CURRENT MARKET TRENDS AND REGULATORY ASPECTS OF HERBAL ANTIOXIDANTS AND NATURAL DIETARY SUPPLEMENTS: A BOON FOR HEALTH AND TREATMENT OF DISEASES

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ABSTRACT
The present review details about various antioxidants and dietary supplements such as tocopherol, ascorbic acid, rosemary, oregano, marjoram, sage, thyme, basil, ginger, ginko, licorice, schizandra, turmeric, quercetin, cinnamon, clove, nutmeg, black pepper, garlic, tea extracts and grape seed extract. It also summarizes the chemical pathways of their action. These antioxidants offer a huge advantage as compared to allopathic medicines for the treatment of various ailments. They provide an overall wellbeing and fitness with minimal or almost no side effects. The article also gives details of market trends and regulatory issues surrounding these antioxidants and nutraceuticals. The licencing and regulatory requirements related to these products have been highlighted so as to make the readers aware of the extremely high potential of these products for the benefit of mankind and a need to revive our traditionally available knowledge and resources like some of these listed here which are a precious gift of nature to us. Thus, there is a certain need to utilize these resources for the therapeutic and overall wellbeing of mankind.

KEYWORDS: tocopherol, nutraceuticals, minimal, quercetin, ginko, schizandra, tocopherol.

1.1 INTRODUCTION
The ultimate food quality is defined in terms of consumer acceptability, taste, aroma, appearance and characteristics. The increasing demand for convenient foods has led to rapid
growth in the ready-to-eat product category.\textsuperscript{[1]} Many of the food ingredients contain unsaturated fatty acids that are quite susceptible to quality deterioration, especially under oxidative stress. For this reason, efforts to reduce oxidation have increased.

Most often, the best strategy is the addition of antioxidants. Synthetic phenolic antioxidants (butylated hydroxyanisole [BHA], butylated hydroxytoluene [BHT], and propyl gallate) effectively inhibit oxidation; chelating agents, such as ethylene diamine tetra acetic acid (EDTA), can bind metals reducing their contribution to the process. Some vitamins (ascorbic acid [AA] and \( \alpha \)-tocopherol), many herbs and spices (rosemary, thyme, oregano, sage, basil, pepper, clove, cinnamon, and nutmeg), and plant extracts (tea and grapeseed) contain antioxidant components as well.\textsuperscript{[2]} Natural phenolic antioxidants, such as synthetics, can effectively scavenge free radicals, absorb light in the ultraviolet (UV) region (100 to 400 nm), and chelate transition metals, thus stopping progressive autoxidative damage and production of off-odors and off-tastes.\textsuperscript{[3]}

Herbs and spices are traditionally defined as any part of a plant that is used in the diet for their aromatic properties with no or low nutritional value.\textsuperscript{[4]} However, more recently, herbs and spices have been identified as sources of various phytochemicals, many of which possess powerful antioxidant activity.\textsuperscript{[5]} Thus, herbs and spices may have a role in antioxidant defense and redox signaling.\textsuperscript{[6]}

Antioxidant factors found in plants are based upon constituent nutrients with demonstrated radical-scavenging capacities as well as upon non-vitamin or mineral substances. So, in addition to alpha-tocopherol, ascorbate, carotenoids, and zinc, plant-based medicines may contain flavonoids, polyphenols, and flavoproteins. Further, some plants or specific combinations of herbs in formulations may act as antioxidants by exerting superoxide scavenging activity or by increasing superoxide dismutase activity in various tissues.\textsuperscript{[7]} These groups of compounds are substances that may exert cell-protective action by more than one biochemical mechanism. In addition to antioxidant properties per se, cancer-protective factors are found in many plants including some fruits, vegetables, and commonly used spices and herbs. They can be divided into several different groups based on their chemical structure, e.g., polyphenols, thiols, carotenoids and retinoids, carbohydrates, trace metals, terpenes, tocopherols and degradation products of glucosinolates (isothiocyanates, indoles and dithiiothiols) and others. The model used in this presentation is a generalized initiation-promotion-
conversion model, in which initiators are thought to be directly or indirectly genotoxic, promoters are visualized as substances capable of inferring a growth advantage on initiated cells and converters are believed to be genotoxic, e.g. mutagens, clastogens, recombinogens etc. The quenching of singlet oxygen and radicals by carotenoids, the antioxidant effects of many compounds including ascorbic acid and polyphenols, the inhibition of activating enzymes by some flavonols and tannins, the induction of oxidation and of conjugation (protective) enzymes by indoles, isothiocyanates and dithiothiones, the shielding of sensitive structures by some polyphenols and the stimulation of DNA-repair exerted by sulphur-containing compounds. Mechanisms at the biochemical level in antipromotion include the antioxidant effects of carotenoids and the membrane stabilizing effects reported with polyphenols, the inhibition of proteases caused by compounds from soybeans, the stimulation of immune responses seen with carotenoids and ascorbic acid, and the inhibition of ornithine decarboxylase by polyphenols and carotenoids. [7]

