

Review

# An Overview of Herbal Nutraceuticals, Their Extraction, Formulation, Therapeutic Effects and Potential Toxicity

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**Abstract:** Herbal nutraceuticals are foods derived from plants and/or their derivatives, such as oils, roots, seeds, berries, or flowers, that support wellness and combat acute and chronic ailments induced by unhealthful dietary habits. The current review enlists various traditional as well as unexplored herbs including angelica, burnet, caraway, laurel, parsley, yarrow, and zedoary, which are rich sources of bioactive components, such as aloesin, angelicin, trans-anethole, and cholesterol-7-en-3 $\beta$ -ol. The review further compares some of the extraction and purification techniques, namely, Soxhlet extraction, ultrasound assisted extraction, microwave assisted extraction, supercritical fluid extraction, accelerated solvent extraction, hydro-distillation extraction, ultra-high-pressure extraction, enzyme assisted extraction, pulsed electric field extraction, bio affinity chromatography, cell membrane chromatography, and ligand fishing. Herbal nutraceuticals can be purchased in varied formulations, such as capsules, pills, powders, liquids, and gels. Some of the formulations currently available on the market are discussed here. Further, the significance of herbal nutraceuticals in prevention and cure of diseases, such as diabetes, obesity, dementia, hypertension, and hypercholesterolemia; and as immunomodulators and antimicrobial agents has been discussed. Noteworthy, the inappropriate use of these herbal nutraceuticals can lead to hepatotoxicity, pulmonary toxicity, cytotoxicity, carcinogenicity, nephrotoxicity, hematotoxicity, and cardiac toxicity. Hence, this review concludes with a discussion of various regulatory aspects undertaken by the government agencies in order to minimize the adverse effects associated with herbal nutraceuticals.

**Keywords:** nutraceuticals; herbs; bioactive-compounds; extraction; purification; identification; formulation; market; therapeutic-effect; adverse-effect; regulations



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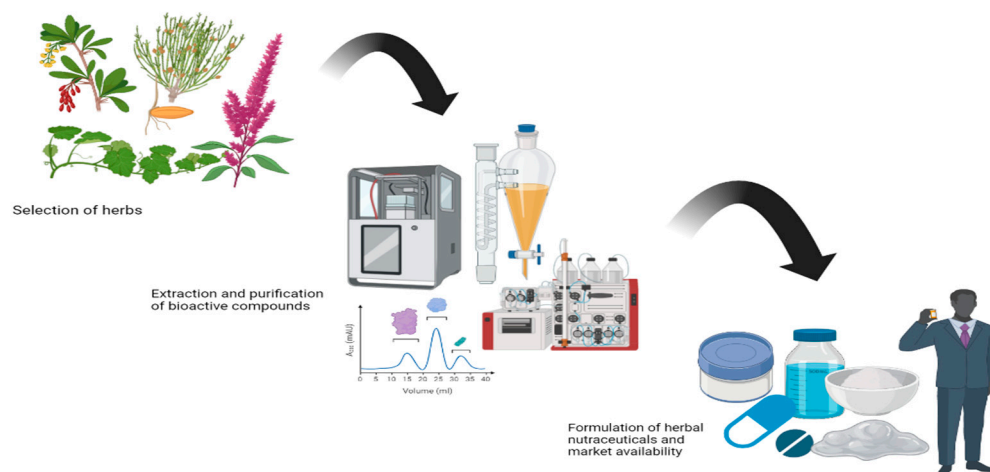
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## 1. Introduction

Nutraceuticals are made from food sources and offer both health benefits and nutrition. Dietary supplements, herbal products, genetically modified foods, and vitamins are some of these products [1]. They are rich in bioactive substances, which offer physiological advantages, and help prevent and treat diseases. Herbal nutraceuticals are foods prepared from plants and/or their oils, roots, seeds, berries, or flowers that support wellness and combat acute and chronic ailments caused by unhealthful eating habits. Many ancient

cultures had a strong belief in the use of herbs for both sustenance and medicine [2]. Societies in India and China have historically employed a variety of plant compounds that are thought to have medicinal properties. Nutraceuticals has developed from its traditional roots to become a highly specialized scientific industry where the effectiveness and safety of the products are supported by data, recent research, and cutting-edge technological advancements (Figure 1) [1].

This review first lists the various plant sources of bioactive nutraceuticals and then proceeds to discuss in detail the different techniques used for their extraction, purification, and characterization. Further, we discuss the recent commercialization of some of these nutraceuticals and highlight their therapeutic actions in various pathophysiological states. Lastly, the negative effects of inappropriate use of some of the nutraceuticals are summarized.



**Figure 1.** Schematic diagram of the common steps involved in the extraction of nutraceutical from source.

### Strategy of Searching Articles

The research articles selected for this study were searched for in online web-databases, viz., Google Scholar, PubMed, and EMBASE. The search keywords items were: {("Herbal nutraceuticals" OR "nutraceuticals" OR "phytochemicals" OR "medicinal plants") AND ("extraction" OR "formulation" OR "characterization" OR "therapeutic potential" OR "negative effects" etc.)}. A few more search keywords, such as ultrasound-assisted extraction, microwave-assisted extraction, supercritical fluid extraction, bio affinity chromatography, etc., were used in combination with the above key words. The search was limited to November 2022. The retrieved articles were evaluated for their relevance, and only then, were included in the study. Further, the citations in the selected articles were also screened and included in the study if found relevant.

## 2. Sources of Bioactive Compounds (Herbs)

### 2.1. Aloe Vera

Aloe vera is scientifically known as *Aloe barbadensis* Miller. Aloe vera, largely cultivated as a houseplant is succulent in nature and can be utilized as a herbal alternative to treat minor skin irritations, such as sunburns and wounds. In addition, it is often used to heal acne, ease the symptoms of dermatitis, soothe mild stomach aches, and even to promote hair growth [3]. Some of the bioactive components in aloe vera are flavonoids, lectins, terpenoids, fatty acids, tannins, anthraquinones, pectins, hemicelluloses, glucomannan, campesterol,  $\beta$ -sitosterol, salicylic acid, and vitamins, such as A, C, E,  $\beta$ -carotene, B1, B2, B3, B6, choline, B12, folic acid. These divergent bioactive components are extensively efficacious for anti-hyperlipidemic, anticancer, anti-diabetic, anti-mutagenic, anti-inflammatory, and antioxidant properties [3,4]. Interestingly, a recent study on the anticancer properties of aloe-emodin, an anthraquinone bioactive compound from aloe vera leaf, reported a notable efficacy of the extract against lymphoblastic leukemia cells

in comparison to the standard drugs in clinical usage [5,6]. Antidiabetic evaluation by Huseini et al. proposes that aloe vera gel can be potentially employed as an anti-hyperglycemic and anti-hypercholesterolemic agent with positive outcomes on blood glucose and lipid levels [7].

## 2.2. Angelica

Angelica, which is scientifically known as *Angelica archangelica*, has been widely used as a spice and a medicine since the 12th century. Fruits, stems, and roots of this herb are well-known for their beneficial effects on human health. The bioactive components in *Angelica* (particularly in the roots) include  $\beta$ -phellandrene, umbelliprenin, phenols, and furocoumarins, such as bergapten, xanthotoxin, and angelicin. The herb is used to treat arthritis, heartburn, flatulence, anorexia, circulation problems, respiratory catarrh, insomnia, nervousness, and plague [3,5].

## 2.3. Anise

With consumption patterns ranging from whole, dried, and crushed forms, anise is well-known as a medicinal herb in traditional, folk, and conventional medicine, and also in the modern pharmaceutical industry. Scientifically known as *Pimpinella anisum* and with a taste pattern comparable to licorice, it is used as an additive to enrich flavor and as an agent to aid digestion. Trans-anethole, coumarins including umbelliferone, umbelliprenine, bergapten; and scopoletin, flavonoids ranging from flavonol, flavone, glycosides, rutin, isoorientin, and isovitexin; and lipids such as fatty acids, beta-amyrin, stigmasterol, and their salts are some of the bioactive components in anise. Several studies on the beneficial effects of anise propose its involvement in the treatment of constipation, indigestion, menopausal symptoms, and migraine [3,6]. In addition, there are reports on the antioxidant, antifungal, anti-inflammatory, antibacterial, anticonvulsant, gastro-protective, anti-diabetic, analgesic, and antiviral potencies of this herb [8–10].

## 2.4. Aralia

Aralia is scientifically known as *Polyscias fruticosa* and is used medicinally in Asia and the Americas. The American spikenard root, *Aralia racemosa*, is indigenous to the eastern United States. Aralia root is frequently used in balsamic-flavored teas and tonics. They are acknowledged to have benefits similar to ginseng root, as aralia is a member of the ginseng family. Additionally, rheumatism and eczema can be treated using a poultice made from American spikenard. The species are known to have several classes of bioactive components, such as petroselinic acid, triterpenoid saponins, sterols, diterpenoids, and acetylenic lipids, and are used to treat hepatitis bruises, carbuncles, and lumps [2,3].

## 2.5. Bay

Bay, which is also called laurel leaf or sweet bay, is native to the Mediterranean region and enjoys a widespread presence in warm climatic regions. Scientifically identified as *Laurus nobilis*. L., bay is commonly used in soups, stews, sauces, pickling brines, and other French, Spanish, Italian, and Creole dishes. Some of the bioactive components in bay include cholesteric-7-en-3 $\beta$ -ol, cholesteric-4-en-3 $\beta$ ,6 $\beta$ -diol, batilol, and ceramide. This medicinal plant can be used to reduce uric acid levels and control blood cholesterol [11]. Reports on anti-inflammatory, antidiarrheal, and anti-diabetic potencies of bay leaf extracts have been proposed by several authors [3,7].

## 2.6. Bayberry

Bayberry is a plant with a high medicinal value owing to the presence of different bioactive components, ranging from anthocyanidins, such as delphinidin–hexoside, cyanidin-3-O-galactoside, cyanidin-3-O-glucoside, pelargonidin-3-O-glucoside, and peonidin-3-O-glucoside, and flavonols including myricetin-3-O-rhamnoside, myricetin deoxyhexoside–gallate, quercetin-3-O-galactoside, quercetin-3-O-glucoside, quercetin-3-O-rhamnoside,

kaempferol-3-O-galactoside, and kaempferol-3-O-glucoside [12]. Bayberry fruit is considered to be a rich source of cyanidin-3-glucoside, accounting for 85% of anthocyanins in the fruit [13]. It is used in the treatment sore throat, vaginal discharge, colitis, wounds, ulcers, headache, colds, nausea, and diarrhea, and can also enhance systemic circulation [3,8].

