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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 their derivatives, such as oils, roots, seeds, berries, or flowers. They 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 cholesteric-7-en-3β-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 the 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, hepatotoxicity, and cardiac toxicity. Hence, this review concludes with a discussion of various regulatory aspects undertaken by government agencies to minimize the adverse effects of herbal nutraceuticals.

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

INTRODUCTION

Many ancient cultures had a strong belief in the use of herbs for both sustenance and medicine. Societies in India and China have historically employed a variety of plant compounds that are thought to have medicinal properties. Nutraceuticals have developed from their 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).

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.

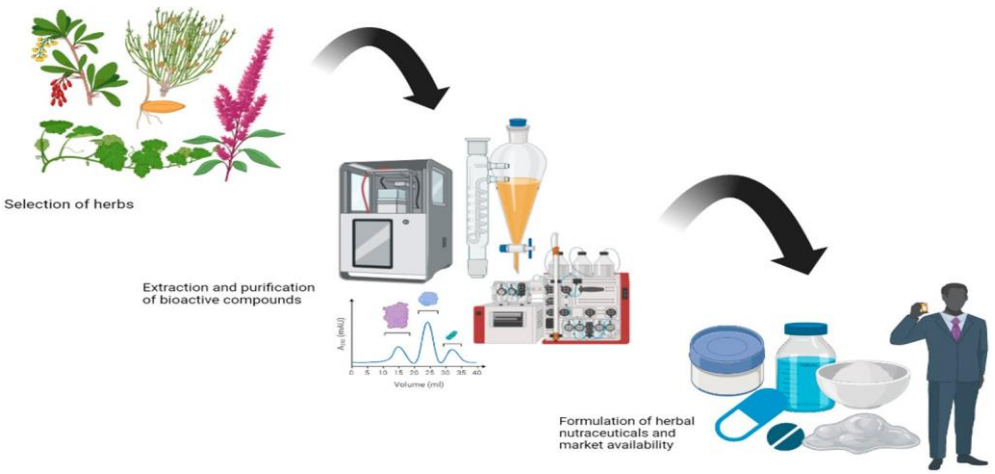

Figure 1. Schematic diagram of the common steps involved in the extraction of nutraceuticals from source

1. Sources of Bioactive Compounds (Herbs)

- ***Aloe Vera:*** Aloe vera is scientifically known as *Aloe barbadensis Miller*. Aloe vera, largely cultivated as a houseplant is succulent 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 promote hair growth. Some of the bioactive components in aloe vera are flavonoids, lectins, terpenoids, fatty acids, tannins, anthraquinones, pectins, hemicelluloses, glucomannan, campesterol, β-sitosterol, salicylic acid, and vitamins, such as A, C, E, β-carotene, B1, B2, B3, B6, choline, B12, folic acid. These divergent bioactive components are ex-extensively efficacious for anti-hyperlipidemic, anticancer, anti-diabetic, anti-mutagenic, anti-inflammatory, and antioxidant properties. 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. 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.

- ***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 β-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.

- ***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 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. In addition, there are reports on the antioxidant, antifungal, anti-inflammatory, antibacterial, anticonvulsant, gastro-protective, anti-diabetic, analgesic, and antiviral potencies of this herb.

- ***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.

- ***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 the bay include cholesteric-7-en-3β-ol, cholesteric-4-en-3β,6β-diol, batilol, and ceramide. This medicinal plant can be used to reduce uric acid levels and control blood cholesterol. Reports on anti-inflammatory, antidiarrheal, and anti-diabetic potencies of bay leaf extracts have been proposed by several authors.

- ***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. Modern medicine has also implicated many of its bioactive principles as potent antioxidants, and anti-inflammatory, anti-mutagenic, antimicrobial, and anticancer agents.

- ***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, β caryophyllene, and oleanolic acid. It exhibits antimicrobial, anti-diabetic, adaptogenic, hepatoprotective, anti-carcinogenic, anti-inflammatory, radio-protective, neuroprotective, immunomodulatory, and cardioprotective actions.