A well known hepatic antioxidant, silymarin, from the milk thistle (Silybum marianum), for example, inhibits liver damage by scavenging free radicals among other mechanisms. [8] This powerful antioxidant protects the liver against alcohol and pharmaceutical injury and even poisoning from extremely toxic compounds found in the deathcap mushroom. [8] The contemporary laboratory science confirms and elucidates the liver-protecting temporary attributes of milk thistle, well known to folk medicine for 2000 years. [9]

1.2 CLASSIFICATION OF THE NUTRACEUTICALS THAT ARE AVAILABLE [10]

1.3 Chemical Pathways for Natural Antioxidants
Various different mechanisms may contribute to oxidative processes in complex systems, such as foods. These include reactions that generate reactive oxygen species
that target different structures (lipids, proteins, and carbohydrates), and Fenton reactions, where transition metal ions play a vital role. It should be noted that antioxidant activity of food extracts can be determined using a variety of tests (stable free radical scavengers: galvinoxyl, diphenyl-b-picrylhydrazyl [DPPH]; lipid oxidation: peroxide oxygen, conjugated dienes, Rancimat [measurements of oxygen consumption of a linoleic acid emulsion and oxidation induction period in lard at 100 °C], oxygen radical absorbance capacity [ORAC] values), active oxygen method, iodine value (measure of the change in number of double bonds that bind I), anisidine value (reaction of acetic acid p-anisidine and aldehydes to produce a yellow color that absorbs at 350 nm), measurement of absorbance at 234 nm (conjugated dienes) and 268 nm (conjugated trienes) to assess oxidation in the early stages, and chromatographic methods; however, extraction procedures strongly influence the composition of the extracts and, therefore, also influence the antioxidant activity results.\(^{11,12,13}\) In addition, the effect of the antioxidant compound in a food matrix may be significantly different than the activity of a purified extract.

Food tissues, because they are (or were) living, are under constant oxidative stress from free radicals, reactive oxygen species, and prooxidants generated both exogenously (heat and light) and endogenously (H2O2 and transition metals). For this reason, many of these tissues have developed antioxidant systems to control free radicals, lipid oxidation catalysts, oxidation intermediates, and secondary breakdown products.\(^{14-18}\) These antioxidant compounds include flavonoids, phenolic acids, carotenoids, and tocopherols that can inhibit Fe3+/AA-induced oxidation, scavenge free radicals, and act as reductants.\(^{19,20}\) Spices and herbs, used in foods for their flavor and in medicinal mixtures for their physiological effects, often contain high concentrations of phenolic compounds that have strong H-donating activity.\(^{21,22}\)

2. SOME NATURAL AND HERBAL ANTIOXIDANTS ALONG WITH THEIR USES

2.1 \(\alpha\)-Tocopherol

\(\alpha\)-Tocopherol (vitamin E) is a fat-soluble carotenoid whose antioxidative capacity has been studied extensively. \(\alpha\)-Tocopherol is the major vitamin E compound in plant leaves where it is located in the chloroplast envelope and thylakoid membranes in proximity to phospholipids (Onibi and others 2000).\(^{23}\) It deactivates photosynthesis-derived reactive oxygen species and prevents the propagation of lipid peroxidation by scavenging lipid peroxyl radicals in thylakoid membranes (Munn’ e-Bosch 2005).\(^{24}\)
It is commonly found in several types of products such as cereals, grains, broccoli, Brussels sprouts, in cooking oils like olive oil, sunflower oil, in nuts like almonds and hazelnut,[25,26]

