2002/46/EC despite its harmonization of certain aspects of food supplements, such as labeling and the use of vitamins and minerals, the use of other substances different from these last two is still pending further harmonization at the European level and is therefore subject to national legislation within the EU framework (Real Decreto 130/2018). The preamble of the Spanish Royal Decree 1487/2009 states that specific rules regarding other nutrients or substances used in food supplements may be adopted in the future if there is sufficient scientific data and in the absence of an EU regulation. However, a report presented in 2008 by the European Parliament and the Council concluded that establishing specific rules for substances other than vitamins and minerals in food supplements was not necessary because existing EU legislation already provided sufficient regulation in this area (Real Decreto 130/2018). Regardless of this conclusion, many EU Member States have chosen to create their own lists of substances that can be used on food supplements due to the lack of prospects for harmonization at the EU level (Real Decreto 130/2018).

Given the circumstances, the Ministry deemed important to create a national list of substances that can be used in food supplements within Spanish territory with the purpose to safeguard consumer protection while maintaining the competitiveness of food businesses in the European market (Real Decreto 130/2018). Currently, due to the absences of specific regulations, food supplements containing substances other than vitamins and minerals can only be sold in the country through the principle of mutual recognition (Real Decreto 130/2018). This is because they do not meet the composition criteria outlined in the annexes of the Decree. Nonetheless, the modification carried out

[20] In the likes of Austria and Sweden (Trovato and Ballabio, 2018).

[21] Real Decreto 1487/2009, de 26 de septiembre, relativo a los complementos alimenticios. Official publication: Boletín Oficial del Estado (B.O.E); Number: 244/2009; Publication date: 09/10/2009; Page number: 85370-85378

[22] Real Decreto 130/2018, de 16 de marzo, por el que se modifica el Real Decreto 1487/2009, de 26 de septiembre, relativo a los complementos alimenticios. Official publication: Boletín Oficial del Estado (B.O.E); Number: 75/2018; Publication date: 27/03/2018; Page number: 33335-33342.

in 2018 included the addition of "*other substances with nutritional and physiological effects that can be utilized in the manufacturing of food supplements*" within the annexes. The list is divided into eight different categories: fatty acids, amino acids and other nitrogen-containing compounds, dipeptides and peptides, coenzymes, flavonoids and carotenoids, nucleotides, polysaccharides and oligosaccharides, and other substances (Real Decreto 130/2018).

According to article 9 of the Decree on "information on product marketing", in Spain, the entity responsible for marketing a food supplement must notify the relevant authorities before or at the same time as the first placement of the product in the national market (Real Decreto 1487/2009). Said notification is mandatory and can be done by the manufacturer, the entity responsible for the initial market placement, or the importer for third-party countries. This process differs depending on whether the food supplement is manufactured domestically or in other EU countries (Real Decreto 1487/2009). In the case of the responsible entity being based in Spain, meaning they have a registered office established in the country, they must submit the notification to the competent autonomous community authorities, who will then forward the notifications they receive to the Spanish Agency for Food Safety and Nutrition (la Agencia Española de Seguridad Alimentaria y Nutrición or AESAN) (Real Decreto 1487/2009). On the other hand, when the entities are not based in Spain or the product is from a third-party country, the notification should be directly submitted to the AESAN.

In spite of the most recent modification made to the Royal Decree 1487/2009 which expanded the catalog of approved substances for food supplements aside from vitamins and minerals to this day, Spain does not count with a legislation on the use of plant and plant extracts in food supplements (Trovato and Ballabio, 2018, p. 12). With no issued list of plants and products thereof that can be used in food supplements, such products can therefore only be marketed if they have been legally introduced to the market of another Member State, in accordance with the principle of mutual recognition, as has been mentioned before. Trovato and Ballabio (2018) mention how a handful of negative and positive lists of plants are used as guidance documents by the Spanish authorities when it comes to accepting these products into their market.

The United Kingdom's membership into the EEC only came about in the 1970s; according to Coricelli and Campos (2015), this was a strategy to stop the nation's relative economic decline. After the Second World War, the UK's per capita GDP stood at almost a third larger than the EU6[23] average, at the time of its integration, in 1973, it was about 10% below. On this basis, joining the EU worked, as it aided in halting Britain's relative economic decline in relation to the EU6 (Coricelli and Campos, 2015). With the decision to leave the European Union in 2016, the United Kingdom become

[23] Sometimes referred to as the "Inner Six" or "The Six", EU6 were the founding members of the EEC (France, Federal Republic of Germany, Italy, Belgium, Netherlands, Luxembourg).

a third party, meaning a non-EU country, as of February 1st, 2020. This critical point in European history opened many discussions surrounding the future of the economic relations between both parties involved. The foundation for Brexit[24] was to "*take back control of [their] money, laws and borders* (Keating)", as a way to re-shore and reset legal and decision-making powers once managed at the European Union level (Lydgate and Anthony, 2022). It is important to point out how before Brexit, it was estimated that around 90 per cent of UK food law and policy was made at EU level (Lydgate and Anthony, 2022). Lydgate and Anthony (2022) emphasize how as Member States, countries were integrated into a highly developed multi-level governance system with extensive legislative frameworks, well-established institutions, scrutiny mechanisms and enforcement procedures, including the UK. Months into the referendum, the topic of food emerged, revealing the numerous ways in which the UK had merged into the EU's Internal market and political economy (Millstone *et al*., 2019). A significant portion of the EU *acquis communautaire*[25] pertains to food and agriculture; on that account, it quickly became apparent that separating the UK from the EU's "*dense web of interconnections*" would prove to be considerably more complex than expected.

Following the official departure of the United Kingdom from the European Union on January 31, 2021, and hence their departure from the EU's Single Market and Customs Union, the trading of goods between businesses in Great Britain and the EU has undergone significant changes (Cabinet Office, 2021). Exporting goods to the EU now requires compliance with new customs procedures, including UK export declarations and adhering to import requirements upon entry into EU Member States. As for importing goods into the UK, border controls were being introduced gradually to allow businesses time to adapt (Cabinet Office, 2021). The UK now possesses autonomy over technical regulations, standards, and conformity assessment procedures necessary for placing products on the UK market. In cases where conformity assessment procedures require approval from a third-party conformity assessment body, certification from both the UK and the EU is necessary for products intended to be sold in both markets (Cabinet Office, 2021).

However, the EU-UK Trade and Cooperation Agreement coming into force on May 1, 2021, marked the establishment of preferential arrangements for trade in goods and in services, among other areas, between the European Union and the United Kingdom (European Commission, 2021). Although it does not fully replicate the economic integration that existed when the UK was a Member State, this agreement goes beyond typical free trade agreements (FTAs), serving as a strong foundation for preserving the "long-standing friendship and cooperation" between both parties (European Commission, 2021). The Agreement ensures that goods complying with the appropriate

[24] "Britain" and "exit".

[25] Collection of common rights and obligations that constitute the body of EU law (Eur-Lex).

rules of origin will be traded between the EU and the UK with zero tariffs and quotas. According to the EC (2021), both sided are committed to maintaining a fair competition environment by upholding high standards in various areas, such as environmental protection.

With Brexit the UK's set of regulations for food supplements, which were previously governed by the EU's Directive 2002/46/EC, changed. During the UK's membership in the EU, the specific vitamins, minerals, and their substances allowed for use in food supplements were outlined in the annexes to the Directive (Department of Health and Social Care, 2022). In England, these provisions were implemented through the Food Supplements (England) Regulations 2003[26]. Nowadays, in order to maintain their validity in Great Britain after Brexit, these lists have been included as Schedules in the Nutrition (Amendment etc.) (EU exit) Regulations 2019 (Department of Health and Social Care, 2022). It's important to note that these regulations solely govern the usage of vitamins, minerals, and related substances in food supplements, meaning other substances utilized are not directly regulated (Department of Health and Social Care, 2022). However, they must still meet the criteria of being safe for human consumption and to not pose any health risks.

The Food Supplement (England) Regulations 2003 allow the use of substances with nutritional or physiological effects in food supplements. However, these regulations do not provide a specific list of approved or otherwise restricted botanical or other bioactive substances (Trovato and Ballabio, 2018). Unlike Spain, the UK offers companies help to determine the likely status of their products with a list of herbal ingredients that has been put together by regulatory bodied and industry in the country (MHRA, 2020). Noteworthily, the list, which is not exhaustive and has no legal standing, includes various plants along with their recorded uses in the UK, in the likes of food, medicines, cosmetics, and aromatherapy (Trovato and Ballabio, 2018). The newly updated Food Supplements (England) Regulations 2021 applies specifically to England, whilst similar regulations with slight variations exist in Scotland, Wales, and Northern Ireland (Trovato and Ballabio, 2018). Notably, in the UK there has never been a specific national legislation that establishes maximum levels for vitamins, minerals, and related substances in food supplements (Department of Health and Social Care, 2022). In their case, voluntary guidelines exist in the form of safe upper levels (UL), which are based on a report issued in 2003 by the Expert Group on Vitamins and Minerals (EVM) titled "*Safe upper levels for vitamins and minerals*".

Regarding prohibited substances in food supplements, certain products freely available in other countries are either not permitted or classified as medicinal or novel in the UK. Hence, before placing a product in the British market, it is recommended manufacturers contact the Medicines and Healthcare products Regulatory Agency (MHRA) to determine if the product, its ingredients, or

[26] S.I. 2003 No. 1387.

claims fall under the medicinal category (Department of Health and Social Care, 2022). It is important to point out food supplements cannot contain medicinal ingredients in the UK, and the MHRA oversees determining whether they might be a medicine rather than a food.