- ***Saffron:*** Saffron is the dried stigmas of *Crocus sativus* L., which is cultivated mainly in mild and dry climatic regions. Since ancient times, 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.

- ***Mint:*** Mint 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.

- ***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. Some of the bioactive components in milk thistle are apigenin, silybonol, betaine, free fatty acids, silybin, silychristin, and silidianin.

2. Extraction of Bioactive Compounds

The increasing demand for herbal nutraceuticals that offer several health advantages, necessitates 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. During traditional times, extracts were prepared by boiling either the specific plant parts, such as leaves, roots, flowers, or the whole plant in water. This process was both time-consuming and inefficient. It should be noted that the selection of the appropriate extraction techniques is crucial as it greatly

affects the final product obtained. Below, we list the various state-of-the-art extraction methodologies, which are both time-efficient and effective.

- ***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 the extraction of thermo-labile bioactive compounds.

- ***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 forming 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 the source material. Discoursed specifics reveal that acoustic cavitation and sonoporation, which are pivotal in the extraction process, are aligned toward the uniformity of source samples. Uniformity of the cellular matrix leads to uniformity in the pore formation due to cavitation and thereby helps in the effectual release of bioactive components from the matrix. 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 use. It was reported that a 20% higher yield of polyphenols was obtained from *Salvia officinalis* with much less sample consumption and 3-fold lower processing time using UAE. Nanoemulsion 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. 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 the right time is the major factor that determines the efficiency of the method.

- ***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 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 can 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 generate sufficient internal pressure to cause the rupture of cell walls. 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. The 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. 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. Another advantage when compared with the conventional heating process is its energy efficiency. The disadvantages are that it is not appropriate for the extraction of non-polar compounds or temperature-sensitive compounds and is incompatible with highly viscous solvents. The efficiency of MAE depends upon several parameters including the properties of the solvents and compound (dielectric constants, polarity, solubility, partition coefficient, mass diffusivity, volumes of the extracting solvent and sample), microwave power, frequency and duration of irradiation, extraction pressure, and the number of cycles.

- ***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 temperatures and pressure than their critical points making the gaseous and liquid phases indistin- guishable. 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_2 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 the extraction yield of bioactive components from *Calamintha nepeta* subsp. *nepeta* from 0.73 to 1.21 wt% at 90 and 300 bar, respectively. On the other hand, lower pressures of parsley fruit extracts comprised mainly of phenylpropene, and apiole, were reported to have stronger antibacterial effects.

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. One of the other major drawbacks of using supercritical CO_2 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.

- ***Accelerated Solvent Extraction (ASE):*** ASE is the process that 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 increases their mass transfer rates, thereby enhancing the kinetics of the 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 an- alyte recovery. It is recognized as a green extraction technique due to the lower consumption of organic solvents for extraction. The major limitations are the requirement for expensive lab equipment and the 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 *Iochroma gesnerioides*, terpenoids from tobacco, etc..

- ***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. Hydro-diffusion, hydrol- ysis, and heat decomposition are the processes involved in this methodology. This process cannot be employed in the extraction of thermo-labile compounds. 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 the 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.

- ***Ultra High-Pressure Extraction (UPE):*** UPE is one of the most prominent environment-friendly technologies that employ 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 organelles and thereby enhancing the yield of bioactive principles. The raw materials along with solvents in a polythene bag are placed in a pressure vessel. Subsequently, 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 the 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.

- ***Enzyme-Assisted Extraction (EAE):*** **E**AE 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 the EAE of grape skins can yield high-quality bioactive polyphenols, such as anthocyanins and resveratrol. Similarly, a notable enhancement of extraction yield was reported by enzyme-assisted extraction of curcumin from turmeric using a mixture of α-amylase and amyloglucosidase enzymes. 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.

- ***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 a 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, betanine, betulin, carotenoids, lycopene, etc. from different plant sources. It has also been observed that polyphenols extracted from red grapes show the highest yields regarding the field strength.