### 2.7. Bee Balm

Bee balm, scientifically known as *Monarda didyma* L., belongs to the mint family and is occasionally referred to as Oswego tea, horsemint, and bergamot. It has red, white, pink, lilac, or purple flowers, which thrive in full sun and their perennial forms are well recognized for drawing pollinators to gardens. Some of the bioactive components in bee balm are polyphenols (rosmarinic acid, caffeic acid, and protocatechuic acid), flavonoids (quercitrin, rhamnocitrin, luteolin), monoterpenoid aldehyde, monoterpene glycosides, triterpenes (ursolic and oleanolic acids), sesquiterpenes, resin, tannin, and essential oils (citral-geraniol and neral, linalool, eugenol, citronellal, geraniol). The extracts have been discerned to exhibit diaphoretic, antiseptic, emmenagogue, antimicrobial, antispasmodic, and anti-inflammatory properties [1,3].

### 2.8. Burnet

The herb burnet is indigenous to western, central, and southern Europe, as well as northwest Africa and southwest Asia. It is also widely cultivated and dispersed in North America. The herb, scientifically known as *Sanguisorba minor*, has a taste profile similar to cucumber and is used as a salad and a dressing ingredient. The bioactive profile includes components such as phenolic acids (chlorogenic, ellagic, gallic, caffeic, and rosmarinic acid), flavonoids, catechin derivatives (catechin, epigallocatechin gallate), and neolignans. Efficacies in treating ulcerative colitis, dysentery, diarrhea, bladder problems, hemorrhoids, phlebitis, and varicose veins have been reported widely by several authors [3,9].

### 2.9. Calamint

Native to the UK, calamint plants are bushy herbs with thick stems that spread from rhizomes. The foliage has a hairy or fuzzy feel to the leaves. Acknowledged scientifically as *Clinopodium nepeta*, it has a wide range of beneficial active components including dihydrocarveol, monoterpenes, dihydrocarveol acetate, dihydrocarveol, 1,8-cineole, cis-carvyl acetate, and pulegone. These bioactive components elicit noted antioxidant, antimicrobial, anti-ulcer, anti-inflammatory, and insecticidal properties [3,9]. Monoterpene components from this plant species have been reported to harbor significant antifungal potencies, with highest activity against *Trichophyton mentagrophytes* among the evaluated species [14].

### 2.10. Caraway

Caraway, a biennial plant indigenous to western Asia and Europe is scientifically known as *Carum carvi*. The consumable portions include seeds and roots, with licorice-flavored seeds commonly used in breads, soups, sauces, pickles, and sauerkraut formulations. Caraway is a common herbal remedy for rheumatism, eye infections, and toothaches. Bioactive component profile in caraway includes carvacrol, carvone,  $\alpha$ -pinene, limonene,  $\gamma$ -terpinene, linalool, carvenone, and p-cymene. It acts as an expectorant, stimulant, and antispasmodic agent. It can also be used to treat nausea, stomach aches, and constipation [3,10].

### 2.11. Chamomile

Chamomile is considered to be one of the most ancient medicinal herbs identified for their medicinal usage dating back to ancient Greek and Roman cultures. It is scientifically known as *Matricaria recutita*. Some of the bioactive components in chamomile include levomenol and its oxides, apigenin, azulenes, farnesene, spathulenol, and spiroethers. These are widely used to treat many human ailments, such as hay fever, muscle spasms, inflammation, menstrual disorders, wounds, ulcers, insomnia, gastrointestinal disorders, hemorrhoids, and rheumatic pain [3,11].

### 2.12. Dill

This annual herb belongs to the same genus as celery and is often consumed fresh since it loses its flavor very quickly. Dill is scientifically known as *Anethum graveolens* L. The herb is known for its medical potencies with a wide range of bioactive components including sinapic, vanillic acids, and rutin. It has traditionally been used for treating stomach ailments, colic, hiccups, bad breath, flatulence, and hemorrhoids [3,12].

### 2.13. Zedoary

Zedoary, commonly referred to as white turmeric, is a rhizomatous herb of Indonesian and Indian native. Scientifically known as *Curcuma zedoaria*, this herbaceous plant marks its role in traditional folk medicine being used for the treatment of menstrual disorders, vomiting, dyspepsia, fatigue, anxiety, stress, inflammation, and even cancer [3,13]. Furanodienone, zederone, demethoxycurcumin, germacrone, bisdemethoxycurcumin, 1,7-diphenyl-(4E,6E)-4,6-heptadien-3-ol, curcumin, and ar-turmerone are some of the major bioactive components in zedoary. This traditional medicinal plant was evidenced to have strong anti-proliferation and anti-metastatic activities against esophageal cancer TE-8 cells and was also found to be effectually hostile to tumor formation [15].

### 2.14. Yarrow

Yarrow is scientifically known as *Achillea millefolium*. It is regarded as a therapeutic herb because of the variety of its blossom hues. Some of the bioactive components in yarrow are azulene, caryophyllene, thujone, eucalyptol,  $\alpha$ - and  $\beta$ -pinene, and borneol, as well as lactones, tannins, and alkaloids. It is used to treat hay fever, the common cold, menstruation issues, diarrhea, dysentery, loss of appetite, gastric discomfort, and to induce sweating [2,3].

### 2.15. Wormwood

Wormwood is a native plant belonging to temperate parts of Europe and northern Africa. Upstretched as a decorative plant, it is scientifically known as *Artemisia absinthium* L., and is used as a component of the alcoholic beverage absinthe. The bioactive component profile of wormwood includes dimeric guaianolides–absinthins, and monoterpene hydrocarbons–chamazulene. It is used to treat upset stomachs, loss of appetite, gall bladder and liver dysfunction, and intestinal spasms. It can be used to treat fever, worm infections, to increase sexual desire, and simulate sweating [3,14].

### 2.16. Valerian

*Valeriana officinalis* is the scientific name of valerian, which has traditionally been used as perfume. The medical potencies of the herb are well-known and are utilized widely to treat headaches, depression, insomnia, anxiety, premenstrual syndrome (PMS), and abnormalities associated with menopause [3,15]. Some of the bioactive components in valerian are non-glycosidic iridoid esters, alkaloids, valepotriates, and flavonoids.

### 2.17. Turmeric

Turmeric, which is also called Indian saffron, has medicinal usage dating back almost 4000 years in history. Scientifically known as *Curcuma longa*, turmeric is a rhizomatous, herbaceous, and perennial plant. It has a wide range of bioactive components, including curcumin, curcumin II (demethoxycurcumin, 1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxy-phenyl)-1,6-hepta-diene-3,5-dione), and curcumin III (bisdemethoxycurcumin, 1,7-bis(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione). It has been widely used as a traditional medicine for multiple purposes, such as relieving gas, dispelling worms, regulating menstruation, improving digestion, and regulating and relieving arthritis [3,16]. Modern medicine has also implicated many of its bioactive principles as potent antioxidants, and anti-inflammatory, anti-mutagenic, antimicrobial, and anticancer agents.



### 2.18. Tulsi (Holy Basil)

Tulsi, also known as holy basil, is regarded as “the queen of herbs” in Indian culture because of its numerous therapeutic benefits. It has been utilized in Ayurvedic treatment for countless years to reduce stress, promote natural cleansing, and enhance general health. Some of the major bioactive components in tulsi are ursolic acid, eugenol, rosmarinic acid, linalool, carvacrol,  $\beta$  caryophyllene, and oleanolic acid. It exhibits antimicrobial, anti-diabetic, adaptogenic, hepatoprotective, anti-carcinogenic, anti-inflammatory, radio-protective, neuroprotective, immunomodulatory, and cardioprotective actions [4,17].

### 2.19. Thyme

Thyme is a fragrant, perennial, and evergreen herb with a wide range of culinary, therapeutic, and decorative applications. Thyme, scientifically known as *Thymus vulgaris*, has a bioactive component profile including carvacrol, thymol,  $p$ -cimenol, monoterpene hydrocarbons,  $\gamma$ -terpinen,  $\gamma$ -Tocopherol, and  $\alpha$ -tocotrienol. It is used to treat acne, coughs, and blood pressure abnormalities, and may also enhance immunity, boost moods, and act as a pest repellent [3,18].

### 2.20. Saffron

Saffron is the dried stigmas of *Crocus sativus* L., which is cultivated mainly in mild and dry climatic regions. From ancient time, saffron has been consumed as a medicinal entity to fight multiple diseases and promote general health. As a food additive and colorant, it has often been associated with therapeutic properties. The phytochemicals picrocrocin and safranal are responsible for saffron’s flavor and iodoform- or hay-like aroma. Additionally, saffron contains the carotenoid pigment crocin, which gives textiles and dishes a deep golden-yellow tint. Multiple studies have indicated the therapeutic actions of these bioactive components in saffron [3,19].

### 2.21. Sage

Sage, scientifically known as *Salvia officinalis*, is a Mediterranean native that is used as a flavoring agent in various dishes, especially in stuffings for pork and poultry as well as in sausages. Sage can be used fresh or dried. Some of the bioactive components in sage are borneol, camphor, caryophyllene, cineole, elemene, humulene, ledene, pinene, thujone, rosmarinic acid, luteolin-7-glucoside, caffeic acid, 3-caffeoylquinic acid, chlorogenic acid, ellagic acid, epicatechin, epigallocatechin gallate, quercetin, rutin, luteolin-7-glucoside, camphor, and thujone [3,20].

### 2.22. Savory

Savory is an annual herbaceous crop which is native to north Africa and Eurasia, where it is grown in abundance, especially in France and Spain. The extracts and essential oil fractions obtained from the herb are dominated by coumarin, phenolic acids, hydroxybenzoic acids, flavonoids, linoleic acid, oleic acid, phytosterols ( $\beta$ -sitosterol and stigmasterol), and pectic polysaccharides; and accounting for the herb’s antimicrobial, pesticidal, anti-parasitic, antioxidant, anti-inflammatory, hepatoprotective, analgesic, and anticancer properties [3,21]. Recently, Boroja et al. proposed the hepatoprotective role of savory in treating cisplatin-induced liver injury in rats. They reported that the beneficial effects of savory (*Satureja hortensis* L.) extract were similar to silymarin, a known natural hepatoprotective drug [17]. Although the herb exhibits its own medicinal profile, the traditional culinary applications are well known among different populations. The dried leaves are greenish brown in color, aromatic, and have a mildly warm and sharp flavor. Many meals, especially chicken and stuffings, can be flavored with the dried leaves and flowering tops of savory.

### 2.23. Rosemary

The Mediterranean region is home to the fragrant herb rosemary, which is scientifically known as *Salvia rosmarinus*. It is employed as a culinary seasoning, in the creation of personal fragrances, and possibly even for health reasons. Some of the bioactive components in rosemary are caffeic acid, carnosic acid, chlorogenic acid, monomeric acid, oleanolic acid, rosmarinic acid, ursolic acid, alpha-pinene, camphor, carnosol, eucalyptol, rosmadial, rosmanol, rosmaquinones A and B, secohinokio, and derivatives of eugenol and luteolin. It is used to treat muscle pain, boost memory, the circulatory system, immune system, and promote hair growth [3,22].