Distinct to Spain, in the UK there is no requirement to register food supplements, i.e., the equivalent of the notification process (Department of Health and Social Care, 2022). According to the Food Standards Agency (2023), in order to sell food supplements food business operators (FBO) must register with their local authority; if they adhere to the relevant legislation regarding food supplements and other applicable food laws, they are allowed to be sold in the market. The manufacturer, importer, or retailer bear the responsibility of ensuring their compliance with the law (Food Standards Agency, 2023).

The Regulations in the UK have streamlined the definition of food supplements, simplifying it in principle (Department of Health and Social Care, 2011). However, it should be noted that the lack of precise specifications within this definition, there is a chance for introducing a greater level of interpretive discretion. According to the S.I. 2003 No. 1387, food supplements are "*a concentrated source of vitamins, minerals and other substances with a nutritional or physiological effect, alone, or in combination, sold in dose form*" (Department of Health and Social Care, 2011). Currently, the legislation specifically includes positive lists for vitamins and minerals, while other substances like fatty acids, amino acids, and other nutrients or botanicals are not required to be listed. However, all substances, regardless of whether they are listed or not, must comply with the general aspects of the legislation in regard to packaging, labelling, and safety (Department of Health and Social Care, 2011).

Majority of food supplements are covered by food law, however, if a food supplement exhibits medicinal properties or makes claims regarding the prevention, treatment, or cure of diseases or medical conditions, it must comply with medicines legislation and be licensed accordingly by the MHRA[27] (Department of Health and Social Care, 2011). Many herbal ingredients and products are classified as medicines and must have a Traditional Herbal Registration (THR), which falls under MHRA jurisdiction (Department of Health and Social Care, 2011). According to The Human Medicines Regulations 2012, a product qualifies as an herbal medicinal product if it contains only herbal substances and/or herbal preparations as active ingredients. Herbal substances refer to various plant or plat-derived materials, while herbal preparations involve specific processes such as extraction, distillation, or purification (S.I. 2012 No. 1916).

The THR is only granted to products intended for minor health conditions that do not require medical supervision, such as the common cold (MHRA, 2021). In order to obtain the registration, it

[27] Since medicines legislation is not harmonized across the European Union, a product that can be freely sold as a food supplement in one Member State might be classified as a medicinal product in another Member State.

is crucial to include (a) scientific evidence related to the safety, quality, and traditional use of the herbal product; (b) a safety review conducted by a registered doctor, registered pharmacist, scientifically qualified competent individual (like a toxicologist), or herbal practitioner; (c) a summary of the product's characteristics, outlining essential information about it, like precautions of use; (d) a mock-up label and patient information leaflet that adhere to best practice guidelines (MHRA, 2021). It is worth noting that prior to submitting the application, it is possible to seek advice on whether the product is likely to meet the requirements of the THR scheme, ensuring better preparation and increased chances of success. Once obtained, the label and the patient information leaflet will include the THR Certification Mark, assuring consumers that the product has undergone rigorous assessments and is deemed safe and of high quality (MHRA, 2021).

2.4 Food, food supplement, or medicinal product*: Echinacea purpurea*

So where does *Echinacea purpurea* fit in among all these different classifications? PLANT food supplements: Levels of Intake, Benefits and Risk Assessment (PlantLIBRA) was a project from the Seventh Framework Programme[28] which started on June 1, 2010, aimed at promoting the safe use of food supplements that contain plants or herbal extracts through the enhancement of science-based decision-making among regulators and those involved in the food industry (Restani, 2018). According to a survey conducted by PlantLIBRA, ginkgo, echinacea, garlic, and ginseng are the most commercially important botanicals in the combined markets of 17 EU Member States, however, echinacea and gingko are also used in products registered as medicines (European Advisory Services, 2007, in Trovato and Ballabio, 2018).

On December 2009, the European Commission published a decision[29] establishing a list of "*herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products*" which took into consideration Directive 2001/83/EC issued by the European Parliament and the Council on November 6, 2001, which focuses on the regulations pertaining to medicinal products for human use, specifically article 16(f) of the Directive (European Commission, 2009). The decision was complemented by an annex stating the Community list entry on *Echinacea purpurea* (L.) Moench whilst establishing the plant's usage guidance in medicinal products. After the European Medicines Agency's Committee on Herbal Medicinal Products (HMPC) conducted scientific evaluations on the medicinal properties of the purple coneflower herb, their conclusions should be considered by Member States when reviewing applications for the licensing of herbal medicines that

[28] A research funding programme ran by the EU from 2007 until 2013.

[29] Commission Decision of 21 November 2008 establishing of a list of herbal substances, preparations, and combinations thereof for use in traditional herbal medicinal products (notified under document number C (2008) 6933)

contain *E. purpurea* (European Medicines Agency, 2015). The HMPC determined *E. purpurea* herb medicines can be beneficial for the prevention and short-term treatment of common cold. This is supported by "well-established use" evidence, meaning, there is scientific data available, spanning at least 10 years within the EU that demonstrates the effectiveness and safety of these medicines for this particular purpose (European Medicines Agency, 2015). Within their assessment, the HMPC considered various clinical studies comparing *E. purpurea* herb medicines with placebos for the short-term prevention and treatment of upper tract respiratory infections. The most relevant trials involving adults, indicated *Echinacea* medicinal products, specifically those containing expressed juice and taken orally, can "*prevent and improve*" common cold symptoms when used early, surpassing the effects go the placebos (European Medicines Agency, 2015).

The products with the well-establish use provision must be herbal preparations, meaning expressed juice or dried juice corresponding to the expressed juice, in solid or liquid forms, intended for oral use (European Medicines Agency, 2015). In regard to the dosage for adolescents, adults, and the elderly, 1.5-4.5 ml of expressed juice as a single dose is recommended, with a daily dose of 6-9 ml (European Medicines Agency, 2015). Doses of dried juice should correspond to the posology of the expressed juice. Caution is advised because its use is not recommended for children under 12 years of age. The treatment should commence at the first signs of a common cold, with duration of use not exceeding 10 days. In the case symptoms persist for more than these days, it is advisable to consult a doctor or pharmacist (European Medicines Agency, 2015). The HMPC (2015) points out how limited data on pregnant women indicate no adverse effects of *Echinacea* on pregnancy or the health of the fetus/newborn, hence the use these preparations during pregnancy and lactation is not recommended without medical advice due to insufficient data. Hypersensitive reactions, such as rash, itching, and swelling of the face, may occur, and severe reaction like Stevens-Johnson Sydrome, angioedema, bronchospasm, asthma, and anaphylactic shock have been reported, although their frequency is unknown (European Medicines Agency, 2015).

Additionally, the Committee has recognized *E. purpurea* as a traditional European herbal medicinal product due to its long-standing use as a topical semi-solid or liquid product utilized to effectively treat small superficial wounds (European Medicines Agency, 2015). Its foundation on traditional use means that although there is insufficient evidence from clinical trials, there is a plausible basis for the effectiveness of these herbal medicines, plus evidence of their safe use for the indicated purpose, for at least 30 years, including 15 years within the EU (EMA, 2015). It is important to note, purple coneflower herb medicines are intended for use only in adults and adolescent aged 12 years and above. This herbal preparation must be derived from the expressed juice and dried expressed juice of the fresh flowering aerial parts (European Medicines Agency, 2015). The specified

strength for the product is 10-20 grams / 100 grams of expressed juice or an equivalent amount of dried expressed juice in liquid or semi-solid dosage forms (European Medicines Agency, 2015). The topical ointment is meant to be applied in small amounts to the affected area 2-3 times a day by adolescents over 12 years, adults, and the elderly only equally. Additionally, to ensure safety, the duration of use should not exceed 1 week, and if symptoms persist, it is recommended to seek medical advice (European Medicines Agency, 2015). It is also notified that individuals with hypersensitivity to the active substance or plants of the Asteraceae (Compositae) family should avoid using this product. And special precautions should also be taken if signs of skin infection are observed. Fortunately, no interactions with other medicinal products have been reported. However, the safety of using this product during pregnancy or lactation has not been established either, or it is important to note that products containing *Echinacea purpurea* should not be applied to the breast of breastfeeding women (European Medicines Agency, 2015). And finally, whilst hypersensitive reactions such as local rash, contact dermatitis, eczema, and angioedema of the lips may occur, the frequency of such reactions is unknown (European Medicines Agency, 2015).

In 2017, the HMPC published an additional herbal monograph, this time for *Echinacea purpurea* products supported by their traditional use with the quantitative and qualitative composition for herbal preparations thought dry extracts (ethanol and water solvent) (European Medicines Agency, 2017). The product's pharmaceutical form must be in solid dosage forms for oral and oromucosal use with the indication of relieving symptoms of the common cold or skin conditions, such as spots, pimples due to mild acne, both based exclusively on its long-standing use (European Medicines Agency, 2017). Several factors agree with the previous 2015 EMA monograph, including the absence of cases reported about overdose, the undesirable effects that come from using the product, the need to carry out studies on the effect on the ability to drive and use machines, the absence of interaction with other medicinal products, the prohibition of use from children under 12, the product's cause of hypersensitivity in patients, and its posology and duration of use with the "well-established use" product . Special warnings and precautions of use were added, declaring the product should not be used in cases of progressive systemic disorders, autoimmune diseases, immunodeficiencies, immunosuppression, or diseases of the white blood cell system (European Medicines Agency, 2017). If symptoms worsen or high fever occurs during product use, it is recommended to consult a doctor or qualified healthcare practitioner. Sensitive individuals have a possible risk of allergic reactions, as atopic patients also have a potential risk of anaphylactic reactions, these patients should seek advice from their doctor too, before using *Echinacea* (European Medicines Agency, 2017).