In general, bodily absorption of Vitamin E is thought to be rather inefficient, with the body absorbing only 20-40% of dietary intake. It has also been seen that when taken in conjunction with dietary fats, tocopherols have a higher bioavailability.[27] In general, vitamin E added to water-based food systems using an oil carrier targets the neutral lipid fraction (triacylglycerols) rather than the polar lipid fraction (phospholipids) and is not an effective antioxidant. However, δ-tocopherol added using a polar carrier can be incorporated into the phospholipid fraction and is an effective antioxidant.[28] In a lard model system, the antioxidative activity of the tocopherols is temperature dependent, [2,9] At 80 °C, the antioxidative activity of δ-tocopherol is about twice that of α-tocopherol; however, it decreases as temperature increases. Antioxidative activity of α-tocopherol decreases above 110 °C, and both lose their activity above 150 °C.

2.2 Ascorbic acid
AA has 4 −OH groups that can donate hydrogen to an oxidizing system. Because the −OH groups (2 pairs of 2) are on adjacent carbon atoms, AA is able to chelate metal ions (Fe++). It also scavenges free radicals and acts as a reducing agent. At high levels (>1000 mg/kg), AA shifts the balance between ferrous (Fe2+) and ferric iron (Fe3+), acts as an oxygen scavenger, and inhibits oxidation. However, at low levels (<100 mg/kg), it can catalyze oxidation (in muscle tissue).[30,31]

Environmental conditions and the presence of other compounds in the system can alter the antioxidative capacity of AA. Allam and Mohamed (2002).[32] reported that, using the induction period for the oxidation of sunflower oil as a measure of antioxidant activity after heating (180 °C), ascorbyl palmitate was less thermally stable than mixed tocopherols, propyl gallate, BHT, or BHA. This maybe a function of the water solubility of AA.[33] Ascorbic acid is one of the most prevalent natural antioxidants in most everyday diets. It is a polar, water soluble antioxidant and is found most commonly in fruit, particularly in citrus fruits such as oranges and lemons.[33] Additionally, it is found in some vegetables, such as tomatoes.[26] It has been observed in laboratory trials that in lower doses (less than 30 mg), absorption of dietary Vitamin C is fairly high (approximately 50%). However, higher the dose, lower is the percentage absorption. Thus, it is commonly recommended that in order to optimize Vitamin C absorption, smaller doses should be
consumed several times throughout the day, instead of consuming one large supplement.\textsuperscript{[27]}

\subsection*{2.3 Rosemary}
Chen and others (2007).\textsuperscript{[34]} reported that, of several herbs (Psidium guajava L., Camellia sinensis [Gamma Amino Butyric Acid tea], T. sinensis Roem., and Rosemarinus officinalis L.), the aqueous extract of rosemary contained the highest concentration of phenolic substances (185 mg/g; Folin–Ciocalteau) and total flavonoids (141 mg/g). This aqueous extract inhibited UVB-induced (100 to 400 nm) oxidation of an erythrocyte ghost system (in vivo model system) at a relatively low concentration (100 \( \mu \)g/mL; Chen and others 2007). At 100 mcg/mL, rosemary extract was able to scavenge 39\% of the DPPH radicals (0.2 \( \mu \)m); at 500 mcg/mL, it scavenged 55\%. Rosemary extract (100 mcg/mL) inhibited liposome (egg lecithin with Fe3+/AA/H2O2) oxidation by 98\%. The most active antioxidant constituents of rosemary (R. officinalis) are phenolic diterpenes (carnosic, carnosol, rosmanol, rosmadial, 12-methoxycarnosic acid, epi-, and iso-rosmanol) and phenolic acids (rosmarinic and caffeic).\textsuperscript{[18,35-39]}

Hra and others (2000).\textsuperscript{[40]} reported that, in sunflower oil, rosemary extract exhibited antioxidant activity superior to \( \alpha \)-tocopherol. Adding \( \alpha \)-tocopherol to rosemary can have either an antagonistic effect,\textsuperscript{[40]} or a synergistic effect.\textsuperscript{[41]} This may indicate that there are components in rosemary, other than rosmarinic acid, which make substantial contributions to the antioxidative capacity of the extract.