### 2.24. Parsley

Parsley, scientifically identified as *Petroselinum crispum*, is a common ingredient in food and beverages as a garnishing, condiment, and flavoring constituent. Parsley seed oil is used in the production of soaps, cosmetics, and fragrances. Some of the bioactive components in parsley are furanocoumarins (e.g., xanthoxin, trioxalen, and angelicin), essentials oils (e.g., sesquiterpene hydrocarbons, monoterpene hydrocarbons and alcohols, furanocoumarins, aldehydes, and aromatic compounds), flavonoids (e.g., quercetin, apiol, myristicin, apigenin, luteolin, and their glycosides), carotenoids (e.g., neoxanthin,  $\beta$ -carotene, lutein, and violaxanthin), vitamins (e.g., tocopherols and A, C and B complexes), minerals (e.g., iron, zinc, calcium, and phosphorous), and fatty acids (e.g., linolenic and palmitic acid). It acts as a diuretic and decreases bloating, and regulates blood pressure. It has an abundance of vitamin K which can stimulate bone growth and build bone mineral density [3,23].

### 2.25. Oregano

Oregano is frequently associated with Italian and Spanish cuisine, but it truly has its roots in Northern Europe, where it grows in the wild. The herb is scientifically known as *Origanum vulgare* and is used to treat asthma, cough, diarrhea, stomach ache, sores, muscle aches, and menstrual inflammatory disorders [3,24]. Some of the bioactive components in oregano are carvacrol,  $\beta$ -fenchyl alcohol, thymol, and  $\gamma$ -terpinene, phenolic compounds, flavonoids, flavones, tocopherols, carvacrol, benzoic acid, and rosmarinic acid, and cinnamic acid derivatives.

### 2.26. Nasturtium

Nasturtium is scientifically known as *Tropaeolum majus*. Nasturtiums have a peppery flavor and are frequently grown as ornamental flowering plants but can also be used as herbs. Some of the bioactive components in nasturtium are flavonoids, glucosinolates, anthocyanin, and fatty acids. It is a strong antiseptic and is used to treat wounds and fungal infections. The pungent vapors can be used to treat bronchitis and other infections of the lungs [3,25].

### 2.27. Mint

Mint, scientifically identified as *Mentha piperita* L., is a perennial herb with small, fragrant, serrated leaves that are purple, pink, or white. Mint comes in a variety of shapes and colors, all of which are fragrant. Some of the bioactive components in mint are eriocitrin, rosmarinic acid, luteolin 7-O-rutinoside, hesperidin, caffeic acid, ferulic acid, eugenol, pebrellin, gardenin B, and apigenin [3,26].

### 2.28. Milk Thistle

Milk thistle is scientifically known as *Silybum marianum*. The medicinal herb milk thistle is well known for supporting liver functions and is also used to treat hepatitis, cirrhosis, jaundice, diabetes, and indigestion [3,27]. Some of the bioactive components in milk thistle are apigenin, silybonol, betaine, free fatty acids, silybin, silychristin and silidianin.

### 2.29. Laurel

The flowering plant family Lauraceae includes laurels, which are aromatic evergreen trees or big shrubs with green leaves. Laurel is scientifically known as *Laurus nobilis* and has a Mediterranean origin where it has been used for seasoning in food. Some of the bioactive components in laurel are cinnamtannin B-1, trimeric A-type procyanidin, polyphenolic compounds, alkaloids, norisoprenoids, sugars, polysaccharides, organic acids, and tocopherols. It is used to treat rheumatism, cardiac diseases, cough and viral infections, and diarrhea. In addition, it may enhance gastric secretion and acts as a diaphoretic, antiseptic, and carminative agent [3,28].

### 2.30. Lemon Grass

Scientifically known as *Cymbopogon citratus*, lemon grass belongs to a group of tropical herbs with a lemon-like flavor which grow in grassy clumps. Some of the bioactive components in lemon grass are myrcene, limonene, citral, geraniol, citronellol, geranyl acetate, neral, and nerol. It is used to reduce pain, fever, blood sugar, and cholesterol. It also helps to enhance menstrual flow and can act as an antioxidant [4,29].

### 2.31. Hyssop

Hyssop (*Hyssopus officinalis*) is a drought-resistant herb well known for its culinary as well as herbal potencies with its bioactive components profile including diosmin, isopinocampheol, and pinocampheol. It is often used as a therapeutic against nervous, pulmonary, uterine, digestive, and urinary system dysfunctions [3,30].

### 2.32. Ginkgo

Ginkgo, which is scientifically identified as *Ginkgo biloba*, is one of the ancient tree species. The dried leaves of the tree have been widely employed for therapeutic purposes. Some of the bioactive components in ginkgo are terpenoids, flavonoids (quercetin, kaempferol, and isorhamnetin), biflavonoids, organic acids, polyphenols, ginkgolides, and bilobalide. It is used to treat memory issues and blood disorders [3,31].

### 2.33. Ginger

Ginger is scientifically known as *Zingiber officinale*. Ginger is a perennial rhizome and has annual stems that can be about three feet tall. The roots are commonly used in Indian and Asian cooking as a flavoring agent. Additionally, ginger offers well-known health advantages. It very often serves to treat motion sickness, indigestion, and upset stomach. The major bioactive components in ginger are gingerols, shogaols, and paradols. It may also be used to treat nausea, flu, and to decrease blood insulin levels [4,32].

### 2.34. Garlic

Scientifically known as *Allium sativum*, garlic is one of the most often used herbs in cooking. Medicinal uses for garlic are also widely appreciated. Some of the bioactive components in garlic are diallyl thiosulfonate (allicin), diallyl sulfide, diallyl disulfide, diallyl trisulfide, E/Z-ajoene, S-allyl-cysteine, and S-allyl-cysteine sulfoxide (L-allyl). It is used to decrease the risk of cancers, osteoarthritis, cardiovascular diseases, and is also thought to regulate blood cholesterol and pressure [3,33].

### 2.35. Fennel

Fennel is scientifically known as *Foeniculum vulgare*. This herb, which may reach a height of five feet and resembles dill, is valued for its stems, leaves, and seeds. Some of the bioactive components in fennel are quinic acid, 4-O-caffeoylquinic acid, p-coumaric acid, 4-O-caffeoylquinic acid, rosmarinic acid, and chlorogenic acids. It is also a source of vitamin C, which is vital for immune health, collagen synthesis and tissue repair, cellular protection, blood sugar regulation, bone development, and wound healing [3,34]. Table 1 depicts the major plant sources of bioactive components and their physiological relevance.



**Table 1.** Elucidation on the bioactive components from different herbs and their functions.

Herbs	Scientific Name	Bioactive Compound	Functions	References
Aloe vera	<i>Aloe barbadensis</i> Miller.	Flavonoids, lectins, terpenoids, fatty acids, tannins, anthraquinones, pectins, hemicelluloses, glucomannan, campesterol, $\beta$ -sitosterol, salicylic acid and vitamins, such as A, C, E, $\beta$ -carotene, B1, B2, B3, B6, choline, B12, folic acid	Anti-inflammatory properties, treatment of skin problems, such as wounds burns; antihyperlipidemic, anticancer, antidiabetic and antioxidant properties.	[3,4]
Angelica	<i>Angelica archangelica</i> .	$\beta$ -phellandrene, umbelliprenin, phenols, furocoumarins, such as bergapten, xanthotoxin and angelicin	Treatment of arthritis, heartburn, flatulence, anorexia, circulation problems, respiratory catarrh, insomnia, nervousness and plague.	[3,5]
Anise	<i>Pimpinella anisum</i> .	Trans-anethole, coumarins, flavonoids and lipids	Treatment of constipation, indigestion, menopausal problems and migraine; also protects against insects.	[3,6]
Aralia	<i>Polyscias fruticose</i> .	Petroselinic acid, triterpenoid saponins, sterols, diterpenoids, and acetylenic lipids	Treatment of rheumatoid arthritis, hepatitis bruises, carbuncles, and lumps.	[2,3]
Bay	<i>Laurus nobilis</i> . L.	Cholesteric-7-en-3 $\beta$ -ol, cholesteric-4-en-3 $\beta$ ,6 $\beta$ -diol, batilol and ceramide	Regulation of uric acid levels and blood cholesterol; also elicits anti-inflammatory, antidiarrheal and antidiabetic activities	[3,7]
Bayberry	<i>Myrica pensylvanica</i> .	Anthocyanidins and flavonols	Treatment of sore throat, vaginal discharge, colitis, wounds, ulcers, headache, colds, nausea and diarrhea; also enhances circulation.	[3,8]
Bee balm	<i>Monarda didyma</i> L.	Polyphenols, flavonoids, monoterpene aldehyde, monoterpene glycosides, triterpenes, sesquiterpenes, resin, tannin and essential oils	Elicits diaphoretic, antiseptic, emmenagogue, antimicrobial, antispasmodic, anti-inflammatory actions; may also acts as a carminative, diuretic, expectorant, and sedative.	[1,3]
Burnet	<i>Sanguisorba minor</i> .	Phenolic acids (chlorogenic, ellagic, gallic, caffeic, and rosmarinic acid), flavonoids, catechin derivatives (catechin, epigallocatechin gallate) and neolignans	Treatment of ulcerative colitis, dysentery, diarrhea, bladder problems, hemorrhoids, phlebitis and varicose veins.	[3,9]
Calamint	<i>Clinopodium nepeta</i> .	Dihydrocarveol, dihydrocarveol acetate, dihydrocarveol, 1,8 cineole, cis-carvyl acetate, and pulegone	Shows antioxidant, antimicrobial, anti-ulcer, anti-inflammatory, insecticidal properties.	[3,9]
Caraway	<i>Carum carvi</i> .	Carvacrol, carvone, $\alpha$ -pinene, limonene, $\gamma$ -terpinene, linalool, carvenone, and p-cymene	It acts as an expectorant, stimulant and antispasmodic agent; can be used to treat nausea, stomach aches and constipation.	[3,10]
Chamomile	<i>Matricaria recutita</i> .	Chamomile are levomenol and its oxides, apigenin, azulenes, farnesene, spathuleno, and spiroethers	Treatment of hay fever, muscle spasms, inflammation, menstrual disorders, wounds, ulcers, insomnia, gastrointestinal disorders, hemorrhoids and rheumatic pain.	[3,11]
Dill	<i>Anethum graveolens</i> L.	Sinapic, vanillic acids and rutin	Has been traditionally used for treating stomach ailments, colic pain, hiccups, bad breath, flatulence, and hemorrhoids.	[3,12]
Fennel	<i>Foeniculum vulgare</i> .	Quinic acid, 4-O-caffeoylquinic acid, p-coumaric acid, and 4-O-caffeoylquinic acid, rosmarinic acid and chlorogenic acids	Beneficial actions on immune system, collagen synthesis, tissue repair, cellular protection, blood sugar regulation, bone development, and wound healing.	[3,34]
Garlic	<i>Allium sativum</i> .	Diallyl thiosulfonate (allicin), diallyl sulfide, diallyl disulfide, diallyl trisulfide, E/Z-ajoene, S-allyl-cysteine, and S-allyl-cysteine sulfoxide (L-alliin)	Decreases the risk of cancers, and osteoarthritis; may treat cardiovascular diseases, elevated cholesterol and blood pressure.	[3,33]
Ginger	<i>Zingiber officinale</i> .	Gingerols, shogaols, and paradols	Treatment of indigestion, nausea, flu, regulates blood insulin levels and BMI	[3,32]
Ginkgo	<i>Ginkgo biloba</i> .	Terpenoids, flavonoids, biflavonoids, organic acids, polyphenols, ginkgolides and bilobalide	Enhancement of memory and can treat blood disorders.	[3,31]
Hyssop	<i>Hyssopus officinalis</i> .	Diosmin, isopinocampone and pinocampone	Treatment of toothache, and dysfunctions of the nervous, pulmonary, uterine, digestive and urinary systems.	[3,30]
Lemon grass	<i>Cymbopogon citratus</i> .	Myrcene, limonene, citral, geraniol, citronellol, geranyl acetate, neral, and nerol	Reduces pain, fever, blood sugar and cholesterol; enhances menstrual flow and acts as an antioxidant.	[3,29]