Within the EU's Novel Food Catalogue, which includes the interpretations at Community level made by groups of experts on novel foods of the EU, *Echinacea purpurea*'s status is labelled with FS, meaning how based on information accessible to the authorities of Member States, *E. purpurea* was exclusively utilized as a food supplement or as an ingredient in such supplements prior to May 15, 1997 (European Commission, n.d.). Any additional uses of the coneflower as a food must be approved in accordance with the Novel Food Regulation (EU) 2015/2283[30]. However, the catalogue should be seen as a tool to refer to when evaluating the classification of a new food or food ingredient, meaning it does not possess legal standing, and it does not encompass a comprehensive list of all foods (Food Supplements Europe, 2019). Silano *et al*. (2011) emphasize how the categorization of botanical species and preparations, like *E. purpurea*, as Traditional Plant Food Supplements (TPFS) and Traditional Herbal Medicinal Products (THMP) in the EU Member States is not clearly defined, hence why some of these botanicals and their preparations are classified as a TPFS in one Member State but considered as a THMP in another Member State. The authors sorted certain popular botanical species included by the EMA in the Community List of substances, preparations, and their combinations, where some data can be excluded in the application file for THMP registration, are also used as food supplements in multiple Member States (Silano *et al*., 2011). *Echinacea purpurea* is found in this classification, where it is stated how the coneflower is indeed found within the Community List of traditionally use medicinal products, yet seven Member States use it as a food supplement (Silano *et al*., 2011).

A model Member State when it comes to food supplement legislations is France. The implementation of the EU provisions in the form of the 2006 Food Supplements Decree No 2006-352[31] acknowledges the use of botanicals and other bioactive substances in food supplements (Coppens and Pettman, 2018). To top it off, France adopted an Order on June 24, 2014[32], on the use of plants and plant preparations (other than mushrooms) permitted to be utilized in food supplements plus their conditions of use. The Order contains three annexes, the first comprises a list of approximately 600 plants whose use is authorized, including *Echinacea purpurea* (Coppens and Pettman, 2018). Whilst Annex II outlines the mandatory information that food business operators

[30] Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001 (Text with EEA relevance), OJ L 327, 11.12.2015, p. 1–22.

[31] Décret n° 2006-352 du 20 mars 2006 relatif aux compléments alimentaires. Official publication: Journal Officiel de la République Française (JORF); Publication date: 25/03/2006

[32] Arrêté du 24 juin 2014 établissant la liste des plantes, autres que les champignons, autorisées dans les compléments alimentaires et les conditions de leur emploi, JORF n° 0163 du 17 juillet 2014.

must provide regarding the characterization of plant preparations, and finally, Annex II focuses on the safety of plant preparations, applicable only when their nature or conditions of use significantly deviate from traditional practices (Coppens and Pettman, 2018). In the case a food supplement contains plants not listed in Annex I or plants used outside the set conditions, it must be declared under article 16 of the French Food Supplement Decree based on the principle of mutual recognition, or otherwise, undergo a pre-marketing authorization procedure as outlined in article 17, which involves a scientific assessment by ANSES (Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail or The French Agency for Food, Environmental and Occupational Health & Safety) (Coppens and Pettman, 2018). Within Annex I of the Order, *Echinacea purpurea* (L.) Moench is listed, providing details such as its botanical family (Compositae), its vernacular name in French (*Echinacée pourpre*), the parts used in food supplements (flowering aerial parts and underground organs, i.e., roots), substances to be monitored (chicory acid) and restrictions which are none in the case of *E. purpurea*.

On the contrary, the Spanish AESAN published guideline back in 2007 for the evaluation of food supplements made from plant components and their preparations, highlighting the existence of products made from plants in the market bring about a challenge when classifying them as either food or medicine due to their traditional use or the physiological actions triggered by their components, creating a significant problem when applying the regulations that govern them. The challenge arises when certain plants and their components are used in both medicinal products and food supplements with similar formulations (Navarro *et al*., 2007). The classification of these "*ambivalent plants*" into one category or the other depends on factors such as the presence of pharmacologically active substances in the final product, the intended use or purpose, and the recommended intake by the manufacturer (Navarro *et al.*, 2007). Therefore, it is necessary to determine the nature of each product must be assessed individually to determine the appropriate classification.

An additional and complementary guide in 2016 on the official control of labelling and composition of food supplements was published to provide the responsible competent authorities with an official document identifying and describing the specific requirements to be controlled regarding the labelling and composition of food supplements (AECOSAN, 2016). The guide emphasizes how if the food supplement contains non-harmonized ingredients, like botanicals, it can only be marketed in Spain if it demonstrates prior marketing within the EU. The safety for these ingredients can be verified either in relation to novel foods or ingredients with pharmacological action, meaning an ingredient could be used in food supplements if it is listed within the EC's Novel Foods Catalogue with the two following marks, the green tick and the blue FS, the latter which classifies *Echinacea purpurea* as previously stated (AECOSAN, 2016).

In terms of ingredients with pharmacological actions, there are certain active ingredients, either due to their presence or dosage, which should be authorized according to the legislation governing human medicinal products, ensuring quality, safety, and effectiveness (AECOSAN, 2016). The Spanish Agency of Medicines and Medical Devices (Agencia Española de Medicamentos y Productos Sanitarios or AEMPS) is the body responsible for evaluating these active substances, meaning if the Agency confirms that a product, at the recommended dosage, has pharmacological effects that warrant its authorization as a medicine, it should be marketed outside the realm of food supplements (AECOSAN, 2016, pg. 10). Within these criteria, at the time of this review there were seven registered *E. purpurea* products authorized to be sold without a medical prescription inside the AEMPS-CIMA's online database, five of which belongs to the Swiss company Bioforce AG A.Vogel, a pharmaceutical laboratory specialized in phytomedicine (AempsCIMA, 2017). Four of these products are specifically indicated as traditional herbal medicines for the relief of symptoms associated with cold and flu, based solely on their traditional use. The other two products registered belong to Spanish Meda Pharma SL and French Arkopharma Laboratoires (AempsCIMA, 2017).

Different to some EU Member States, within the United Kingdom, *Echinacea purpurea* has been classified as an herbal medicine granted a traditional herbal registration (MHRA, n.d.). In accordance with the Regulations, any medicinal product introduced to the UK market must possess a marketing authorization (MA), a traditional herbal registration (THR), or a certificate of registration as a homoeopathic product issued by either the European Commission[33] or the UK Licensing Authority (MHRA, 2020, pg. 5). It is up to the MHRA, acting on behalf of the UK Licensing Authority, to determine whether a product qualifies as a medicinal product on a case-by-case basis, however, this decision is subject to potential review by the courts (MHRA, 2020, pg. 6). Medicinal products are defined within The Human Medicines Regulations 2012 as "*any substance or combination of substances presented as having properties of preventing or treating disease in human beings; or any substance or combination of substances that may be used by or administered to human being with a view to (i) restoring, correcting or modifying a physiological function by exerting a pharmacological, immunological or metabolic action, or (ii) making a medical diagnosis*" (S.I. 2012 No.1916). Under this second limb, the MHRA considers among other factors, characteristics such as the pharmacological, immunological, or metabolic properties of the ingredient(s), as well as any notable impacts the product will have on human physiological function (MHRA, 2020). Or, in the case of a product that meets the definition of a traditional herbal medicinal product[34], where the

[33] Guidance last updated on December 31, 2020.

[34] According to Directive 2004/24/EC.

pharmacological, immunological, or metabolic effects, or efficacy, are deemed plausible based on long-standing use and tradition (MHRA, 2020).

Notably, the MHRA solely classifies complete products, meaning no individual substances and ingredients are taken into consideration (MHRA, 2021). Hence why inside the Agency's product catalog there is multiple entries for *Echinacea purpurea*. Among 13 listings differing in the product's preparation, meaning whether it is a tincture, extract or powder, there are precisely 93 files from various companies showcasing their product that utilize *E. purpurea*, for example Bio-Health and their Ekinalife® capsules, A. Vogel's popular Echinaforce® drops, or Lifeplan® with their *Echinacea* cold & flu relief tablets (MHRA, n.d.). Within these files, companies have provided MHRA and the public with the patient information leaflet and an additional summary of the product's characteristics (MHRA, n.d.). As of March 25, 2022, the guidance of herbal medicines granted a THR contained 30 products containing or composed of *Echinacea purpurea*, these could be divided into categories according to the product indication and/or traditional use (MHRA). It is important to note how due to the legal nature of the registration process, the specific terms used hold significance and can widely differentiate one category from the other despite their similarities at core. These categories address a range of concerns and adhere to the principle of relying exclusively on traditional usage.

The most relevant use for the products within the guidance is to alleviate, relieve, or treat symptoms related to the common cold and influenza-like symptoms, based only on traditional use (MHRA, 2022). The indications here variate on the addition of the phrase "*treatment for minor upper respiratory tract infections*", and on the specification of symptoms it can relieve, such as cough, catarrh, sore throat, and runny or blocked nose (MHRA, 2022). The last two groups of products pertain to the categories focusing on one hand to the symptomatic relief of minor skin conditions, including spots, pimples, and blemishes, and on the other, to the relief of minor urinary complaints in women, particularly those associated with cystitis, such as burning sensation during urination and/or frequent urination (MHRA, 2022). These carefully defined categories ensure a comprehensive coverage of various conditions, while recognizing the legal significance of distinct terminologies within each group.