\subsection*{2.4 Oregano}
Water/ethanol, dichloromethane, and ethanol extracts of oregano (Origanum vulgare L.) also contain high concentrations of phenols, primarily rosmarinic acid, as well as phenolic carboxylic acids and glycosides that are both antioxidative and effective superoxide anion radical scavengers.\textsuperscript{[18, 42-44]} Oregano has a high total phenolic compound concentration (15.8 mg gallic acid equivalent [GAE]/g) and antioxidant activity. Muchuweti and others (2007).\textsuperscript{[22]} determined that oregano had an antioxidant activity of 58.3\% exceeded only by cinnamon (61.8\%).

\subsection*{2.5 Marjoram}
Of a number of herbs and spices (bay leaves, rosemary, sage, marjoram, oregano, cinnamon, parsley, sweet basil, and mint), marjoram (Origanum majorana L.) has the highest proportion of simple phenolic compounds (96\%).\textsuperscript{[22]}
Marjoram essential oil also contains a significant amount of both rosmarinic acid and carnosol. The essential oil can scavenge hydroxyl radicals. It has antiradical activity exceeding that of the phenolic component thymol.\textsuperscript{[45]} Marjoram essential oil is also rich in terpinen-4-ol, cis-sabinene hydrate, p-cymene, and γ-terpinene.\textsuperscript{[46-48]} The bicyclic monoterpenes, cis-sabinene hydrate and cis-sabinene hydrate acetate, appear to be responsible for the flavor of marjoram.\textsuperscript{[49]}

2.6 Sage
The polar extracts of sage (Salvia officinalis) have strong radical scavenging ability and superoxide anion radical-inhibiting ability.\textsuperscript{[50]} The antioxidative activity of sage oil compounds, due primarily to the presence of compounds with vicinal −OH groups, is correlated with the oxygenated diterpene and sesquiterpene concentrations,\textsuperscript{[51]} Sage contains some of the same antioxidant phenolic diterpene compounds found in rosemary such as carnosol, rosmanol, and rosmadial, in addition to some not found in rosemary (methyl carnosate, 9-ethylrosmanol ether, epirosmanol, isorosmanol, and galdosol).\textsuperscript{[18,52-54]}

2.7 Thyme
Thymus vulgaris, T. mastichina, T. caespititius, and T. camphorate all have antioxidative activities comparable to those of α-tocopherol and BHT.\textsuperscript{[55]} Thyme essential oil exhibits very strong free radical-scavenging ability and inhibits lipid oxidation induced by both Fe2+/ascorbate and Fe2+/H2O2.\textsuperscript{[56]} In terms of antioxidative activity, thyme oil > thymol > carvacrol > γ-terpinene > myrcene > linalool > p-cymene > limonene > 1,8-cineole > α-pinene.\textsuperscript{[57]}

2.8 Basil
In basil, a significant correlation exists between the total phenolic content and antioxidant activity.\textsuperscript{[58]}

Purple basil (Ocimum basilicum) extracts have a higher total phenolic acid content and greater antioxidant activity than do green basil extracts. The essential oil contains <18% eugenol as a percentage of the total volatiles; however, it is correlated with antioxidant activity. However, the low contribution of the essential oil to the total antioxidant activity (0.05% to 5.9%) suggests that the antioxidant activity of these plants is not due to the presence of the essential oils as such, but to other phenolic compounds in
green basil and to anthocyanins in purple basil. The aqueous extract of basil is a concentration-dependent superoxide and hydroxyl radical scavenger. The antioxidant activity of this extract has been attributed to its polar phenolic compounds. Rosmarinic acid has been identified as the primary phenolic compound in basil leaves and stems. Linalool, epi-α-cadinol, and α-bergamotene (7.4% to 9.2%) and γ-cadinene have been identified as the most common compounds in basil essential oil. Basil essential oil strongly inhibits lipid peroxidation whether induced by Fe2+ ascorbate or by Fe2+/H2O2. Chicoric acid (caffeic acid derivatized with tartaric acid) has also been identified in substantial quantities.