3. 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**.** In many drug development initiatives, the screening of natural products for the discovary of novel physiologically active metabolites has been a crucial step. The same applies to the discovery of nutraceuticals. The following discussion covers a few of the current methods for the

identification, purification, and phytochemical analysis of physiologically active components.

- ***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 recentlybeen in widespread use for the detection and identification of active chemicals in plant extracts. Because ultrafiltration requires less energy than thermal separation techniques,it may be a desirable concentration alternative in many applications.

- ***Bio affinity Chromatography (BAC):*** Bioaffinity chromatography (BAC) helps in identifying potential therapeutic molecules based on their ability to bind to certain biologically relevant ligands. The targets corresponding to the pharmacologically active molecules are adhered to 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. 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 thebiologically significant compound. Here, solid phase extraction becomes significant. Immobilized enzyme reactors (IMERs) can be employed when enzymes are being used asthe target. They can simultaneously assess the bioactivity of natural product extracts by measuring changes in enzyme activity**.**

- ***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 the purification of the specific target molecules from a complex sample. 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.

4. Herbal Nutraceuticals in the Market

Commercialization of herbal and dietary supplements has been on the rise for the last fewdecades all around the globe, including in India. 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 tothe growing market, there is a high demand for fat burners, multivitamins, and branched-chain amino acids (BCAA). The main category of nutraceuticals is organic foods, which are particularly prominent in the increasing population leading to sedentary lifestyles. This field is further anticipated to bring new products based on 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. The herbal and dietary supplement industry is said to have an estimated growth of USD 50 billion in countries such as the USA and Canada.The growth in dietary supplements is estimated to increase by 19.5% and that of herbal products by 11.6%. To meet the increasing demands of proper diet and healthy nutrition, foods are set to become more attractive and fortified to eradicate malnutrition in the future. 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.

5. 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. 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.

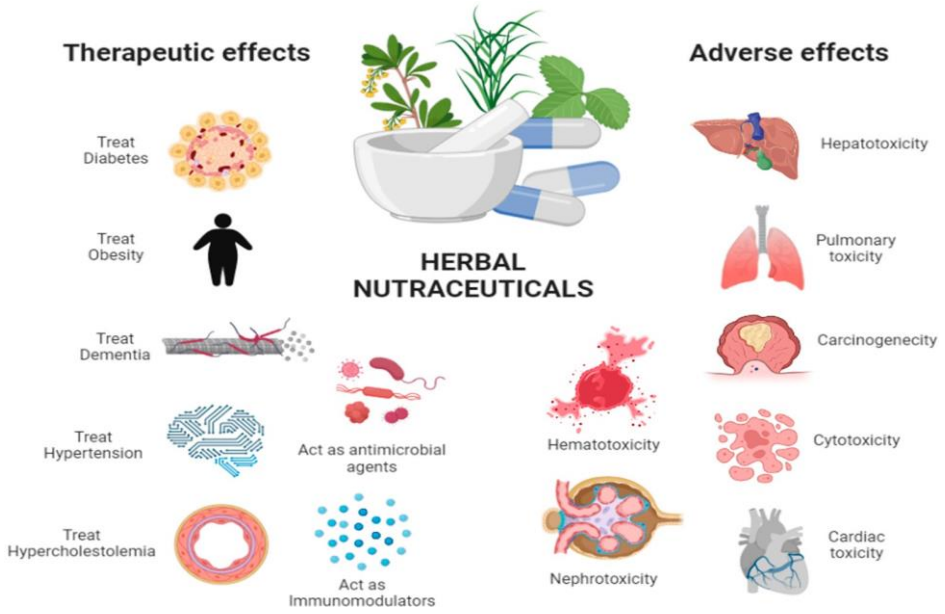

Figure 2. A summary of beneficial and adverse effects of nutraceuticals.