CHAPTER 3
ECHINACEA PURPUREA AS FOOD

3.1 Botanicals and nutraceuticals

Food or food ingredients that have specific physiological effects on the human body, making them not fit neatly into the conventional legal categories of either food or medicine, often residing in a grey area between the two, are known as nutraceuticals. The term "nutraceutical" was first coined by Defelice in 1989 by merging the words "nutrition" and "pharmaceutical" (Gulati *et al*. 2019), it was later, in 1995, that he defined them as "*food or parts of food that provide medical or health benefits, including the prevention and/or treatment of disease* (Defelice, 1995, in Gulati & Ottaway, 2016)". In the European Union law, where a definition does not exist, the classification of a nutraceutical is generally determined by its recognized effects on the body: if the substance contributes solely to the maintenance of healthy tissues and organs, it is considered a food ingredient; on the other hand, if it is shown to have a modifying effect on one or more physiological processes in the body, it is likely to be considered a medicinal substance (Gulati & Ottaway, 2016). Botanical materials make up a significant portion of nutraceuticals and present additional challenges due to their complex nature and composition.

Once published, entered into force, and become applicable, EU regulations and directives harmonize the regulatory framework, with some differences. While regulations are directly applicable and do not require national implementing acts, directives require Member States to adopt national enacting provisions: this can lead to some differences in the legal positions on botanicals products. As an illustration, the marketing of plant food supplements is contingent upon national legislations, leading to variations in regulation extent and control processes. Additionally, an added complexity arises from the principle of mutual recognition, whereby a product lawfully marketed in one Member State can be sold in all 27 Member States. As stated previously, the same botanical may be used as both a food supplement and a medicinal product, plus they often share similar forms of presentation, such as powders, pills, or tablets. Therefore, the presence of a substance with pharmacological activity in a product does not automatically classify it as medicine. Various factors, such as therapeutic dosage, proposed use, and the nature of the induced effect, should be considered to establish the appropriate classification. Consequently, all the above-mentioned factors that make the legal status of botanical products differ create a complex market environment. This "borderline issue" between plant food supplements and herbal medicinal products poses a major obstacle to the marketing of supplements with botanicals in the EU especially.

The use of botanicals, like *Echinacea sp*., their derivates and preparations have been and continue to be widely used for health purposes throughout Europe by the general population as well as by populations with specific needs, including children, pregnant women, and those dealing with conditions like cancer among others (Garcia-Alvarez *et al.*, 2014). Botanicals exhibit a unique versatility due to their extensive range of applications, including foodstuffs like teas and juices, food supplements, herbal medicinal products, homeopathic products, cosmetics, and biocides, each product being govern by a specific legislation depending on its intended use (Garcia-Alvarez *et al.*, 2014).

The following segment will delve into the diverse legal opportunities available for food business operators to sell *Echinacea purpurea* tea within the European Union. It will explore the various regulatory pathways, guidelines, and standards governing the marketing and sale of herbal infusions, considering the intricate classification of nutraceuticals and botanicals as food or medicinal products. By examining these legal avenues, FOBs can gain valuable insights into the requirements and possibilities of introducing *E. purpurea* tea to the EU market, navigating the complexities of EU regulations while contributing to the flourishing landscape of herbal infusions.

3.2 Botanical herbal teas: from foods to remedies

Europe has witnessed diverse historical uses of herbal materials as foodstuffs; in the past, herbal and fruit infusions were commonly used as home remedies, prevalent in most households, as they were relied upon for treating common ailments such as colds or digestive issues (THIE). Over time, the use of these products changed, and due to their delightful aromatic flavors, many of them were embraced as food (THIE). As a result, certain plants serve a dual purpose, capable of being used both as remedies and enjoyed as food. This again clearly illustrates the challenge of classifying many plant products either as foodstuffs or as medicinal drugs, leading to the need of carrying out an evaluation on a single product and its intended use to determine how it should be regarded. Additionally, the absence of harmonized European legislation concerning the raw materials permitted in herbal infusions has resulted in various national plant lists across Member States categorizing certain plant materials as either food plants or medicinal plants.

Back in 2015, the European Herbal Infusion Association (EHIA) and the European Tea Committee (ETC) joined forces to create a new association called Tea & Herbal Infusions Europe, or THIE, with the purpose of serving as a comprehensive knowledge hub for all aspects related to herbal and fruit infusions and their extracts used as foodstuffs (THIE, 2018). Since then, THIE has collaborated with competent EU authorities, as well as with national and international organizations, to safeguard and promote the interests of the herbal and fruit infusions industry.

In regard to tea, herbal infusions, and fruit infusions, these must adhere to all applicable aspects of food legislation in terms of their composition, manufacturing process, and quality control (THIE). To facilitate this, THIE has developed a Compendium of Guidelines for Tea and a Compendium of Guidelines for Herbal and Fruit Infusions, these compendia consolidate all relevant legal provisions and standards currently in force within the EU. Their objective is to establish harmonized quality standards for various product categories falling under THIE's purview, promoting a high-quality policy and preventing food fraud (THIE). Furthermore, these compendia serve as a foundation for facilitating the free trade of these products within the EU market and beyond (THIE). Most importantly, through these initiatives, THIE recognizes the industry's responsibility in ensuring food safety.

Herbal and fruit infusions (HFI) hold significance within European tradition and culture, their growing popularity reflects consumers' increasing appreciation for the diverse and refreshing natural flavors they provide (THIE, 2018). According to THIE (2018), herbal and fruit infusions are defined as plant materials or parts thereof that do not originate from the tea plant *Camellia sinensis* (L.) O. Kuntze and are intended for brewing with freshly boiling water for food consumption. HFI products are named after the specific plant type or plant part used, often combined with the terms "tea" or "infusion" if derived from a single plant type or from a combination of two plant types (THIE, 2018). The plants and plant parts commonly used in HFI are listed in the current version of the THIE's Inventory List of Herbals Considered as Food, available at www.thie-online.eu, where the association has documented and compiled the more than 300 species used for the production of herbal infusions.

The term "herbal teas" refers to a product composed of one or more herbal substances intended for oral aqueous preparations made by decoction, infusion, or maceration methods. As for infusion, it is usually suitable for leaves, flowers, and delicate parts, while decoction or maceration are appropriate for roots, rhizomes, and barks (EMA, 2010b). EMA (2010b) defines infusions as liquid preparations made by pouring boiling water over the herbal substance(s), reduced to a suitable size[35], and letting it steep for a defined time, usually 5 to 15 minutes. The use of boiling water is important as it helps reduce the microbial load of the herbal materials. In the case of decoctions, these liquid formulations are prepared by pouring cold water over the herbal substance(s), heating it to a boil, and steeping it. Decoction is generally not suitable for herbal substances containing volatile active constituents. Lastly, macerates are made by soaking the herbal substance(s) in water at room temperature for a defined period of time. Herbal teas are typically prepared immediately before consumption.

[35] The herbal substances used in herbal teas may undergo prior processing, such as comminution or crushing.

The Inventory was established by the EHIA back in 2000 with the aim to address the growing utilization of plant-based products, preparations, and extracts for food purposes. Recognizing the need for a unified framework and to benefit manufacturers and consumers of such products, THIE compiled a list of plants currently used in the herbal infusions industry across different Member States. This compilation takes into consideration the habits, traditions, and regulatory status of plants in each MS. It is important to note how the Inventory is not exhaustive and remains subject to updates to ensure its relevance and accuracy. The significance of the list lies in the fact Europe has diverse historical practices of using herbal materials as foodstuffs. Moreover, if a plant material has a tradition of safe use in one MS or region, it indicates that it can also be used as a foodstuff in other parts of the European market (THIE, 2019). The list includes *Echinacea purpurea* roots with a recommended restricted quantity mentioned.

3.3 Botanicals as food: Novel Food status and medicinal classification

In the realm of herbal ingredients, Gulati and Ottaway (2016) say it is crucial to consider the assertion, presentation, and the expectations of consumers. For instance, if "peppermint tea" claims to be a refreshing beverage, it would fall under the category of food. On the other hand, if it claims to prevent or treat upset stomachs, it is considered a medicine. Similarly, the authors point out Senna tea with a claim of being a healthy supper-time aid to digestion would also be classified as medicine. Therefore, the objective of these claims is to match the consumers' expectations with the intended pharmacological action (Keller, 2003, in Gulati & Ottaway, 2016).

Two vital factors when considering the use of botanicals in foods within the EU's market are the novel food status and whether the ingredient can be categorized as "*medicinal by function*" (Gulati & Ottaway, 2016). Although the Regulation on Novel Foods and Novel Ingredients was established in early 1997, it wasn't until approximately 7 years later that the European Commission modified its interpretation of the Regulation. This change was ratified by the EU Standing Committee on the Food Chain and Animal Health in February 2005[36] (Gulati & Ottaway, 2016). Consequently, any nutraceutical that was exclusively used in food supplements, like *Echinacea purpurea*, before May 1997 cannot claim exemption from the Regulation for use in other food categories. This means that if a nutraceutical was used solely in supplements before 1997 and now there is an intention to use it in a drink or other food products, it would require a novel foods application and official approval (Gulati & Ottaway, 2016). The application process must include a comprehensive range of toxicity

[36] Amending Act: Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety.

studies. If the nutraceutical was only used in supplements before 1997, there is a high likelihood that additional data would be necessary to support an application for use in food.