**Table 1.** *Cont.*

Herbs	Scientific Name	Bioactive Compound	Functions	References
Laurel	<i>Laurus nobilis</i> .	Cinnamtannin B-1, trimeric A-type procyanidin, polyphenolic compounds, alkaloids, norisoprenoids, sugars, polysaccharides, organic acids and tocopherols	Treatment of rheumatism, cardiac diseases, cough, viral infections, and diarrhea; enhances gastric secretion and has diaphoretic and antiseptic activity.	[3,35]
Milk thistle	<i>Silybum marianum</i> .	Apigenin, silybonol, betaine, free fatty acids, silybin, silychristin and silidianin	Treatment of hepatitis, cirrhosis, jaundice, diabetes, and indigestion.	[3,27]
Mint	<i>Mentha piperita</i> L.	Eriocitrin, rosmarinic acid, luteolin 7-O-rutinoside, hesperidin, caffeic acid, ferulic acid, eugenol, pebrellin, gardenin B and apigenin	Has antiseptic and antibacterial properties and is used to treat digestive problems.	[3,26]
Nasturtium	<i>Tropaeolum majus</i> .	Flavonoids, glucosinolates, anthocyanin, and fatty acids	Strong antiseptic properties and used in treatment of wounds and fungal infections; vapors may treat bronchitis and other lung infections.	[3,25]
Oregano	<i>Origanum vulgare</i> .	carvacrol, $\beta$ -fenchyl alcohol, thymol, and $\gamma$ -terpinene, phenolic compounds, flavonoids, flavanones, tocopherols, carvacrol, benzoic acid, rosmarinic acid, and cinnamic acid derivatives	Treatment of asthma, cough, diarrhea, stomachache, sores, muscle aches and menstrual inflammatory disorders.	[3,24]
Parsley	<i>Petroselinum crispum</i> .	Furanocoumarins, essentials oils, flavonoids, carotenoids, vitamins, minerals (e.g., iron, zinc, calcium and phosphorous) and fatty acids	Acts as a diuretic and decreases bloating; regulates blood pressure; vitamin K stimulates bone growth and increases bone density.	[3,23]
Rosemary	<i>Salvia rosmarinus</i> .	Caffeic acid, carnosic acid, chlorogenic acid, monomeric acid, oleanolic acid, rosmarinic acid, ursolic acid, alpha-pinene, camphor, carnosol, eucalyptol, rosmadial, rosmanol, rosmaquinones A and B, secohinokio, and derivatives of eugenol and luteolin	Treatment of muscle pain; boosts memory, circulatory system and immune system; and promotes hair growth.	[3,22]
Savory	<i>Satureja hortensis</i> L.	Coumarin, phenolic acids, hydroxybenzoic acids, flavonoids, linoleic acid, oleic acid, phytosterols, and pectic polysaccharides	Treatment of cramps, diarrhea, nausea, indigestion and intestinal gas; reduces cough, sore throat and sex drive.	[3,21]
Sage	<i>Salvia officinalis</i> .	Borneol, camphor, caryophyllene, cineole, elemene, humulene, ledene, pinene, and thujone, rosmarinic acid and luteolin-7-glucoside, caffeic acid and 3-Caffeoylquinic acid, chlorogenic acid, ellagic acid, epicatechin, epigallocatechin gallate, quercetin, rosmarinic acid, rutin, and luteolin-7-glucoside, borneol, cineole, camphor, and thujone, Rosmarinic acid and ellagic acid, rutin, chlorogenic acid, and quercetin	Treatment of ulcers, seizures, gout, rheumatism, inflammation, tremor, dizziness, paralysis, diarrhea and hyperglycemia.	[3,20]
Saffron	<i>Crocus sativus</i> L.	Crocin, crocetin, carotene, safranal and picrocrocin	Treatment of libido; boosts mood and memory.	[3,19]
Thyme	<i>Thymus vulgaris</i> .	Carvacrol, thymol, $p$ -cimeno monoterpene hydrocarbons, $\gamma$ -terpinen, linoleic, oleic, stearic, and palmitic, $\gamma$ -Tocopherol and $\alpha$ -tocotrienol	Reduces acne, blood pressure, and cough; also enhance immunity and act as a pest repellent.	[3,18]
Tulsi	<i>Ocimum tenuiflorum</i> .	Ursolic acid, eugenol, rosmarinic acid, linalool, carvacrol, $\beta$ caryophyllene, oleanolic acid, ursolic acid, rosmarinic acid	Exhibits antimicrobial, antidiabetic, adaptogenic, hepatoprotective, anticarcinogenic, anti-inflammatory, radioprotective, neuroprotective immunomodulator, cardioprotective actions.	[3,17]
Turmeric	<i>Curcuma longa</i> .	Curcumin, curcumin II [demethoxycurcumin, 1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione] and curcumin III [bisdemethoxycurcumin, 1,7-bis(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione]	Elevation of overall energy of the body; dispels worms, regulates menstruation, improves digestion and relieves arthritis.	[3,16]
Valerian	<i>Valeriana officinalis</i> .	Non-glycosidic iridoid esters, valepotriates and flavonoids	Treatment of headaches, depression, insomnia, anxiety, premenstrual syndrome (PMS), and menopause symptoms.	[3,15]

**Table 1.** *Cont.*

Herbs	Scientific Name	Bioactive Compound	Functions	References
Wormwood	<i>Artemisia absinthium</i> L.	Dimeric guaianolides–absinthins, monoterpene hydrocarbons–chamazulene	Treatment of upset stomach, loss of appetite, gall bladder dysfunction, liver diseases and intestinal spasms; can be used to treat fever, worm infections and increase sexual desire.	[3,14]
Yarrow	<i>Achillea millefolium</i> .	Azulene, caryophyllene, thujone, eucalyptol, $\alpha$ - and $\beta$ -pinene and borneol, as well as lactones, tannins and alkaloids	Treatment of hay fever, common cold, menstruation problems, diarrhea, dysentery, loss of appetite, and gastric discomfort; induces sweating.	[2,3]
Zedoary	<i>Curcuma zedoaria</i> .	Curcumin, demethoxycurcumin, bisdemethoxycurcumin, 1,7-diphenyl-(4E,6E)-4,6-heptadien-3-ol, germacrone, furanodienone, zederone, and ar-turmerone	Treatment of indigestion, spasms and loss of appetite, fatigue, anxiety, stress, pain and inflammation.	[3,13]

### 3. Extraction of Bioactive Compounds

The increasing demand for herbal nutraceuticals that offer a number of health advantages, necessitate the importance of efficient extraction methodologies for obtaining optimal amounts of high-quality bioactive compounds in a more efficient and time-efficient manner. Faster extraction methodologies are preferred as they reduce any potential degradation of the active compounds [36]. During traditional times, extracts were prepared by boiling either the specific plant parts, such as leaves, root, flower, or the whole plant in water [37]. This process was both time consuming and inefficient. It should be noted that selection of the appropriate extraction techniques is crucial as it greatly affects the final product obtained [38]. Below, we list the various state-of-the-art extraction methodologies, which are both time-efficient and effective.

#### 3.1. Soxhlet Extraction

Soxhlet extraction, which is otherwise known as continuous hot extraction, is one of the simplest and most inexpensive extraction methodologies. The extraction is done using a Soxhlet apparatus made of glass. The apparatus has a round distillation flask at the bottom, an extraction tube, a siphon tube, and a condenser at the top. The sample is placed in a porous thimble, i.e., commonly made using a thick filter paper, and it is then loaded into the extraction chamber. The extraction solvent in the round bottom flask is evaporated upon direct heating of the distillation flask and condenses on passing through the condenser. The condensate reaches the extraction chamber from where the desired compounds can be extracted based on the polarity. When the chamber is about to be filled, it is then emptied by a siphon when it reaches a particular level and the solvent moves back into the distillation flask, carrying the analyte to the bulk liquid. The following cycle is repeated many times with the same batch of solvents being recirculated. Once the process is complete, the extracts are filtered and the solvent is removed with the help of a rotary evaporator.

The major advantage of this technique is the limited consumption of the solvents as they are recirculated multiple times. However, it may be time-consuming, and since the extraction is done at the boiling point of the solvent, it may not be appropriate for extraction of thermo-labile bioactive compounds [38,39].

#### 3.2. Ultrasound-Assisted Extraction (UAE)

UAE uses high frequency (20 kHz) pulses to generate acoustic waves, which create regions of compression and rarefaction while passing through the solvent and form cavitation bubbles. The sample and its appropriate solvents can be taken in a volumetric flask and are then sonicated in a temperature controlled ultrasonic bath for a definite time. When the surface area of bubbles increases during the rarefaction process, there is increased gas diffusion and hence the bubbles expand. During compression, the sample undergoes rapid condensation and releases energy. These ejected shock waves enable improved mass

transfer within the plant cell, thereby releasing the cell contents, which can then be filtered for the separation of the extract from the plant residues. As with every other technology involved in the extraction, this technique is also influenced by certain factors, such as power, intensity, frequency, temperature, period of operation, solvent characteristics, and the characteristics of source material [40]. Discouraged specifics reveal that acoustic cavitation and sonoporation, which are pivotal in the extraction process, are aligned towards the uniformity of source samples. Uniformity of the cellular matrix leads to the uniformity in the pore formation due to cavitation and thereby helps in the effectual release of bioactive components from the matrix [41,42].