2.9 Ginger

Scientific name of Ginger is Zingiber officinale. The part that is used is Rhizome. Currently, Ginger has received new attention as an aid to prevent nausea from motion sickness. Ginger tea has long been an American herbal remedy for coughs and asthma, related to allergy or inflammation. The creation of the soft drink ginger ale, is originated from the common folkloric usage of this herb, and remains a popular beverage for the relief of stomach upset. Externally, ginger is a rubefacient, and has been believed to relief headache and toothache. The mechanism by which ginger produces anti-inflammatory activity is that of the typical non-steroidal anti-inflammatory drug. This common spice is a more biologically active prostaglandin inhibitor (via cyclo-oxygenase inhibition) than onion and garlic. By slowing associated biochemical pathways an inflammatory reaction is curtailed. In one study, Danish women between the ages of 25 to 65 years consumed either 70 g raw onion or 5 g raw ginger daily for a period of one week. By reducing blood platelet “clumping,” ginger, onion and garlic may reduce our risk of heart attack or stroke. In a series of experiments with rats, scientists from Japan discovered that extracts of ginger inhibited gastric lesions by up to 97%. In a series of experiments with rats, scientists from Japan discovered that extracts of ginger inhibited gastric lesions by up to 97%. The authors concluded that the folkloric usage of ginger in stomachic preparations was effective due to the constituents of zingiberene, themain terpenoid, 6-gingerol and the pungent principle.

2.10 Ginkgo

Scientific name of Ginkgo is Ginkgo biloba (G. biloba) and the part that are used are leaves. The free-radical scavenging properties of G. biloba extract have been demonstrated as being
at least as effective as uric acid, a potent, naturally occurring antioxidant. The plant extract has further capacity to inhibit the formation of radicals which uric acid does not have. The most interesting and important results are related to vascular diseases, brain function, impotency, dopamine synthesis, inflammation, and asthma. An extract from ginkgo leaves is marketed as Tebonin. Clinical research has shown that Tebonin achieves vasodilation and improved blood flow, especially in deeper-seated medium and small arteries. The flow rate in capillary vessels and end arteries is increased. In elderly subjects, Tebonin alleviated dizziness and loss of memory. A double-blind, placebo controlled study showed another powerful benefit from this ancient Chinese herbal medicine. The extract contained 24% flavonoid glycosides and 6% terpenes. The results show that extract of G. biloba “has a beneficial effect on mental efficiency in elderly patients showing mild to moderate memory impairment of organic origin.” Sixty patients suffering from arterial erectile dysfunction received a daily treatment with 60 mg of an extract of G. biloba. This herbal product was found to be as effective as vitamin E and glutathione in protecting against such damage. The protective effects of G. biloba extract were diminished in the presence of iron, owing to the limits imposed by this powerful oxidant. Ginkgo’s effect as an anti-allergic, antiasthmatic agent has also been demonstrated. The platelet activating factor has been implicated in pathophysiological states including allergic inflammation, anaphylactic shock, and asthma. [66-69,9]

2.11 Licorice
Scientific name of Licorice is Glycyrrhiza glabra and the part that is used is the root. The multitude of pharmacological effects of licorice rhizomes and roots are practically all attributed to the presence of a triterpene saponin called glycyrrhizin, which is about fifty times sweeter than sugar, and has a powerful cortisone-like effect. When mixed with water, the resulting preparation has a very pleasant odor and taste, and acts as an effective demulcent on irritated mucous membranes, such as a sore throat. One study found that glycyrrhizin was as effective a cough suppressant as codeine. Glycyrrhetic acid is obtained when acid hydrolysis is applied to the main component of licorice. This compound is extensively used in Europe for its anti-inflammatory properties, especially in Addison’s disease and peptic ulcer. A study in 1990 demonstrated that glycyrrhetic acid exerts its activity not as a direct effect but by reducing the conversion of cortisol to cortisone, its biologically inactive product. The authors concluded that hydrocortisone, a “weak anti-inflammatory agent,” can be greatly potentiated by the addition of 2%
glycyrrhetic acid. To lessen the toxic effects of corticosteroids, the authors suggested that patients use hydrocortisone together with glycyrrhetic acid. Glycyrrhizin has also exhibited anti-viral activity. A study in 1979 demonstrated that glycyrrhizin inhibited Epstein-Barr virus, cytomegalovirus, and hepatitis B virus. In Japan, glycyrrhizin has long been successfully used to treat chronic hepatitis B. This has led to speculation that glycyrrhizin holds promise in the treatment of HIV. Side effects from the ingestion of large amounts of licorice have been reported. Glycyrrhizin in very large amounts can promote hypokalemia and hypertension. For these reasons people with heart problems and high blood pressure are advised to avoid consuming large quantities of licorice or its components.[70-75, 9]