Aside from the novel food status, it is imperative to ensure that the type of nutraceutical ingredient and the anticipated consumption levels do not classify it as "medicinal by function"; if it were the case, its use in food would be prohibited (Gulati & Ottaway, 2016). Within the framework of the European Medicines law, a nutraceutical can be classified as medicine for two reasons: (i) if it is presented for the prevention, treatment, or cure of a condition or disease; or (ii) if it can be administered to restore, correct, or modify physiological function in human beings (Gulati & Ottaway, 2016). According to the Directive, any substance or combination of substances that can do the latter, by exerting a pharmacological, immunological, or metabolic action, or for medicinal diagnosis, can be considered a medicinal product (Directive 2001/83/EC, art. 1, par. 2). This means that if any component of the product has a pharmacological effect on the human body, the entire product may be regarded as medicinal, even if no explicit medicinal claims are made in its labeling or presentation. There are several possible categorizations for nutraceuticals and botanicals within EU law, as discussed in the previous chapter:

1. If medicinal claims are made based on its traditional use as defined in Directive 2004/24/EC[37] on traditional herbal medicinal products, or the herb is considered medicinal by function, the product may be categorized as such, provided the time-related criteria are met, meaning the years of use.
2. If it is categorized as food or food ingredient, Article 2 of the General Food Law Regulation must be considered. For whole foods with benefits beyond basic nutrition, proper identification and characterization on the material are essential.
3. If it falls under the scope of the Novel Food Regulation, which defines novel foods as those that have not been significantly consumed in the EU before 15 May 1997. In such cases, a comprehensive safety evaluation is required before approval for use in foods can be granted.

The classification of nutraceuticals and botanical products in the European Union presents a complex and evolving landscape, situated between the realms of food and medicine. Botanicals like *Echinacea purpurea* have a rich historical tradition of use in food products such as herbal infusions. While the legal status of botanical products remains unharmonized at the EU level, the establishment of guidelines and standards by organizations like Tea & Herbal Infusions Europe (THIE) provides a framework for food business operators to ensure the quality and safety of their herbal infusion

[37] Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use, OJ L 136, 30.4.2004, p. 85–90.

products. Leveraging the appreciation for natural flavors and potential health benefits, food business operators have a valuable opportunity to enter the market with *Echinacea purpurea* food products, must specifically as tea. By adhering to relevant food legislation and following THIE's guidelines, they can tap into the growing consumer demand for herbal infusions and contribute to the rich and diverse European tradition of using botanicals for both enjoyment and well-being.

3.4 Can tea be classified as a THMP?

Certain botanicals are recognized as traditional herbal medicinal plants and are utilized in both medicinal products and food supplements (Bilia and do Ceú Costa, 2021). Determining whether a botanical should be classified as a medicine or a food supplement is not the role of the EFSA or the EMA, however, the latter is responsible for evaluating the safety and effectiveness of herbal preparations when used as medicines (Bilia and do Ceú Costa, 2021).

But what specific type of products can be classified as THMP? Herbal Drugs (HDs)[38] are defined in a comprehensive monograph of the European Pharmacopoeia as "*whole, fragmented, or cut plants, plant parts, algae, fungi, and lichens*" in their natural, typically dried, form, although sometimes they can be fresh (Bilia and do Ceú Costa, 2021). The precise definition of HDs includes the identification of the plant part used and its botanical name. Furthermore, Herbal Drug (Substance) Preparations (HDPs), also defined in a general monograph, encompass comminuted, meaning powdered or cut, HDs, extracts, tinctures, essential oils, expressed juices, and processed exudates (Bilia and do Ceú Costa, 2021). Therefore, Herbal Medicinal Products (HMPs) are products where the active ingredient exclusively consists of HDs or HDPs sold with the view of "*restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action*" as defined in Directive 2001/83/EC[39].

In April 2021 the Traditional Herbal Medicinal Products Directive (THMPD) came into force across the EU, with the aim to ensure both the safeguarding of public health and the facilitation of unrestricted movement of herbal products within the European Union (Gilbert, 2011). According to the Directive, herbal medicines are intended to treat minor health conditions only and need to be officially registered as traditional-use products with the respective regulatory agency of each Member State where the product is anticipated for sale (Gilbert, 2011). Nevertheless, it is expected that national regulatory agencies should acknowledge licenses that have been granted by other Member States. By ensuring a consistent criterion across all MS for determining whether a product classifies

[38] The EMA acknowledges the term "herbal substance" corresponds to HDs.

[39] Amended by Directive 2004/27/EC.

as a medicine or a food supplement, the Directive can be applied universally to all manufactured herbal products, regardless of where they are sold, in health food shops or pharmacies (Gilbert, 2011).

Prior to the implementation of the THMPD, countries had a fragmented collection of regulations pertaining to herbal medicines. Certain countries had no regulations governing traditional herbs, while others categorized herbal products as food supplements instead of medicines, resulting in a less rigorous oversight (Gilbert, 2011). As a result, some traditional herbal products were accessible to consumers without the assurance of quality and safety that come with proper regulation (Gilbert, 2011). Therefore, the system created by the Directive should reduce the chances of a product being marketed as a traditional herbal medicine in one country and as a different product in another.

As stated in the previous chapter, for a product to be eligible for a traditional herbal medicine license, it must have a documented history of at least 30 years of use treating a specific health condition, with a minimum of 15 years of use in Europe (Directive 2004/24/EC). However, instead of conducting original clinical trials like pharmaceutical drug manufacturers must, makers of traditional herbal medicines are allowed to rely on the extensive history usage of their products (Gilbert, 2011), with the assessment based generally on bibliographic safety and efficacy data (EMEA, 2006), as seen in the case of *Echinacea purpurea* and its long-standing use not only in Europe, but in America too. Dick Middleton (in Gilbert, 2011), technical director of Schwabe Pharma UK, points out how the presence of some of these products for thousands of years and their continued use, is an indication of their effectiveness.

In an effort towards true harmonization within the European Community, the European Medicines Agency has published several EU herbal monographs[40] with the objective to simplify the registration process of HMPs by incorporating all available information, including non-clinical and clinical data, as well as evidence of plausible efficacy based on documented longstanding use and traditional experience within the community (Bilia and do Ceú Costa, 2021). In contrast to the framework of food law, the classification established by the Committee on HMPs and outlined in the EMA herbal monographs is obligatory for each Member State to either accept or reject these monographs (Bilia and do Ceú Costa, 2021). Said monographs are harmonized through the Committee on HMPs of the EMA for pre-market approval, they include the provision of a Summary of Product Characteristics detailing the specifications for extracts, recommended doses, interactions, special warnings. However, as Bilia and do Ceú Costa (2021) point out, it appears that the food law which food supplements are subjected to does not take these aspects into account.

Silano *et al.* (2011) detail the registration of HMPs as a facilitated procedure which can be done at national level. The specific authorization which allows such product to be marketed is based

[40] Previously known as Community herbal monographs.

on considerations of quality, safety, and efficacy, keeping in mind how they are intended for use without a prescription from a medical practitioner and are not administered via injection. The authorization only applies to products intended for oral, external, or inhalation administration, additionally, vitamins and minerals can be added as long as their effects are secondary to the active substances (Silano *et al.*, 2011). In the case a product is already included in the Community List of substances for THMP, certain data can be omitted when completing the registration process; likewise, similar products with the same active substances, indications, dosage, posology, and administration routes are considered equivalent (Silano *et al.*, 2011). Lastly, the mutual recognition procedure applies to the registration of THMPs that have been authorized and released by a Member State based on the Community Monographs. The European Medicines Agency (EMA) assists in the facilitation of national registrations for these products.

In order to register for a THMP, applicants must provide evidence of traditional use, including bibliographic or expert references for the proposed indication (HPRA, 2018). While EU herbal monographs can be used as reference material, additional traditional use data is required. Various sources such as medical handbooks, expert reports, and product-related documents can be used as to provide evidence, plus EU herbal monographs can support the registration but aren't legally binding, whereas EU list entries are legally binding and allow applicants to refer to them instead of demonstrating traditional use[41] (HPRA, 2018). However, quality assurance is still necessary. THMP registrations are typically valid for five years starting from the date of the first issue, with the option of renewal as a way to maintain the registration valid (HPRA, 2018). After the renewal, the registration continues to be valid without a specific time limit, unless the competent national authorities determine that further renewals are required based on safety considerations. Noteworthily, manufacturers of THMPs must have a Manufacturer's Authorization, and the same applies to importers of THMPs from outside the European Economic Area (HPRA, 2018). Finally, application dossier should be submitted through the Common European Submission Platform, and national fees for registrations are the responsibility of each EU Member State's competent authority (HPRA, 2018).

A perfect example of a flower with traditional use to relieve symptoms associated with the common cold, like *E. purpurea*, is that of mullein flower[42]. The flower's monograph clearly states how the pharmaceutical form of the product is as an herbal tea, either as an herbal substance or comminuted herbal substance for oral use only. Whilst the recommended posology for adolescents, adults, and the elderly is as follows: a single dose of 1.5-2.0 grams of the herbal substance or

[41] However, the product must be in the form and for the indications specified in the list entry (HPRA, 2018).

[42] Botanical name: Verbascum thapsus L., V. densiflorum Bertol. (V. thapsiforme Schrad), and V. phlomoides L., flos.

comminuted herbal substance should be infused in 150 milliliters of boiling water, to be taken three to four times daily, meaning the daily dose ranges from 4.5 to 8.0 grams. Now, according to the Committee on Herbal Medical Products of the EMA (2010a), herbal teas "*consist exclusively of one or more herbal substance(s) intended for oral aqueous preparations by means of decoction, infusion or maceration*", the preparation is ensured right before utilization, and typically supplied either in bulk or sachet (tea bags) form.