The advantages of this technique are its inexpensiveness, simple procedure, rapid nature, and lower solvent consumption, in addition to improved yield and quality of the extract, thus making it a better option for commercial uses [43]. It was reported that 20% higher yield of polyphenols was obtained from *Salvia officinalis* with much less sample consumption and 3-fold lower processing time using UAE. Nano emulsion of anise extracts formulated using the ultrasound assisted technique was found to be effective against most of the tested pathogens and exhibited a more notable antimicrobial activity than the bulk extract [43,44]. The disadvantage lies in the fact that both yield and kinetics of extraction largely depend on the nature of the plant matrix. Moreover, the active part of the ultrasound waves may be restricted to areas around the ultrasonic emitter only. In addition, optimization of the solvent composition, appropriate agitation, input power, and right time is the major factor that determines the efficiency of the method [45,46].

### 3.3. Microwave-Assisted Extraction (MAE)

MAE is a widely used technique for rapid extraction of compounds from the sample using microwaves with frequencies of around 300 MHz to 300 GHz. Microwaves heat up the solvent mixture of the sample, causing disruption of the cell membranes and thus partitioning the analytes from the sample to the solvent. Liquid solvents, such as water or alcohol, which have the capability to absorb energy from microwaves and elicit differential affinities for the different compounds of interest are used in the process. During the process, heat generated is due to the alignment of the polar compounds in an electric field; rotation of these molecules at a very high speed further leads to cell disruption. The extraction process begins with an increase in temperature and pressure resulting in the release of solute molecules from the active sites of the sample matrix into the solvent. This coactive amalgamation of heat and mass transfer phenomena, combined with volumetric heat dissipation, are the distinctive features of the technique that generates sufficient internal pressure to cause the rupture of cell walls [47,48]. For example, the MAE separation technique has conveniently and effectively been used to isolate the polyphenols including aloe-emodin, aloin A, aloin B, aloeresin D, aloesin, etc. from the aloe vera sample [49,50]. Authors involved in this study also noted the importance of the different parameters, such as extraction time, temperature, solvent volume on the extraction yield, and bioactive component quantity [51].

The major advantages of MAE are the requirements of lower extraction time and solvent consumption, simultaneous operation with multiple (up to 40) samples, reduced equipment size, reduced thermal gradients, and increased extract yield. The comparative effectiveness of MAE over Soxhlet extraction has been evidenced in a recent study focusing on oil yield [52]. Another advantage when compared with the conventional heating process is its energy efficiency. The disadvantages are that it is not appropriate for extraction of non-polar compounds or temperature-sensitive compounds and is incompatible with highly viscous solvents [53,54]. The efficiency of MAE depends upon several parameters including the properties of the solvents and compound (dielectric constants, polarity, solubility, partition coefficient, mass diffusivity, and volumes of the extracting solvent and sample), microwave power, frequency and duration of irradiation, extraction pressure, and the number of cycles [55,56].

### 3.4. Supercritical Fluid Extraction (SFE)

SFE enables the extraction of bioactive compounds in a non-degraded form and with very high specificity using supercritical fluids as solvents. Supercritical fluids have higher temperature and pressure than its critical points making the gaseous and liquid phases indistinguishable. They have similar densities to ordinary fluids, similar to gases, and also enable easy penetration of gases. The density will be changed upon a small change in the temperature or pressure, which can thereby alter the solvation power, allowing convenient separation of extract and solvent. Supercritical CO<sub>2</sub> is a widely used solvent in this process due to its moderate temperature (31.3 °C) and pressure (72.9 atm), low toxicity, non-inflammable nature, high purity, and because it can be separated by depressurization to yield an extract free of solvent, which can also be reused. As in other separation techniques, operating conditions influence the capacity and quality of the extraction process. Debbabi et al. have reported a change in extraction yield of bioactive components from *Calamintha nepeta* subsp. *nepeta* from 0.73 to 1.21 wt% at 90 and 300 bar, respectively [57]. On the other hand, lower pressures of parsley fruit extracts comprised mainly of the phenylpropene, apiole, were reported to have stronger antibacterial effects [58].

Supercritical fluids allow faster mass transfer properties and can readily diffuse through the raw materials giving improved extraction efficiency and yield of the bioactive compounds. SFE is ideal for thermally labile compound extraction. Moreover, SFE is environment friendly and less time consuming. The main disadvantages of SFE, however, are its expensiveness and the complex configuration of the system, which requires properly trained personnel to operate the process [39,45]. One of other major drawbacks of using supercritical CO<sub>2</sub> is its lipophilicity and non-polar nature, which can be resolved by using modifiers or co-solvents, such as methanol. Interestingly, SFE can be used in the extraction of carotenoids from tomatoes and to separate lycopene from it by coupling it with supercritical fluid chromatography [59,60].

### 3.5. Accelerated Solvent Extraction (ASE)

ASE is the process which uses high temperatures of about 50–200 °C and pressures (10–15 MPa) to extract compounds from solid or semisolid matrix. The high temperature favors the increased extraction efficiency of the analyte and the high pressure helps in preventing the solvent vaporization at temperatures above their boiling point and also increases their mass transfer rates, thereby enhancing the kinetics of reaction. The low solvent viscosity enhances the diffusion rates of analytes into the solvent, enabling a much more efficient and faster extraction process. A variety of solvents can be utilized in the process; however strong acids or bases cannot be used.

Advantages of ASE include time-efficiency, less solvent consumption and better analyte recovery. In fact, it is recognized as a green extraction technique due to the lower consumption of organic solvents for extraction. The major limitations are requirement for an expensive lab equipment and unsuitability for thermally labile compounds. Thus, there are comparatively fewer applications of ASE in the field of nutraceuticals. Some of these include catechin extraction from green tea, steroids from the leaves of *Lochroma gesnerioides*, terpenoids from tobacco, etc. [35,39].

### 3.6. Hydro-Distillation Extraction

Hydro distillation is most widely used for essential oil extraction. It may be in the form of water distillation, water-steam distillation, or steam distillation. For example, steam distillation is used in the extraction of essential oils in saffron [61]. Hydro-diffusion, hydrolysis, and heat decomposition are the processes involved in this methodology. This process cannot be employed in the extraction of thermo-labile compounds [62,63]. The process is carried out in an apparatus called the Clevenger apparatus. When heat or direct steam is applied, the sample solvent mixture placed in a closed chamber vaporizes, and the vapor causes bursting of small sacs containing essential oils. Upon condensation, oils are



separated from the water by a density-based separator. The process should be done within a specific duration to ensure complete extraction of oil components.

The advantages of this process include cost effectiveness as it requires only water as a solvent. The major disadvantages are the long extraction time, degradation of the compounds, and alterations in the chemical structures [49,64].

### 3.7. Ultra High-Pressure Extraction (UPE)

UPE is one of the most prominent environment friendly technologies that employs super-high pressure (100 to 1000 MPa) and a mild temperature (20–50 °C), enabling the enhanced extraction of thermolabile bioactive compounds. The ultrahigh pressure leads to increased mass transfer rates and induces a greater penetration of solvents, causing the rupture of cellular walls, membranes, and the organelles and thereby enhances the yield of bioactive principles. The raw materials along with solvents in a polythene bag are placed in a pressure vessel. Subsequently, a high pressure is applied at room temperature using an ultrahigh pressure booster pump for 5 to 15 min. Then, the mixture is concentrated using a rotary evaporator.

The major advantages of UPE lie in its short extraction time, increased extraction yields, decreased consumption of solvents, and enhanced quality of the extract. However, impurities in the extract are the major drawback of this method. It was reported that high pressure extraction method, when compared to other methods, such as heat reflux extraction and ultrasonic extraction, gave the shortest time (ca. 1 min) for 30% polyphenols extraction from green tea leaves in water [65].

### 3.8. Enzyme-Assisted Extraction (EAE)

EAE is a sustainable extraction technique and is highly efficient. Enzymes are biological catalysts with high specificity and selectivity, enabling the extraction of various bioactive compounds by promoting hydrolysis of plant cell walls, thereby significantly increasing the extraction yield. The efficiency of this process depends greatly on several parameters, such as temperature, pH, extraction time, and enzyme concentration. The substrate and its bonding with the components of the cells determine the enzyme type to be used. It was reported that EAE of grape skins can yield high-quality bioactive polyphenols, such as anthocyanins and resveratrol [66]. Similarly, notable enhancement of extraction yield was reported by enzyme-assisted extraction of curcumin from turmeric using a mixture of  $\alpha$ -amylase and amyloglucosidase enzymes [67].

The major advantages of EAE are its high yield with a much higher purity, reduced time of extraction, and diminished solvent requirement. The major limitations are the cost and availability of the enzymes required [68].

### 3.9. Pulse Electric Field Extraction (PEF)

The pulsed electric field (PEF) technology is another non-thermal processing method that induces cell membrane permeabilization by using the transmembrane potential across cell membranes, resulting in increased permeability and conductivity. The PEF technique is used to create pores in the cell membranes, which allows large molecules to be transferred across the cell membrane. An optimized pulsed electric field is applied to the sample for enhanced extraction, resulting in reversible electroporation of the cell membranes and aiding easy mass transfer of compounds through the pores into the surrounding medium.

The major advantages of PEF-assisted extraction are its high extract yield, low energy consumption, and shorter treatment time. In addition, using a square wave with larger pulse width can help in saving the energy requirements for the process. Reports show that PEF technology can give enhanced yield in the extraction of intracellular bioactive compounds, such as polyphenols, anthocyanin, lutein, betanin, betulin, carotenoids, lycopene, etc. from different plant sources. It has also been observed that polyphenols extracted from red grape show the highest yields regarding the field strength [69].

#### 4. Purification and Characterization of Bioactive Compounds

Once the extraction is done, the next step is the purification of the bioactive compounds of interest from the extract. Column chromatography can be employed as a simple technique for purification purposes. Complex protocols, such as high-pressure liquid chromatography (HPLC), can accelerate the process and are more efficient. However, column chromatography and thin-layer chromatography remain the methods of choice for many bioactive compounds because of their simplicity, cost-efficiency, and the ease of availability of stationary phase materials, such as alumina, cellulose, silica, etc. Multiple mobile phases with varied polarity can be utilized in the case of separation of complex component mixtures [64,70].

In many drug development initiatives, the screening of natural products for the discovery of novel physiologically active metabolites has been a crucial step. The same applies for the discovery of nutraceuticals. The following discussion covers a few of the current methods for identification, purification, and phytochemical analysis of physiologically active components.