2.12 Schizandra
Scientific name os Schizandra is Schizandra chinensis and the part that is used is the berry. This plant has many biological activities such as antibacterial, sympathomimetic (stimulant), resistance stimulation, liver protective, anti-toxic, anti-allergenic, antidepressant, glycogenesis stimulant and antioxidants effects. A very interesting study on performance in race horses tends to confirm the folkloric claims. Polo horses given the berry extract of this species showed a lower increase in heart rate during exercise, a quicker recovery of respiratory function, a reduction of plasma lactate, and improved performance. A study in 1990 reported that a lignan component of schizandra fruit suppresses the arachidonic cascade in macrophages. The arachidonic cascade pushes the production of leukotrienes, which may play a role in inflammatory diseases. By inhibiting the arachidonic acid cascade, schizandra both protects the liver and stimulates the immune system—two key roles of an ideal adaptogen. An interesting non-Western study tested the “tonifying and invigorating yang” powers of schizandra and other herbs in mice. The researchers measured the animal’s body weight, thymus weight, leukocyte count, and other parameters of “yang”. They observed a direct correlation between the amounts of herb ingested (as hot water extracts) and improved immunocompetence. They also noticed a distinct anti-fatigue quality, which was measured by reduced excitability of the parasympathetic nervous system. No toxicity was reported.[76-83, 9]

2.13 Turmeric
Scientific name of Turmeric is Curcuma longa and part that is used is Rhizome. Currently, Turmeric is used in India to treat anorexia, liver disorders, cough, diabetic wounds,
rheumatism, and sinusitis. In one study turmeric extract was tested for its anticarcinogenic and antimutagenic properties. Laboratory (non-human) experiments found that this ancient spice reduced both the number of tumors in mice and the mutagenicity of benzo(a)pyrene and two other potent mutagens, 4-nitro-o-phenylenediamine and dimethylbenzanthracene. The active principle of turmeric (curcumin) is a potent antimutagenic agent. For those interested in how curcumin may act to prevent cancer we turn again to the by-now all pervasive theory of free-radical inactivation. The test carcinogen enzo(a)pyrene and dimethylbenzanthracene are metabolically activated to proximate mutagenic/carcinogenic epoxides, which then bind to macromolecules. One study concluded that since curcumin is a potent antioxidant, it may scavenge the epoxides and prevent binding to macromolecules. In other words, this spice’s cell-protective properties are similar to nutrient antioxidants, vitamins C and E, which inhibit free radical reactions. This type of herb is known as a nonsteroidal anti-inflammatory drug (NSAID). Curcumin inhibits cyclooxygenase and lipoxygenase enzymes. It has three main mechanisms of action: 1) antioxidant activity; 2) lipoxygenase inhibitor; and 3) cyclooxygenase inhibition. By inhibiting the associated biochemical pathways, inflammation is curtailed. A pharmacological review in 1991 confirmed many of turmeric’s folkloric effects, including wound healing, gastric mucosa protection, antispasmodic activity, reduction of intestinal gas formation, protection of liver cells, increasing bile production, diminishing platelet aggregation (i.e. blood clumping), lowering serum cholesterol (at very high doses), antibacterial properties, antifungal properties, and potential antitumor activity.\(^{[84-93,9]}\)

### 2.14 Quercitin

Quercitin is the commonest flavonoid in higher plants. It is usually present as a glycoside such as rutin, isoquercitrin, quercitrin, hyperin, and quercimeritrin, but is also isolated in the free state from the families Compositae, Passiflorae, Rhamnaceae, and Solanaceae, where it mainly occurs on leaf surfaces, in fruits and bud extracts.\(^{[94]}\)

Quercitin is a powerful antioxidant that decreases the concentration of superoxide anions in enzymic and nonenzymic systems. A recent animal study demonstrated its antiulcer and gastroprotective effects, especially against ethanol injury. The cyto-protective activity was affected through several interacting pathways involving stimulation of prostaglandin and inhibition of leukotriene production and through quercitin’s antioxidant properties. Pretreating experimental animals with 200 mg/kg (a very high dose) 120 min before
administering ethanol was found to be the most effective dosage in prevention necrosis.\[9,94\] According to Nuutila and others (2003),\[95\] methanol extracts of onions have significantly higher radical-scavenging activities than garlic and red onion has higher activity than yellow onion. Quercetin content is highest in red onions.\[96\] The radical scavenging activities are positively correlated with the total phenolics in these extracts.