In essence, *Echinacea purpurea* tea marketed as a traditional herbal medicinal product could be a viable opportunity for business operators in the market taking into consideration the relevant registration/authorization processes within the European Union's legislation. According to the Health Products Regulatory Agency (Ireland) (2018) guidelines and in line with Directive 2004/24/EC, a corresponding product should have the same active ingredient, indication(s) of use, equivalent strength and dose, and the same or a similar route of administration. However, unlike the final monograph by the HMPC where the proposed indication is applicable to herbal preparations only in the form of expressed juice and its dry form, an herbal tea would mean variations inside the monograph's factors. Starting with the qualitative and quantitative composition as an herbal tea involves the use of the dried aerial parts and/or roots of the purple coneflower, meaning the herbal substance alone is applicable, whilst an herbal preparation could allow for a comminuted herbal substance in a product using other ingredients alongside *E. purpurea*. The other two differentiating factors inside the monograph are the pharmaceutical form and the posology; with the first having to state "*Herbal substance or comminuted herbal substance as herbal tea for oral use*" instead of "*Herbal preparations in solid or liquid dosage forms for oral use*", and the latter having to specify the single and daily dosage for adolescents, adults and the elderly, of the herbal substance or the comminuted herbal substance in grams, as well as the indications of preparation of the tea itself, meaning how much boiling water most be added. Every other factor inside the herbal monograph would most likely comply with a new registration for an herbal tea made from *Echinacea purpurea*.

3.5 A novel food: *Echinacea* tea as a traditional food from a Third Country

As the European Union witnesses a growing trend of "new" and previously unknown food arising from scientific and technological advancement as well as from the expanding global trade and market globalization, its legislation came under scrutiny due to the restrictive rules and trading barriers set upon food business operators in developing countries specifically trying to market their "traditional foods coming from Third Countries" (Scaffardi, 2022). These foods are products that are derived from primary production, as defined in point 17 of Article 3 of the Regulation (EC) no 178/2002 and have a history of safe food use in said Third Countries. For these products, a specific

notification and authorization procedure is necessary, provided that certain information is supplied (European Parliament and Council, 2015, in Pisanello and Caruso, 2018).

According to the Regulation (EU) 2015/2283, within the definition of traditional foods from a Third Country are included foods made from plants or their parts, with the exception of when the food has a history of safe food use within the European Union and has been obtained through one of the following methods: (i) traditional propagating practices that were used for food production within the European Union before May 15, 1997; (ii) non-traditional propagating practices that were not used for food production within the European Union before May 15, 1997, however, these practices must not result in significant changes in the composition or structure of the food, affecting its nutritional value, metabolism, or levels of undesirable substances (Art. 3, par. 2(a)(iv)).

Silano *et al.* (2011) clarify that Directive 2002/46/EC additionally regulates traditional plant food supplements (TPFS) and novel plant food supplements (PSF). With TPFS having been present to a significant degree inside the EU market before May 15th, 1997, and novel PSF, as the name states it, were not present on the EU market at a significant degree before May 15th, 1997, meaning they are subject to Regulation (EU) 2015/2283, the Novel Food Regulation. At the European level, the regulation on novel food encompasses various types of foods, including botanicals from two different sources: (1) foods derived from microorganisms, fungi, algae, or (2) foods derived from plants or their parts (Colombo *et al*., 2020). Additionally, novel food also includes products created using new technologies. Like most products, before novel food products can be marketed within the EU, appropriate documentation must be provided to demonstrate their safety. Regulation (EU) 2015/2283 introduced a new authorization process for "traditional foods deriving from Third Countries". This category includes foods that have a proven history of safe consumption in a third country for at least 25 years, and, in comparison to the novel food procedure, the authorization for these traditional foods requires less documentation for approval (Colombo *et al*., 2020).

The first Novel Food regulation, introduced in 1997, adopted a "precautionary" approach, characterized by a rigorous assessment of potential risks and a lengthy authorization process which included a thorough evaluation of risks before granting an approval. Scaffardi (2022) describes traditional foods as both new and part of the food heritage of populations outside the EU, becoming the subject of intense and complex political and regulatory debates at international and EU levels. In response, the European Commission proposed a simplified notification procedure (Scaffardi, 2022), with a focus on providing compositional and evidence of use data.

The new notification process under Regulation (EU) 2015/2283 for traditional foods introduces provisions aimed at expediting the authorization phases; this faster process was deemed better suited for these foods coming from Third Countries. At present, the responsibility for risk

assessment evaluation is shifted from the centralized procedure managed by the European Commission to the independent evaluation provided by the ESFA (Scaffardi, 2022). Therefore, to qualify as a Novel Food under this simplified notification procedure, traditional foods must meet specific criteria; they should have a history of safe food use in a Third Country and must have been consumed continuously as a customary part of the diet of a significant number of people for at least 25 years (Regulation (EU) 2015/2283, art. 3, par. 2(b)) (Scaffardi, 2022). Unlike other "new" foods, the dossier required from FBOs for traditional foods only includes documented data demonstrating this safe use rather than scientific evidence proving the absence of safety risks. This streamlined process significantly reduced the costs, complexity, and documentation required compared to the previous 1997 Regulation (Scaffardi, 2022).

The notification procedure itself has also undergone a reduction in processing time, with the Commission evaluating the submitted notification within one month to ensure its validity and completeness (Scaffardi, 2022). Afterward, the Commission forwards the notification to Member States and EFSA, who have four months to present any safety objections (Regulation (EU) 2015/2283, art. 15, par. 2). In the case no objections are raised, the Commission authorizes the novel food for inclusion in the Union List (Regulation (EU) 2015/2283, art. 15, par. 4). However, if objections are raised, the product cannot be authorized though the notification process, and the applicant must submit a standard application which would include specific scientific data to address the objection (Regulation (EU) 2015/2283, art. 16) (Scaffardi, 2022). According to Article 17, within six months, EFSA conducts a comprehensive risk assessment, evaluating the safety of the traditional food for human health and the reliability of the historical data on safe use. This differentiated risk assessment procedure for traditional foods from Third Countries is explicitly recognized in the 2015 Regulation, emphasizing the importance of considering the "*history of safe food use*" (Scaffardi, 2022).

All in all, the updated 2015 Regulation affirmed the significance of a pre-authorization procedure while also allowing for a faster and simplified notification path. This approach ensures a more proportionate burden of proof, considering the reduced level of risk associated with these foods already consumed over time (Scaffardi, 2022). Simultaneously, it guarantees proper food safety control by addressing scientific doubts or objections that may arise.

The Novel Food Regulation (art. 26 & 28) offers applicants protection over the data they provide surrounding their product. In this context, data protection refers to the right of the first applicant to ensure that newly presented data or scientific evidence supporting an applicant cannot be used for the benefit of subsequent applications within five years of the authorization date, without the consent of the first applicant. However, this protection does not prevent other applicants from seeking

the inclusion of a novel food in the Union list based on their own scientific data or by referencing the protected data with the agreement of the first applicant (Pisanello and Caruso, 2018).

Pisanello and Caruso (2018) argue how the need to safeguard the high expenses associated with research and development investments, as well as the economic significance of data and information, requires the implementation of some form of protection. From this perspective, ensuring confidentiality and data protection emerge as crucial factors addressing the market entry of novel foods in the EU. Above all, transparency is a fundamental principle in EU law and is similarly applicable to Food Law. Therefore, it is essential to ensure the broadest possible access to information provided during an authorization process, unless specific and justified exceptions exist as per EU legislation (Pisanello and Caruso, 2018). However, extensive disclosure of sensitive information can potentially harm competitive position of businesses, hence why it is essential to strike a balance between transparency and confidentiality (Pisanello and Caruso, 2018).

In general, EU law guarantees the confidential treatment of reserved information, except when overriding public interests require disclosure, within the food sector, such overriding interests would primarily revolve around risks to public health (Pisanello and Caruso, 2018). The EFSA assesses the confidentiality of information by considering whether its disclosure would likely result in financial loss, facilitate improper gain for individuals or companies, breach commitments to maintain the confidentiality of third-party information, violate statutory restrictions on information disclosure, or significantly disrupt the activities of the EFSA (EFSA, 2005, in Pisanello and Caruso, 2018). Under the Novel Food Regulation, applicants have the option to request confidential treatment for specific information they submit (Pisanello and Caruso, 2018). In doing so, applicants must specify the portions of the information they wish to keep confidential and provide all necessary details to support their confidentiality request. It is also recommended to provide a non-confidential summary of the production process, typically ranging from half a page to one page, along with a documented justification (Pisanello and Caruso, 2018). However, certain elements are excluded from confidentiality protection, including summaries of submitted studies, the results of studies conducted to demonstrate food safety, the analysis method(s) used, and any prohibition or restrictions imposed on the food by a third country (Pisanello and Caruso, 2018). It is important to note that, according to the Commission, any request for the protection of proprietary data must be justified, and all relevant data should be kept separate from the rest of the application. Additionally, the protection cannot be extended or renewed.

As previously underlined, within the EU's Novel food catalogue, *Echinacea purpurea* (L.) Moench has an "FS" status, meaning how based on the information available to Member States' competent authorities, *E. purpurea* was exclusively used as or in food supplements prior to 15 May

1997. The catalogue explicitly delineates that any additional uses of it in food would require approval in accordance with The Novel Food Regulation, Regulation (EU) 2015/2283[43]. However, the concept of Echinacea tea is not novel, and such product can actually be found throughout the European market sold as a food supplement.