##### 4.1. Ultrafiltration

Combinatorial libraries have been tested using the ultrafiltration HPLC-MS technique to look for novel therapeutic leads. This technique is largely used to separate active substances for synthetic or combinatorial libraries and to evaluate the thermodynamic and kinetic parameters of their ligand–protein binding abilities. The technique has recently been in widespread use for the detection and identification of active chemicals in plant extracts [71]. Because ultrafiltration requires less energy than thermal separation techniques, it may be a desirable concentration alternative in many applications [72].

##### 4.2. Bioaffinity Chromatography (BAC)

Bioaffinity chromatography (BAC) helps in identifying potential therapeutic molecules based upon their ability to bind to certain biologically relevant ligands. The targets corresponding to the pharmacologically active molecules are adhered as the stationary phase in the chromatographic plates. For the investigation of natural products, three BAC modes—conventional BAC mode, solid phase extraction (SPE) mode, and immobilized enzyme reactors (IMERs) mode—have been frequently used [73]. The difference in analyte retention periods on the chromatographic columns is the foundation of the traditional BAC mode. However, most of the natural product extracts contain lower concentrations of the biologically significant compound. Here, solid phase extraction becomes significant [74]. Immobilized enzyme reactors (IMERs) can be employed when enzymes are being used as the target. They can simultaneously assess the bioactivity of natural product extracts by measuring changes in enzyme activity [75].

##### 4.3. Cell Membrane Chromatography (CMC)

Membrane receptors interact with their ligands in a specific manner inside the body. This specific interaction is the basis for the technique known as cell membrane chromatography (CMC). Therefore, the CMC approach aids in purification of the specific target molecules from a complex sample [21]. CMC rapidly screens complicated samples based on the affinity between a phytomedicine and a membrane receptor. As a result, CMC offers an efficient analytical technique for target identification in complicated samples, drug quality control, drug mechanism research, and new drug discovery [76].

##### 4.4. Ligand Fishing

The protein-coated beads are submerged into the extract using this method, and any substances that have an affinity for the immobilized protein are retained while non-binders are left in the supernatant. This method enables the identification and detection of novel potential therapeutics when combined with chromatographic and spectroscopic methods. This technique is aptly named the ligand fishing screening method [71]. The majority of ligand fishing techniques exhibit great efficiency, specificity, and minimal

sample pretreatment, which makes them particularly well-suited for identifying active ingredients in complicated mixtures of natural materials. The two types of ligand fishing techniques are online and offline. Active substances that have been trapped on the stationary phase by immobilized biomolecules, such as metabolites, enzymes, or receptors must first be rinsed off before being analyzed in the off-line mode. After the bio-extraction process, the incubated sample solution is directly examined by chromatographic methods in on-line mode, and the active components in the mixture can be inferred inferentially by comparing the chromatograms of the original sample [77].

## 5. Herbal Nutraceuticals in Market

Commercialization of herbal and dietary supplements has been on the rise for the last few decades all around the globe, including in India (Table 2). Consumers may be young adults who are into sports, muscle building, and toning of the body that requires the consumption of protein and other supplements. Dietitians also recommend the use of certain nutraceuticals for their therapeutic effect on various diseases, diabetes, kidney disorders, anemia etc. According to the growing market, there is a high demand for fat burners, multivitamins, and branched-chain amino acids (BCAA). The main category of nutraceuticals are organic foods, which are particularly prominent in the increasing population leading sedentary lifestyles [78]. This field is further anticipated to bring new products based on the customer interests. The global nutraceuticals market in 2016 was valued at approximately USD 383 billion and by 2022 it is expected to reach USD 561 billion [79]. The herbal and dietary supplement industry is said to have an estimated growth of USD 50 billion in countries such as USA and Canada. The growth in dietary supplements is estimated to increase 19.5% and that of herbal products to 11.6%. To meet the increasing demands of proper diet and healthy nutrition, foods are set to become more attractive and fortified in order to eradicate malnutrition in the coming future [80]. Thus, the Indian nutraceuticals market was expected to show an increase of 20% by 2020 with sale values up to USD 6.4 billion. While, India constitutes only 2% of the global nutraceutical products based on the per capita spent as per the report of Assocham, functional foods such as beverages including antioxidant supplements may elicit increased demand in the Indian market [78].

**Table 2.** Various formulations of commercially available nutraceuticals and their benefits.

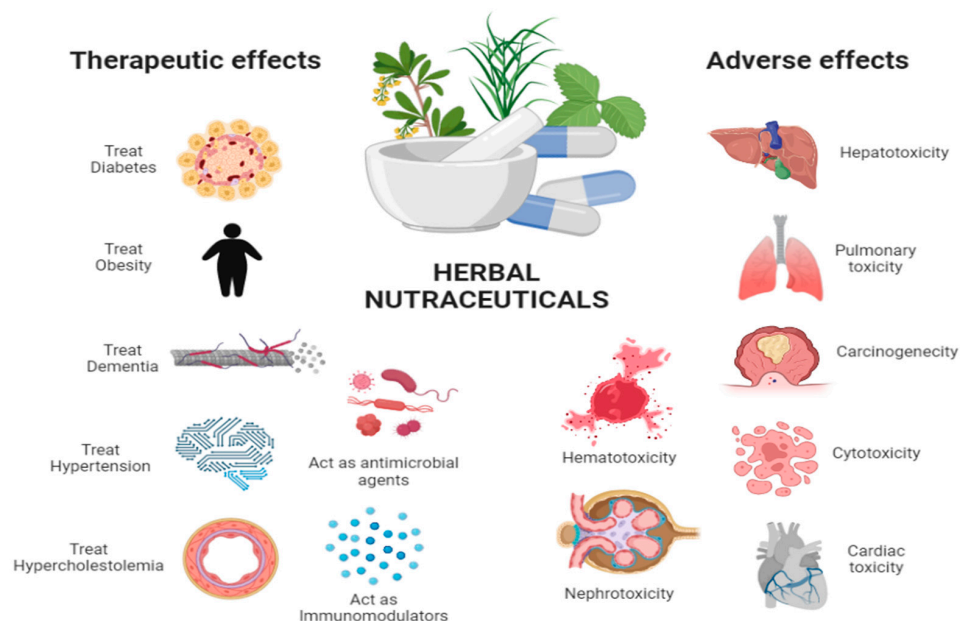
Product Name	Form	Herbal Ingredients Used	Benefits	Manufacturer
Aloe vera 200x	Powder	Aloe vera	Anti-viral, anti-bacterial and anti-inflammatory	Purenso Select
Amla powder	Powder	<i>Emblica officinalis</i>	Antioxidant, enhances cardiac health and decreases levels of bad cholesterol, offers a rise in immunity and boosts energy in a frail body	Bixa Botanical
Ayurvedic hair and vitality booster juice	Syrup	Winter cherry, false daisy, spikenard	Helps men tackle issues, such as decreased energy levels and recurring hair problems	Sesa Care Pvt. Ltd.
Bramhi	Pill	Water hyssop	Increases and improves intelligence, stimulates mental agility and treats weak memory	Himalaya Wellness Company
Nutrilite soft gels	Gel	Green tea extract	Positively affects skin health	Amway
De-stress	Syrup	Water hyssop, spikenard, winter cherry, ginseng, aloe-weed	Relieves from sleep and stress related issues	Naturamore
Dr noni juice	Syrup	Garcinia	Helps in joint pains, maintain a healthy heart, aids in maintaining healthy blood sugar levels, stimulates the release of digestive enzymes	LA Nutraceuticals
Fenugreek tablets	Pill	Fenugreek	Enhances immunity, stimulates lactation and improves wellness	Bhumija Lifesciences
<i>Ginkgo biloba</i> , bilberry, and lutein	Capsule	<i>Ginkgo biloba</i> , bilberry, lutein	Boosts blood flow to the brain, which may be beneficial for depression, headaches, vertigo, tinnitus, and memory loss; also enhances eyesight.	Healthvit
Go365 nutra tablet	Pill	Turmeric and Boswellia	Reduces inflammation and prevents cartilage degradation, reduces chronic joint pain, stiffness, and swelling	Charak Pharma Pvt. Ltd.
Hair skin vitamins	Capsule	Turmeric and primrose oil, hyaluronic acid	Stimulates hair strength and glowing skin	Neuherbs
Herbalance	Gel	Chasteberry, <i>Rhodiola rosea</i> , red raspberry	Aids in maintaining hormonal balance and treats menstrual problems	Oziva
Holistic calcium and curcumin	Pill	Curcuminoids and piperine	Fights cancer, ageing, arthritis and inflammation	Zeroharm Sciences

**Table 2.** *Cont.*

Product Name	Form	Herbal Ingredients Used	Benefits	Manufacturer
Joint-fit 90N	Capsule	Nut grass, winter cherry, holy basil, moonseed	Maintains healthy function of joints and muscles, reduces chronic inflammation	Organic Wellness
Long looks Capsules	Capsule	<i>Vitex negundo</i> , moonplant, <i>Cassia tora</i> , <i>Acacia nilotica</i>	Stimulates optimal physical growth, enhances bone growth	Orgovedic
Numoringo juice	Syrup	<i>Moringa oleifera</i> , <i>Oregano vulgare</i> , <i>Piper nigrum</i>	Regulates blood pressure, joint functions, enhances endurance and aids digestion	Hawaiian Herbal
Organic spinach	Capsule	Spinach	Elicits antioxidant activity and boosts immunity, promotes eye, skin, bone and heart health, aids in weight loss and ameliorates anemia	Xovak Pharma
Organic <i>Tribulus terrestris</i> powder	Powder	<i>Tribulus terrestris</i>	Testosterone and muscle booster	Herbadiet
Plump up Anti wrinkle gel	Gel	Winter cherry, grapeseed and fennel	Protects against environmental and sun-induced skin problems	Just Herbs
Rose and aloe vera facial massage gel	Gel	Aloe vera, <i>Azadirachta indica</i> and basil	Wound healing and anti-inflammatory property	Khadi Natural Healthcare
Sat isabgol	Powder	Psyllium from <i>Plantago ovata</i>	Controls cholesterol levels and promotes digestion and laxation.	Sidhapur Sat-Isabgol Factory
Spirulina green food supplement	Pill	Spirulina	Antioxidant functions, promotes metabolism, increases strength and boosts immunity	Ayur Champ
Steel-libido peak testosterone	Gel	Winter cherry extract	Peak performance enhancer and testosterone booster	Irwin Naturals
Upakarma ayurveda ginger drops	Syrup	Ginger	Boosts immunity and strength	Upakarma Ayurveda
Yakrit plihantak churna	Powder	<i>Phyllanthus niruri</i> , <i>Eclipta alba</i> , <i>Andrographis paniculate</i> , <i>Tephrosia purpurea</i> , <i>Cichorium intybus</i>	Supports healthy liver and spleen, maintains overall health and well being	Planet Ayurveda

## 6. Functional Properties of the Nutraceuticals

Numerous plant bioactive substances have demonstrated functional properties that imply that they might have a significant impact on preventing a variety of chronic diseases. It is well known that fruits, vegetables, and medicinal herbs have numerous biological activities and antioxidant benefits. Due to their ability to prevent the generation of reactive oxygen species, phenolic chemicals in plant materials are directly linked to their antioxidant activity [81]. Indeed, due to their potential for both nutrition and treatment, nutraceuticals are currently receiving a lot of attention. Herbal nutraceuticals aid in promoting and sustaining good health as well as extending life expectancy and improving the quality of life (Figure 2). Numerous disorders, including cancer, neurological diseases, and cardiovascular diseases, can be treated using nutraceuticals, as per research.