- *Diabetes:* Diabetes is a metabolic illness that 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. 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. 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. According to an animal study, grape seed proanthocyanidin extracts can considerably lower blood glucose levels in type 2 diabetic rats. However, proanthocyanidins isolated from the rhizome of *Fagopyrum debtors* outperformed grape seed proanthocyanidins in anti-diabetic action. 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).

- *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. 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 a significant drop in total cholesterol (TC). It was also found to increase the levels of high-density lipoprotein. *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. An animal study proposed that activating TRPV1 channels with dietary capsaicin may result in the browning of white adipose tissue (WAT) to combat obesity. Additionally, dietary capsaicin diminishes the risk of hepatic steatosis and insulin resistance brought on by obesity in mice. 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.

- *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. Sage boosts memory in both young and old people, and a randomized controlled experiment demonstrates its positive cognitive and behavioral effects. 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. Caffeine from coffee is a neuroprotective that can potentially reverse memory loss, lower brain beta-amyloid levels in vivo, and stimulate the central nervous system. 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 regard to cognitive improvement in dementia patients. Indeed, the major metabolite of vinpocetine, cis-apovincaminic acid (cAVA), has multimodal neuroprotective effects.

- *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. Ginger used as a supplement has a considerable beneficial impact on endothelial function and blood pressure. Adding ginger to the diet in amounts of 2–6 g/day has been suggested to significantly lower blood pressure. Low-density lipoprotein (LDL) and cholesterol levels are also reduced. Additionally, ginger provides a lot of potassium, which is crucial for controlling blood pressure. Recent alities. In hypertensive rats, saffron (200 mg/kg/day) supplementation for five weeks can prevent blood pressure increases and induce aortic remodeling. 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. In addition, cinnamon's polyphenols help improve insulin sensitivity, which is implicated in blood pressure regulation.

- *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. 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. 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. In a broad-spectrum activity evaluation of diverse nutraceutical plant extracts, *Psidium guajava* demonstrated the best antibacterial activity and may be a promising can- didate in the quest for effective and efficient antimicrobial agents. 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. Apigenin, a compound found in parsley, exhibits anti-inflammatory properties by inhibit-ing inducible nitric oxide synthase (iNOS), lipoxygenases (LOXs), and COX-2, lowering IL-6 production.

- *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 comparedto the placebo-treated group. 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 β-hydroxy β-methylglutaryl-coenzyme A (HMG- CoA) reductase. Human blood lipid concentrations and soy protein intake were compared in a meta-analysis of 38 subjects in a controlled clinical trial study. The findingsshowed 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. The effects of the herbal drink derived from the plant was (*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. 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.

6. 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. 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).

- *Hepatotoxicity:* Herbal and dietary supplements (HDS) have been linked to liver damage, which appears to be amongst the most common side effect. 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). It isobservable 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. 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.

- *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, *Gingko biloba*, ginseng, grape seed, glucosamine, methylsulfonylmethane, St. John's wort, and saw palmetto were the major herbal additives used by these patients. 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.

- *Carcinogenicity:* Many herbal products claimed to be safe for users, tend to either directly cause carcinogenicity or disturb 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 β-asarone, estragole, methyl eugenol, or safrole, which showcased the need for higher priority of risk management. 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.

- *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.

- *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 heartbeat in healthy individuals by 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.

7. 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. Such herbal remedies are classified as foodsupplements 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. Herbal supplements exist either as crude extracts or as commercial products consisting of roots, leaves, seeds, or tea, which are mainly used in underdeveloped 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.

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 the benefits and risks of HDS while providing customers with continuous access and affordability. FDA warnings have been imposed on several products that 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. Herbal supplements are regulated and monitored in the European Union (EU) under the Traditional Herbals Medicine Products Directive 2004/24/EC. Following this regulation, only if a product has been proven to be used safely for enough 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 (AFSA) 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.

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 in-formation 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 carelessly 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 the development of any HDS-linked side effects, the consumers should be advised to halt the regimen immediately. Further, 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.

8. Conclusion

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. The 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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