*Echinacea purpurea'*s history of food use in the form of tea starts from the tribes within the North American territory, from the Cheyennes to the Yuchi, the first who used the tea made by boiling the coneflower's roots to relieve conditions like rheumatism, arthritis, mumps, and measles; and when mixed with blazing star[44], the tea was believed to relieve smallpox symptoms. As for the Yuchi tribe, when prepared as tea, *E. purpurea* was thought to cure advanced cases of venereal disease within seven days only. Professor Kelly Kindscher (2016), plant ecologist and ethnobotanist of the University of Kansas, known for his extensive research on the Echinacea species native to North America, establishes that overall Echinacea is considered relatively safe due to its long history of use by the indigenous groups in North America, its extensive use as a phytomedicine in Europe, its incorporation into food, tea, and dietary supplements, and the recent scientific evidence on the flower. Kindscher (2016) highlights how reports do suggest that Echinacea is relatively nontoxic when taken at recommended doses, and although a few individuals may experience rare allergic reactions, particularly with intravenous use, these occurrences are minimal compared to the vast number of doses taken. Notwithstanding varying clinical results and uncertainties about the purple coneflower's efficacy, the lack of adverse effects indicates that the use of Echinacea by the general public is "*probably harmless and should not be discouraged*" (Giles *et al*., 2000, in Kindscher, 2016). In this regard, Craft and Kindscher write how:

> "[…] *the idea of taking a whole plant, such as Echinacea, as a tea, with varying degrees of myriad compounds swirling around your cup, and somehow quantifying the positive effects, such as subsiding physical symptoms and reduced duration of the flu, is novel but not really part of the current dominant medical paradigm*" (2016, p. 177).

Based on the aforementioned information, it can be inferred that *Echinacea purpurea* holds promising potential as a novel food option for interested food business operators. The numerous health benefits associated with its consumption, including immune-boosting properties and potential anti-inflammatory effects, make it an attractive ingredient in the modern food industry. However, despite having a relevant history of consumption in the form of tea, the opportunity to sell *Echinacea*

[43] This regulation replaced Regulation (EC) 258/1997, coming into effect in 2018.

[44] Scientific name *Liatris*, a plant from the Asteraceae family, also native to North America.

purpurea in this form as a novel food under the category "traditional food from a Third Country" would require the applicant to demonstrate the adequate history of safe food use in a Third Country, most likely to be the United States, for at least 25 years. By providing the necessary documentation and meeting the criteria set by the Regulation, food business operators can potentially market *E. purpurea* tea as a novel food, offering consumers an innovative and health-enhancing hot beverage option.

3.6 Selling *E. purpurea* tea as a food supplement: a legislative loophole?

Over the last decade or so, the sales for food supplements in Europe have experienced dynamic growth, leading to increased competition in the industry. According to Kowalska *et al.* (2019), this heightened competition has motivated potential wrongdoers to engage in deceptive practices for their financial gain. The authors make mention of the so-called "fraud diamond" model, proposed by Wolfe & Hermanson in 2004, which identifies four factors influencing the likelihood of deviance in the food supplement sector: motivation, pressure, capability, and opportunity.

Based on Czepielewska *et al.*'s investigation (2018), studies on food supplement have shown how only 30% of these products comply with food laws, and how unlike medicines, manufacturers of food supplements are not legally obligated to provide evidence of the safety or effectiveness of their products. An analysis of EU data revealed that reported incidents of non-compliance related to food supplements are relatively frequent compared to other food products (Kowalska *et al.*, 2019). Both the EU Food Fraud Network and the Administrative Assistance and Cooperation System and the IH Report[45] indicate similar trends, with most irregularities associated with mislabeling, particularly in terms of composition and nutrition/health claims. Zhang and Xue (2016, in Kowalska *et al.*, 2019) suggest fraudulent activities are more likely to occur in places where regulatory loopholes exist. In the case of food supplements, they are legally recognized as foods in the EU during the marketing process, which means they do not undergo the same rigorous testing, registration, and checks as medicine or synthetic drugs. Rocha *et al.* (2016) point out how consequently "*in the EU several phytoformulations are being sold under the guise of PFS allowing them to circumvent the requirements and official registration procedure needed if they were considered as being traditional medicinal products*".

However, the FBOs should be aware of how the regulations vary between Member States: while goods can move freely within the EU, each Member Sate can have different requirements for food supplements being sold in their own market (Hoebink, 2023). Most EU countries require a notification be made before marketing these products. For example, on one hand, since 2018,

[45] Polish Trade Inspection (IH) Report.

businesses selling food supplements in Italy must register on a platform set up by the Health Ministry and complete the mandatory fields (LegaleGo, 2019); whilst on the other hand, the Netherlands does not ask FBO to notify their products before selling them (Hoebink, 2023). But generally, food supplements do not undergo specific regulatory pre-approval requirements before they are brought to the market (Czepielewska *et al*., 2018).

The differences in how plant food supplements are regulated within the EU have caught the attention of food safety policymakers. The European Commission has been taking steps to evaluate and improve the regulatory approach to health claims, including investigating the safety, quality, and distribution of botanical food supplements in the EU (European Commission, 2016, in Low *et al*., 2017). To aid risk assessors and food manufacturers, EFSA has released a toolkit consisting of a safety assessment guidance for botanicals and botanical preparations, case studies of selected botanicals, and a compendium of botanical containing substances of concern.

In the argument of whether a UK food business operator could sell tea containing *Echinacea purpurea* in the EU as a food and not a food supplement, brings about an interesting legal conundrum. If the provider can provide evidence that *E. purpurea* tea was indeed sold in the UK before May 15, 1997 –when the UK was still a Member of the EU –it could potentially argue that the product was consumed within the EU before that date. This could serve as a basis for claiming how the product should not be classified as a "novel food" under current EU regulations. However, the second point to consider is the UK's current status as a "third country" in relation to the EU following Brexit. This complicates the matter, as EU regulations may not automatically recognize historical sales in a country that has since left the Union. The third point involves the EU's provisions for traditional foods from third countries. The Novel Food Regulations allows for a notification process rather than a full authorization for such foods, therefore, if the UK food business operator can demonstrate that this E. purpurea tea has a history of safe food use and has been consumed for the past 25 years in the UK, this could offer an alternative route for gaining authorization to sell the product in the EU. Lastly, it's important to note that individual Member States have their own regulations and interpretations of the EU law. These local laws could either facilitate or complicate the FBO's efforts to place the product on the market without prior authorization. Hence why understanding the specific regulation of the target markets within the EU is crucial for the FBOs.

In summary, while there may be historical basis for arguing that *Echinacea purpurea* tea should not require prior authorization for sale in the European Union, the legal and regulatory landscape is complex considering Brexit. The UK's status as a third country, the possibility of using the traditional food notification process, and the regulations of individual EU Member States all add layers of complexity which would likely require specialized legal advice.

3.7 Dietary supplement regulations in the EU and the United States: definitions and health claims

The regulations of food supplements in the EU and the United States follow different approaches with some common underlying goals. In the United States, dietary supplements, including botanical food supplements, fall under the regulation of the Dietary Supplement Health and Education Act (DSHEA) of 1994[46]. The Act provided a clear definition of "dietary supplement" as "*a product […] intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (a) a vitamin; (b) a mineral; (c) a herb or other botanical; (d) an amino acid; (e) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or, (f) a concentrate, metabolite, constituent, extract, or combination of any ingredient describe in clause (a), (b), (c), (d), or (e)* (Dietary Supplement Health and Education Act, 1994)". These ingredients can be presented in various forms, such as pills, tablets, capsules, gummies, soft gels, liquids, and powders. Differently to the EU, supplements may also be in the same form as conventional foods, likes teas and bars, but only if they are not presented as conventional foods or a complete meal replacement (Dietary Supplement Health and Education Act, 1994, Sec. 1. (a)) (Food and Drug Administration, 2022). Noteworthily, there are no specific laws or regulation limiting the serving size or the amount of a dietary ingredient in a supplement, meaning the decision on these aspects is left to the discretion of the manufacturer and does not require FDA approval (Food and Drug Administration, 2022).

The DSHEA prohibits the marketing of adulterated (Dietary Supplement Health and Education Act, 1994, Sec. 4) or misbranded (Dietary Supplement Health and Education Act, 1994, Sec.7) dietary supplements and places the responsibility for product safety and compliance with labeling requirements on manufacturers and distributors (Low *et al*., 2017). The U.S. Food and Drug Administration, known as FDA, also monitors the marketplace for unsafe or misleading supplements and takes enforcement actions when necessary. Low *et al*. (2017) indicate how although the FDA is responsible for acting against adulterated dietary supplements in the market, pre-approval from the FDA is not required before marketing these products. Nevertheless, manufacturers must follow current good manufacturing practices (GMPs) to ensure the quality, strength, purity, and composition of their dietary supplements (Food and Drug Administration, 2022). As for "new dietary ingredients (NDIs)" or ingredients not marketed in the US before 1994, they must be notified to the organization with the FDA information on their identity and safety before being marketed (Low *et al*., 2017).

[46] S. 784 — 103rd Congress: Dietary Supplement Health and Education Act of 1994.

If a manufacturer makes specific claims about the effects of a dietary supplement on the human body, they must have substantiation that the claim is truthful and not misleading (Food and Drug Administration, 2022). The FD&C Act[47] and FDA regulations define three categories of claims that can be used on dietary supplement labels: health claims, structure/function claims, and nutrient content claims (Food and Drug Administration, 2022). Health claims relate to the relationship between a dietary ingredient or food substance and a reduced risk of a disease or health condition. Structure/function claims refer to the effects of the supplement on the structure or function of the human body. Lastly, nutrient content claims describe the levels of nutrients or dietary ingredients in the supplement. If a product sold as a supplement is explicitly or implicitly represented as a treatment, prevention, or cure for a specific disease or class of disease, it is considered a drug and therefore, subject to drug regulations (Food and Drug Administration, 2022).