**Figure 2.** A summary of beneficial and adverse effects of nutraceuticals.

### 6.1. Diabetes

Diabetes is a metabolic illness which occurs when the body either produces insufficient insulin or cannot use it as effectively as it should. It affects approximately 422 million individuals globally. Furthermore, diabetes is directly responsible for 1.5 million fatalities annually. In advance of World Diabetes Day, the WHO published a report that details the disturbing state of insulin and diabetes care access globally and concluded that the main barriers to widespread access are high prices, scarcity of human insulin supply, insulin market dominated by a few manufacturers, and subpar health systems. The overall conclusion from the research to date suggests that plant-based diets provide a rich source of minerals, vitamins, and phytochemicals, many of which have anti-diabetic properties. Furthermore, taking such meals reduces the negative effects of synthetic chemical medications [82]. Genistein, an essential nutraceutical molecule present in soybean seeds, has been discovered to be an effective drug for managing diabetes. According to in vitro investigations, genistein boosted insulin secretion in a mouse pancreatic beta-cell line, MIN-6 cells; and in cultured islets from mice and rats [83]. In a human study, genistein treatment improved insulin sensitivity scores in postmenopausal women. A daily dose of 54 mg of the compound raised glucose tolerance and improved insulin sensitivity while lowering fasting blood sugar [84]. According to an animal study, grape seed proanthocyanidin extracts can considerably lower blood glucose levels in type 2 diabetic rats [85]. However, proanthocyanidins isolated from the rhizome of *Fagopyrum dibotrys* outperformed grape seed proanthocyanidins in anti-diabetic action [86]. In several nations, diabetics have been reported to be treated using sage (*Salvia officinalis*). *Salvia officinalis* extract is demonstrated to have anti-diabetic properties, which can be attributed to its ability to activate the nuclear receptor peroxisome proliferator-activated receptor (PPAR) [87].

### 6.2. Obesity

The abnormal or excessive accumulation of fat that is associated with obesity is a serious condition affecting people all over the world. Many plants, plant extracts, and chemicals produced from plants are being researched for their potential health benefits against obesity and liver disorders. The most prevalent liver disease in Western nations is non-alcoholic fatty liver disease (NAFLD), which is linked to obesity. According to scientific research, *Lamiaceae* plants may be an affordable source of nutraceuticals and phytochemicals that can be used to treat metabolic-related diseases including obesity and NAFLD [88]. Amla (*Emblica officinalis*) is well-known in India for its medicinal properties. *E. officinalis* consumption reduced liver triacylglycerol and cholesterol levels. It reduces oxidative stress by reversing hyperlipidemia associated with aging. Additionally, studies show that oral delivery of amla results in significant drop in total cholesterol (TC). It was also found to increase the levels of high-density lipoprotein [89]. *Salvia officinalis* L. (sage) leaf methanolic extract has shown significant pancreatic lipase inhibition and a considerable reduction in serum triglyceride levels, resulting in robust beneficial effects on body weight and obesity [90]. An animal study proposed that activating TRPV1 channels with dietary capsaicin may result in browning of white adipose tissue (WAT) to combat obesity [91]. Additionally, dietary capsaicin diminishes the risk for hepatic steatosis and insulin resistance brought on by obesity in mice [92]. In in vitro tests, it was discovered that green tea extract AR25 (Exolise) exerted a direct inhibition of stomach and pancreatic lipases and an activation of thermogenesis, making it a suitable natural product for the treatment of obesity [93].

### 6.3. Immunomodulation

Immunomodulators enhance the body's defense against infectious diseases and injuries. Plant-derived nutraceuticals have been proven to have immunomodulatory properties. Rosmanol, a sage and rosemary extract, has anti-inflammatory effects. It acts by blocking the signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappa B (NF- $\kappa$ B) activation [94]. Numerous studies conducted over the past two decades have revealed that curcumin with a variety of biological targets, exerts its anti-



inflammatory actions by suppressing the expression of inflammatory transcription factors (such as NF- $\kappa$ B), enzymes (such as cyclooxygenases, COX-2 and LOX-5), and cytokines [95]. Anti-inflammatory effects of oregano (*Origanum vulgare*) extracts containing trans-sabinene hydrate, thymol, and carvacrol have also been investigated and found to increase the levels of anti-inflammatory cytokine interleukin IL-10, while decreasing pro-inflammatory cytokine secretion (IL-1b and IL-6) in vitro [96].

#### 6.4. Dementia

With more people being diagnosed with dementia, it is not unexpected that more over-the-counter medications and nutraceuticals are being used to treat such cognitive issues. Eight commercially available terpenoids from *Salvia lavandulaefolia* have had their in vitro anti-acetylcholinesterase (AChE) activities examined. The findings demonstrate that the oil's inhibitory function is the consequence of a complex interplay between its constituent terpenes, which can have both synergistic and antagonistic effects [97]. Sage boosts memory in both young and old people, and a randomized controlled experiment demonstrates its positive cognitive and behavioral effects [98]. Traditional Chinese medicine has employed the moss *Huperzia serrata* to treat and prevent dementia. It has huperzine A, an effective anti-AChE alkaloid with prominent neuroprotective properties [99]. Caffeine from coffee is a neuroprotective that can potentially reverse memory loss, lower brain beta-amyloid levels in vivo, and can stimulate the central nervous system [100]. Lesser periwinkle (*Vinca minor* L.) has been shown to enhance blood flow to the brain, and vinpocetine, a synthetic vincamine alkaloid derivative, has been shown to elicit significant neuroprotective qualities. Vinpocetine has also produced some encouraging clinical trial results with regards to cognitive improvement in dementia patients. Indeed, the major metabolite of vinpocetine, cis-apovincaminic acid (cAVA), has multimodal neuroprotective effects [101].

#### 6.5. Hypertension

The worldwide epidemic of hypertension is one of the most significant causes of serious health concerns. Numerous studies have suggested links between certain dietary components and lowering hypertension. Sour tea (*Hibiscus sabdariffa*) contains essential compounds, such as polyphenols, anthocyanins, flavonoids, alkaloids, L-ascorbic acid, beta-carotene, pectin, and wax, which play a vital part in decreasing blood pressure. Pre-clinical animal studies have demonstrated that consuming *Hibiscus sabdariffa* extract lowers blood pressure in a dose-dependent way [102]. Ginger used as a supplement has a considerable beneficial impact on endothelial function and blood pressure [103]. Adding ginger to the diet in amounts of 2–6 g/day has been suggested to significantly lower blood pressure [104]. Low density lipoprotein (LDL) and cholesterol levels are also reduced. Additionally, ginger provides a lot of potassium, which is crucial for controlling blood pressure [105]. Recent investigations have shown that saffron's antioxidant and radical scavenger actions underlie its cardioprotective qualities [106]. In hypertensive rats, saffron (200 mg/kg/day) supplementation for five weeks can prevent blood pressure increases and induce aortic remodeling [107]. Cinnamon is also useful in treating heart disease, diabetes, hyperlipidemia, and hypertension. It has been shown to lower blood pressure and glucose levels in rodent models [108]. In addition, cinnamon's polyphenols help improve insulin sensitivity, which is implicated in blood pressure regulation [109].

#### 6.6. Antimicrobial Activity

According to experimental data, tannins and other phytochemicals from *Samanea saman* pod may include substantial natural antimicrobials and antifungals that might be used in the production of tannins or energy-rich nutraceutical tea formulations [110]. The antibacterial activity of larch (*Larix decidua*) bark was tested against respiratory-tract pathogens in a study, and the results show that larch bark extract (LBE) had stronger antimicrobial activity than grapefruit seed extract. LBE phytochemicals can therefore be employed as active antibacterials in nutraceutical formulations [111]. Quercetin is

a flavonoid found primarily in vegetables and fruits that has antiviral, anti-atopic, pro-metabolic, and anti-inflammatory properties. Quercetin's ability to interfere with SARS-CoV-2 replication has been demonstrated using computer modeling in a study aimed at the discovery of candidate chemicals displaying potential efficacy against SARS-CoV-2 viral targets [112]. In a broad-spectrum activity evaluation of diverse nutraceutical plant extracts, *Psidium guajava* demonstrated the best antibacterial activity and may be a promising candidate in the quest for effective and efficient antimicrobial agents [113]. In vitro tests of *Thymus vulgaris* essential oil demonstrated very significant bactericidal and antifungal activity, with minimum inhibitory concentrations (MIC) ranging from 75 to 1100 g/mL and 80 and 97 g/mL, respectively. The plant could therefore be regarded as another appropriate natural source for nutraceutical formulations. It can also be used in conjunction with antibiotics as a synergistic agent or as a natural antibacterial and fungicidal [114]. Apigenin, a compound found in parsley, exhibits anti-inflammatory properties by inhibiting inducible nitric oxide synthase (iNOS), lipoxygenases (LOXs), and COX-2, lowering IL-6 production [115].

#### 6.7. Hypercholesterolemia

In a double-blind, placebo-controlled research, total cholesterol concentrations were found to have dropped considerably in the red-yeast-rice-treated group when compared to the placebo-treated group [116]. Berberine, an isoquinoline alkaloid found in many medicinal plants including *Coptis chinensis* may lower plasma lipids by decreasing the production of hepatic cholesterol and triglycerides, potentially by activating AMP-activated protein kinase, which then inactivates  $\beta$ -hydroxy  $\beta$ -methylglutaryl-coenzyme A (HMG-CoA) reductase [117]. Human blood lipid concentrations and soy protein intake were compared in a meta-analysis of 38 subjects in a controlled clinical trial study. The findings showed that consuming soy protein as opposed to animal protein significantly reduced serum levels of triglycerides, total cholesterol, and LDL cholesterol without significantly influencing levels of HDL cholesterol [118]. The effects of the herbal drink derived from the plant tiwai (*Eleutherine americana* Merr.) on individuals with hypercholesterolemia's lipid profiles were examined in a clinical trial. According to the findings, consuming tiwai herbal drink for seven days could lower total cholesterol by 5.33 mg/dL compared to the control [119]. Meta-analysis has also been performed to evaluate the effects of tree nuts on blood lipids. As per the findings, eating tree nuts reduces triglycerides, apolipoprotein B (ApoB), LDL cholesterol, and total cholesterol. Further, nut dose, not the nut type, appears to be the main factor in decreasing cholesterol [120].