2.15 Cinnamon

Cinnamon (Cinnamomum zeylanicum) contains a number of antioxidantive components including vanillic, caffeic, gallic, pro-tochatechuic, p-hydroxybenzoic, p-coumaricd, and ferulic acidsand p-hydroxybenzaldehyde.\[22\] Of a number of herbs and spices(bay leaves, rosemary, sage, marjoram, oregano, cinnamon, pars-ley, sweet basil, and mint) evaluated, cinnamon has been reported to have the highest polyphenolic compound concentration(13.7 mg GAE/g).\[22\] Of 42 commonly used essential oils, cinnamon bark, oregano, and thyme have been reported to have the strongest free radical-scavenging abilities.\[97\] At 5 mg/mL, cinnamon a radical-scavengingactivity of 92%.\[22\] The major components responsible for this activity were identified as eugenol,carvacrol, and thymol. Jayaparakasha and others (2003),\[98\] identified27 compounds in the volatile oil of cinnamon stalks. The volatileoil was 44.7% hydrocarbons and 52.6% oxygenated compounds. The antioxidant capability of cinnamon essential oil is stronger than its free radical-scavenging capacity.\[16\] However, it is a better superoxide radical scavenger than propyl gallate, mint, anise, BHA, licorice, vanilla,ginger, nutmeg, or BHT.\[100\] Cinnamon (bark and leaf) oleoresin can significantly inhibitformation of primary and secondary oxidation products. Singh and others (2007).\[99\] identified 13 components, which accountedfor 100% of the total amount, in cinnamon bark volatile oil. The bark oleoresin contained 17 components that accounted for 92.3%of the total amount. The major component in cinnamon barkoleoresin was (E)-cinnamaldehyde (49.9%). Schmidt and others (2006).\[100\] identified small amounts of β-caryophyllene, benzyl ben-zoate, linalool, eugenyl acetate, and cinnamyl acetate in cinnamonleaf essential oil.

2.16 Clove

The primary components of clove (Eugenia caryophyllus) essential oil are phenylpropanoids such as eugenol, carvacrol, thymol,and cinnamaldehyde.\[102\] Clovealso contains a variety of nonvolatile compounds (tannins, sterols,flavonoids, and triterpenes). Jirovetz and others (2006).\[107\] identified 23 compounds in clove oil including
eugenol (76.8%), β-caryophyllene (17.4%), α-humulene (2.1%), and eugenyl acetate (1.2%).

Clove essential oil is inhibitory toward hydroxyl radicals and can chelate iron. Comparing 16 spices, Khatun and others (2006)[103] found that clove had the highest radical-scavenging activity followed by allspice and cinnamon. Eugenol has been reported to have an antioxidative activity equivalent to Trolox, carvacrol (oregano), and thymol (thyme).[105] The essential oil scavenges free radicals at concentrations lower than those of eugenol, BHT, and BHA alone. Using peroxide values and formation of conjugated dienes, Marinova and others (2008)[104] established that in sunflower oil at 100 °C, myricetin is a more effective and stronger antioxidant than α-tocopherol. Mixtures of the 2 exhibited a synergistic effect that was optimized in an equal molar ratio of the 2. The antioxidant activity of glycosidically bound volatile compounds in clove essential oil has been reported to be significantly greater than that of the volatile aglycones.[106]

### 2.17 Nutmeg

Jukic and others (2006)[108] isolated glycosidically bound volatiles from nutmeg and identified free aglycones in the essential oil. The glycosidically bound and aglycone fractions had only 2 compounds in common, eugenol and terpinen-4-ol. The aglycone fraction had stronger antioxidant properties than did the free volatiles from the oil. Nutmeg (Myristica fragans and M. argentea) contains argenteane, a flavanol diglycoside, which appears to be the primary antioxidative compound.[109] Nutmeg also contains significant amounts of myristicin and safrole that are responsible for the characteristic aroma of nutmeg.[110] Myristicin and safrole have similar structures: a 6-membered aromatic ring bound to an oxygenated 5-carbon ring on one side and a hydrocarbon side chain on the other. After heating (180 °C, 10 min), nutmeg oil has a significantly higher freeradical-scavenging activity, compared to basil, cinnamon, clove, oregano, and thyme.[111]