Regarding health claims for food components and nutraceuticals, the main objective of European legislation is to ensure proper justification and scientific substantiation of these claims (Byrne, 2003, in Gulati & Ottaway, 2016). A forthcoming regulation proposal from the European Parliament and the European Council is expected to allow the use of "health claims" and "reduction of disease risk claims" for foods that fall outside the scope of medicinal law. Health claims can only be approved for use on labelling, presentation, and advertising of foods in the EU market after undergoing a scientific evaluation of the highest standard. The proposed legislation suggests that the European food Safety Authority should be responsible for conducting these assessments.

In comparison to the regulations governing food supplements in the European Union, the United States adopts a broader approach, allowing for a wider range of substances to be marketed and sold as dietary supplements. Additionally, supplements are also permitted to be presented in various forms, including teas and other conventional food forms. This flexibility in the presentation of dietary supplements in the US opens more possibilities for manufacturers to meet consumer demands and preferences. This means that in the US, products like *Echinacea purpurea* tea can be legally labeled and categorized as dietary supplements, whilst also taking advantage of the herb's well-known health benefits, such as its immune-stimulating properties, to add health claims to the product. The US regulations allow manufacturers to make claims about the effects of dietary supplements on the human body, provided they have substantiation that these are truthful and not misleading. This leniency in health claims offers FBOs the opportunity to promote the potential benefits of their products, subject to compliance with labeling requirements and safety standards enforced by the FDA.

[47] Federal Food, Drug, and Cosmetic Act.

CONCLUSION

Beyond *Echinacea purpurea*'s beauty lies a long history of use far away from European grounds. Well before the development of synthetic drugs and chemical-based treatments, Native Americans in the Midwest and the Great Plains of the United States had the tradition to use plants as medicine which was grounded on the tribes' religious beliefs in a holistic healing system by which *Echinacea* was viewed as a spiritual remedy. However, due to the lack of interest shown by European settlers and the subsequent loss of information, much of the traditional knowledge surrounding *Echinacea* was lost. Despite this, Europe, and most specifically, Germany, has played a pivotal role in the research and study of medicinal plants even with the emergence of synthetic drugs in Westerns societies. The popularity of *Echinacea* in modern phytomedicine is attributed to a German patent medicine salesman named H.C.F. Mayer, who learned about its value from native Americans and developed a patented herbal medicine based on *E. angustifolia*. Since then, *Echinacea* has been recognized as a versatile remedy for various ailments, with immunological support being the most recognized and popularized nowadays, helping alleviate cold and flu symptoms by reducing the severity and duration of these.

E. purpurea has stood out among other botanicals and herbal supplements for its known therapeutic properties, ranging from virucidal to antimicrobial properties, which have been recognized throughout history by physicians and medical botanists. With the rise of phytomedicine and the increasing demand for herbal medicines in Europe, *Echinacea*-based products began to be used as immunostimulants to treat minor pathologies and maintain general health. These immune-stimulating effects come from the plant's various bioactive compounds, with the most important ones being alkylamides, caffeic acid derivatives, glycoproteins, and polysaccharides.

Notably, *E. purpurea's* ethanol tinctures, rich in alkylamides, have demonstrated anti-inflammatory activity by inhibiting the 5-lipoxygenase (5-LOX) enzyme of the arachidonic acid pathway, making them potentially useful for developing antifungal drugs. As for the plant's caffeic acid derivatives (CADs), namely caftaric and cichoric acids, these exhibit a variety of therapeutic effects. Their antioxidative, anti-inflammatory, anti-cancer, and antiviral activities contribute significantly to the flower's known health benefits. The manifestation of these properties is evident in products like Echinaforce®, an *E. purpurea* extract, which has been observed to interfere with viral activity, alleviate cold symptoms, and potentially protect the respiratory epithelium. Lastly, the immune-stimulating polysaccharides and glycoproteins, primarily found in the aerial parts of the plant, augment *Echinacea*'s resistance to viral infections and stimulate immune cell activation. These

compounds are readily extracted in hot water, making *E. purpurea* teas and other water-extracted products a valuable source of these beneficial elements. Collectively, the unique combination of these compounds not only underpins *Echinacea purpurea*'s therapeutic potential but also strengthens its position in the market. Its array of bioactive compounds and the associated health benefits make it an important player in the realm of botanical and pharmacological research.

The EU has taken a comprehensive approach to regulate food supplements under Directive 2002/46/EC, where the definition of these products is lied out as concentrated sources of nutrients or other substances with a nutritional or physiological effect, available in various dose forms. While nutrients like vitamins and minerals are explicitly covered in the Directive, the lack of clarity surrounding "other substances" has led to variations in regulations across Member States. This has created challenges in ensuring a harmonized approach to regulating food supplements containing substances like enzymes, amino acids, essential fatty acids, pre- and probiotics, and of course, botanicals. The regulatory frameworks for botanicals used in supplements can be seen as interconnected with medicinal products regulations, further building complexities and potential overlaps for the use of these substances.

The availability and categorization of commercial botanical products in the likes of *Echinacea purpurea* as THMPs or food supplements are heavily influenced by how competent national authorities and manufacturing businesses interpret and apply the existing EU regulations. Fundamentally, this determination is not solely based on the inherent properties of the botanical products and their constituents. As a result of their nature, decisions regarding the safety, efficacy, and effectiveness of plant food supplements remain primarily reliant on individual national legislation and the practices of manufactures too. Likewise, the supervision of the market by Member States' competent authorities is guided by their own specific criteria, which have not been standardized at the EU level. France provides an exemplary case study of a Member State effectively integrating EU provisions into its national framework. The French regulatory approach offers a constructive model for understanding the necessary steps to market *Echinacea* products while complying with safety and usage requirements.

This lack of harmonization has led to divergent and sometimes contradictory conclusions on the use of plant food supplements between different Member States. These variations, evident in both negative and positive national lists, or the lack thereof, have contributed to fragmentation in the European market of food supplements made from botanicals and botanical parts. It is worth noting that national competent authorities tend to assess plant food supplements on their long-term experiences and the common practices prevalent in their respective countries. This approach further accentuates the difference in regulatory approaches and underscores the need for greater

harmonization and collaboration among Member States to create a more cohesive and unified regulatory framework for botanical products across the European Union.

To aid industries in determining the appropriate classification of their medicinal products, some EU authorities have provided non-legislative guidance. Similarly highlighting the intersection between food supplements and medicines, the European Commission's decision to establish a list of herbal substances for traditional herbal medicinal products continues to offer some clarity around the use of such substances. The conclusions provided by the European Medicines Agency's Committee on Herbal Medicinal Products through the published monographs on the different botanicals, including *E. purpurea*, should be taken into consideration by Member States when evaluating applications for licensing herbal medicines. The HMPC has acknowledged *E. purpurea* as a well-established and traditional European herbal medicinal product for its beneficial properties in treating common colds and superficial wounds. The strict recommendations for its usage in the prevention and short-term treatment of common colds, and for treating small superficial wounds, underlines the rigorous standards set forth by the HMPC in ensuring public safety.

Overall, the handling of *E. purpurea* within the EU legislative framework offers a revealing lens into the procedures, challenges, and opportunities that business operators encounter when marketing such products. It is indicative of the EU's broader approach to managing the complexity of integrating traditional medicines and food supplements into modern healthcare and nutrition, thereby setting a high standard for global food and medicinal product legislation. The rigorous regulatory pathways established by EU bodies provide both a protective shield for consumers and a guiding beacon for producers navigating the intricate and evolving landscape of *E. purpurea* and similar botanical products in the market.

Since botanicals showcase remarkable versability due to their wide array of applications, aside from food supplements and medicinal products, when used in foodstuffs like herbal teas, it is crucial to adhere to all relevant aspects of food legislation, ensuring their composition, manufacturing process, and quality control meet the required standards. With the likes of associations like Tea and Herbal Infusion Europe creating the Compendium for Herbal Infusions, which features *Echinacea purpurea*, and serving as a foundation for facilitating the free trade of these products within the EU market and beyond, they provide the necessary groundwork to promote the exchange and commerce of herbal infusions across different regions and market. The list of botanicals created by THIE serves as a valuable resource, and if a plant material has a tradition of safe use in one Member State or region, it indicates its potential use as a foodstuff throughout the European market.

In conclusion, the sale of *Echinacea purpurea* tea in the EU involves navigating through various regulatory aspects related to its classification as a food supplement, a traditional herbal

medicinal product, or a novel food. While *Echinacea purpurea* has a documented history of use in Europe alone and potential health benefits, including immune-boosting properties, the specific avenue for selling it lawfully depends on the intended use and the product's history of safe consumption.

For business operators looking to market *E. purpurea* tea as a Traditional Herbal Medicinal Product, they must meet the criteria set by the European Medicines Agency (EMA) provided through all the information compiled in the HMPC's monographs. However, it is up to each Member State to approve or not of such monographs, meaning this factor such also be considered by businesses seeking to sell a THMP. The process involves providing evidence of at least 30 years of traditional use in treating a specific health condition, with a minimum of 15 years of use within Europe. The registration procedure involves compiling non-clinical and clinical data, along with evidence of plausible efficacy based on longstanding use and traditional experience within the community. Alternatively, if the goal is to sell *E. purpurea* tea as a novel food, the applicant must demonstrate a history of safe food use for at least 25 years in a Third Country, likely to be the United States. This process requires a specific notification and authorization procedure, which, if successful, could offer a reduced cost and processing time to applicants compared to the traditional herbal medicine license.

Ultimately, the viability of marketing *Echinacea purpurea* tea in the European Union depends on complying with the appropriate registration or authorization processes under the relevant legislation. The potential benefits and unique versatility of botanicals, such as *Echinacea purpurea*, present an attractive opportunity for the food industry, but a thorough understanding of the regulatory landscape is essential for successful market entry.

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