### 7. Negative Impact of Herbal Nutraceuticals

Herbal medications and supplements have been used by people as their primary source of healthcare to treat various illnesses. It was found that sales of herbal supplements in the US grew from 8.8 billion in 1994 to 18.8 billion in 2003; and it is expected to increase further [121]. Unfortunately, the notion that herbal dietary products are natural and safe in all doses, and the lack of information regarding the composition of these supplements have led people to adopt detrimental self-medication regimens. This inappropriate use of supplements can lead to several toxicities, such as hepatotoxicity, pulmonary toxicity, cytotoxicity, carcinogenicity, nephrotoxicity, hematotoxicity, and cardiac toxicity (Figure 2) [122].

#### 7.1. Hepatotoxicity

Herbal and dietary supplements (HDS) have been linked to liver damage, which appears to be amongst the most common side effect [123]. Hepatotoxicity is mainly caused due to the presence of compounds, such as pyrrolizidine alkaloids of comfrey, I species, *Heliotropium* species, *Piper methysticum* (kava), and *Valeriana officinalis* (valerian) [122]. It is observable as hepatocellular, cholestasis, or a mix of both patterns, which are similar to the injury caused by drug overuse. The frequency of liver injury is higher in patients using HDS than the conventional medications according to some prospective and retrospective

studies. The need for liver transplantation is more evidently seen in liver injury caused by HDS [124]. There is a broad spectrum of clinical characteristics that result from liver toxicity due to HDS, which includes autoimmune disorders, cirrhosis, hepatic fibrosis, necrosis, and cholestasis. Young and middle-aged patients with HDS-linked hepatotoxicity are more prevalent since they consume certain HDS to burn fat, lose weight, and as body building supplements. HDS-associated hepatotoxicity can vary from mild liver injury to severe acute liver failure. Furthermore, 88% of patients in the US Drug Induced Liver Injury (DILI) network showed mild to moderate severity whereas severe to fatal conditions were elicited by 12% of the respondents. Most patients were female in the age range of 48 to 53 [124].

### 7.2. Pulmonary Toxicity

The injudicious continual use of herbal and dietary supplements has been reported to cause lung cancer. In research conducted on 77,125 patients with HDS regimens, 665 subjects developed lung cancer. The majority of them were males with an average age of 70 years and above. Fish oil, garlic pills, *Ginkgo biloba*, ginseng, grape seed, glucosamine, methylsulfonylmethane, St. John's wort, and saw palmetto were the major herbal additives used by these patients [121]. An 11-membered pyrrolizidine alkaloid identified as monocrotaline (MCT) has been evidenced to cause pulmonary disorders, which include vascular syndrome with pulmonary vasculitis and hypertension in rats. The pathogenesis of MCT-induced pulmonary toxicity is hypothesized based on suggestions that MCT becomes a reactive compound in the liver which is then transported in the blood to reach and cause injury to endothelial cells of the lung [125].

### 7.3. Carcinogenicity

Many herbal products claimed to be safe for users, tend to either directly cause carcinogenicity or disturb the cellular homeostasis. A study was conducted in which 30 herbal compounds posed a potential carcinogenic risk for humans. Most of these compounds are alkylbenzenes or unsaturated pyrrolizidine alkaloids, which includes  $\beta$ -asarone, estragole, methyl eugenol, or safrole, which showcased the need for higher priority of risk management [126]. Another herbal medicine called comfrey contains 14 pyrrolizidine alkaloids, which may cause carcinogenicity in experimental animals. Studies suggest that certain phytochemicals potentially interact with the genetic material of the endothelial cells and induce cancer development [127].

### 7.4. Nephrotoxicity

Nephrotoxicity is one of the side effects related to the usage of HDS, which is mainly attributed to Chinese herbs. A few underlying causes of kidney injury are its high metabolic activity, relatively high blood flow, and glomerular reabsorption by the renal tubules, which allows the accumulation of toxic compound inside the cells. Adulteration of potentially detrimental herbal supplements with contaminants, such as dichromate, cadmium, and phenylbutazone may also contribute to nephrotoxicity. The *Aristolochiaceae* plant family contains plants having aristolochic acid, which is associated with the development of cancers and nephropathy (aristolochic acid nephropathy or AAN). AAN is prominently associated with some Chinese herbs. The mechanisms of AAN have been studied using cellular and animal models. According to these studies, AA interacts with oxidases of NADPH or anti-oxidative enzymes to induce oxidative stress in the kidney. It may also cause mitochondrial damage and induce apoptosis in renal tubule cells due to mitochondrial and endoplasmic reticulum dysfunction, damage to DNA, or due to the mitogen-activated protein kinase (MAPK) pathway activation. Induction of pro-inflammatory signaling is another pathway of AAN [128].

### 7.5. Cardiac Toxicity

HDS that are used to treat cardiovascular diseases may also induce a range of side effects. For instance, in the USA, ephedra was banned in 2004 due to numerous cases

of serious cardiovascular side effects, which included infarction, stroke, and even death. Bitter orange is another stimulant that increases heart beat in healthy individuals up to ten beats per minute. It also increases blood pressure in healthy individuals by 9–10 mm Hg when combined with caffeine. Non-stimulant herbal products, such as licorice, may lead to ventricular arrhythmias. Some herbs, such as foxglove, oleander, and squill, contain cardiac glycosides and may lead to digitoxin-type toxicity [129].

## 8. Safety, Quality and Regulatory Aspects of Herbal Nutraceuticals

The usage of herbal medicine and dietary supplements is on the rise at the global level. In some places, these are used as medication whereas in others, they may be employed as additives to enhance overall well-being [130]. Such herbal remedies are classified as food supplements by the US Food and Drug Administration (FDA) and have different regulations when compared to the laws governing conventional foods and drugs. Unlike the market drugs, herbal and dietary supplements do not undergo the stringent FDA drug approval process. Only supplements that are adulterated or misbranded are prohibited by the FDA from being marketed. Since 2004, around half of the class 1 drugs have been recalled as they were found to be adulterated dietary supplements contaminated with banned ingredients. Studies on safety, efficacy, and scientific evidence of such products are very limited and little incentive is given by the government for conducting varied and randomized controlled trials. Therefore, there is no legal provision that allows the FDA to examine and sanction herbal supplements. Some frequently used supplements that are known to produce mild to severe side effects are echinacea, garlic, ginkgo, and St. John's wort, which can lead to detrimental interactions between herbal products and drugs [131].

Herbal supplements exist either as crude extracts or as commercial products consisting of roots, leaves, seeds, or tea, which are mainly used in under-developed countries. These components are mixed to form concoctions containing harmful contaminants, such as heavy metals, corticosteroids, and other banned ingredients. Moreover, commercial dietary supplements in the form of tablets often vary in their constituents and concentrations from batch to batch and also between different manufacturers. Even though known active compounds are standardized, their combination with other compounds may affect the bioavailability and pharmacological interactions in humans [132].

One of the regulatory bodies for HDS, the Dietary Supplement Health and Education Act (DSHEA), was formed in 1994 and an additional guideline for "Current Good Manufacturing Practices for Dietary Supplements" was fomented in 2007. DSHEA's objective is to build a structure that can balance benefits and risks of HDS, while providing customers with continuous access and affordability. FDA warnings have been imposed on several products which caused liver injury or failure, such as OxyElite Pro, since the advent of these regulations. According to the DSHEA, a dietary supplement is facilitated to supplement or complement but not to substitute or replace diet [124]. Herbal supplements are regulated and monitored in the European Union (EU) under the Traditional Herbal Medicines Products Directive 2004/24/EC. Following this regulation, only if a product has been proven to be used safely for a sufficient amount of time of over 30 years with 15 years of use within the EU, can it be registered through a simple process and may not necessitate any medical prescription. The European Food Safety Authority (EFSA) regulates vitamins and mineral food supplements according to Directive 2002/46/EC while the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) monitors herbal medicinal products. However, many dietary supplements can be bought online without proper legal clearance which makes it more complicated to correctly identify the manufacturers [133].

To reduce the risks and toxicity related issues, patients or consumers need to be educated about the proper usage of HDS. It should be made clear that not all herbs, and all doses, are free from risk and all the consumers including patients should have information regarding the potential risks and benefits associated with any such additives. HDS should be treated as medicinal products so that they may not be consumed care-

lessly and injudiciously. Anything consumed at more than the necessary dose may lead to calamities; therefore, the consumers should never assume that nutraceuticals are an exception. It is advisable to thoroughly consult physicians, especially if the consumers are on allopathic medication. In the unfortunate event of development of any HDS-linked side effects, the consumers should be advised to halt the regimen immediately. Further, the consumers should be educated to purchase nutraceuticals and related products only from trusted and reputed sources. However, in this respect, it should be noted that, in most cases, the prices of the products are not directly correlated with the quality of the products. Lastly, for consumers who are being nursed or are pregnant or nursing, HDS usage is not recommended unless advised by the health care provider(s). In addition, infants and children may not be advised not to use these supplements [134].

## 9. Conclusions

Derived from plant sources, nutraceuticals are known to provide health benefits including the prevention or treatment of disease. The herbal nutraceutical market has been on the rise for the last few decades around the world including in India due to their perceived therapeutic effect and with the increase in the public inclination towards sports, muscle building and body toning. This review provides a thorough insight into the medicinal properties of nutraceuticals derived from various herbs/plants, and the different approaches to extract and purify them. Foremost sources of these compounds including herbs, such as aloe vera, anise, bay, caraway, dill, holy basil, thyme, saffron, sage, etc., which entail major portions of bioactive components aiding their functional potential were discussed. Bioactivity of these operational components is greatly reliant on different extraction techniques for acquiring high quality and yield of these compounds in a time effective manner. Extraction methodologies range from the traditional Soxhlet extraction method to more recently developed techniques, such as supercritical fluid extraction, microwave assisted extraction, etc. Safeguarding the potential components is feasible with the selection of appropriate extraction technique followed by purification of bioactive components of interest. These strategies were discussed in detail. There is an ever-increasing global market for nutraceuticals, which is anticipated to flourish to USD 561 billion and more in the coming years. With Indian markets contributing only 2% of the global market, there is a need for enhanced fabrication to meet the rising demand. Herbal nutraceuticals aid in advocating and enduring quality of life by overseeing the issues related to widespread human diseases, such as cancer, diabetes, obesity, hypertension, etc. With various formulations of herbal nutraceuticals available in the market, it is crucial to have awareness about both their positive and ill effects. In this regard, future work must concentrate on both ascertaining the therapeutic actions of different bioactive compounds from the herbs, as well as on exploring strategies to identify and minimize the adverse effects associated with herbal nutraceuticals.

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