### 2.18 Black pepper

Black pepper (Piper nigrum) is a highly valued spice for its distinct biting quality that occurs at 1.35 ppm. It has a pungency 150 times that of capsaiacin (United States Consumer Product Safety Commission 1992) due to the alkaloid piperine.[112] The flavor quality is measured by the volatile oil and by the nonvolatile methylene chloride extract, piperine. Piperine stimulates the digestive enzymes of the pancreas, enhances digestive capacity, and reduces gastrointestinal food transit time. Piperine can also quench free radicals and reactive oxygen species. It can protect against oxidative damage in vitro.
Piperine acts as a hydroxyl radical scavenger at low concentrations.\textsuperscript{113} Kapoor and others (2009).\textsuperscript{114} reported that black pepper (P. nigrum) volatile oil contains 54 components that represent about 97% of the total weight. β-Caryophylline (30%) is the major component along with limonene (13%), β-pinene (7.9%), and sabine (5.9%). Pepper essential oils also contain α-and β-pinene, cyclohexene, 1-methyl-4-(1-methylethylidene)-2,3-cyclohexen-1-ol, limonen-6-ol, (E)-3(10)-caren-4-ol, and t-caryophyllene.\textsuperscript{116} The major component of both ethanol- and ethyl acetate-extracted oleoresins is piperine (63.9% and 39.0%, respectively, Liang and others 2010). Using peroxide, p-anisidine, and thiobarbituric acid tests, the oil and oleoresins have been shown to have stronger antioxidant activity than BHA and BHT (Kapoor and others 2009).\textsuperscript{114} but less than that of propyl gallate. Gurdip and others (2004).\textsuperscript{115} reported that, while extracts were predominantly piperine, piperolein B, piperamide, and guineensine, the predominant compounds in essential oils were β-caryophyllene, limonene, sabine, β-bisabolene, and α-coapene.

2.19 Garlic and related herbs

Garlic (Allium sativum L.) has been widely used as a foodstuff since antiquity. It has acquired a reputation as a therapeutic agent and herbal remedy in many cultures to prevent and treat heart and metabolic diseases, such as atherosclerosis, thrombosis, hypertension, dementia, cancer, and diabetes.\textsuperscript{117} Garlic and shallots (Allium ascalonicum) have antioxidant and free radical-scavenging characteristics and identifiable odors at low concentrations. They contain 2 main classes of antioxidant compounds: flavonoids (flavones and quercetins) and sulfur-containing compounds (allyl-cysteine, diallyl sulfide, and allyl trisulfide). The sulfur-containing amino acid derivative, alliin (S-allyl-L-cystein sulfoxide), can be converted into allicin (diallyldisulfide-S-oxide), the compound commonly associated with garlic odor, by the enzyme alliinase. Thiosulfonates, such as allicin, give garlic its characteristic odor; however, they are not necessarily responsible for all of the various antioxidative and health benefits attributed to it.\textsuperscript{118} Okada and others (2005).\textsuperscript{119} have suggested that a combination of the allyl group (\(-\text{CH}_2\text{CH}═\text{CH}_2\)) and the \(-\text{S(O)}\text{S}−\) group is necessary for the antioxidant action of thiosulfonates in garlic extracts. S-allylcysteine, S-allyl mercaptocysteine, and nonsulfur compounds, such as saponins, may contribute to the health benefits (hypolipidemic, antiplatelet, procirculatory, immune enhancement, anticancer, and chemopreventive activities) associated with garlic. The antioxidative effects of shallots are related primarily to their phenol content.\textsuperscript{120}
2.20 Tea extracts

The 3 primary types of tea, green, black, and oolong, are produced by different processing procedures.

Of these types, green tea extracts have the highest total phenolics content, 94% of which are flavonoids (catechins).\textsuperscript{121} Oolong tea contains about 18% total phenolics and 4.4% flavonoids. Theaflavins and thearubigins predominate in black tea. Black tea also contains chlorogenic, caffeic, p-coumaric, and quinic acids.\textsuperscript{122} Much of the antioxidative activity of green tea (C. sinensis) appears to be due to natural flavonoids, tannins, and some vitamins.\textsuperscript{165} The antioxidant activity is linearly related to the phenol content.\textsuperscript{124} that has been reported to be about 450 mg/g.\textsuperscript{125} Catechins in green tea consist primarily of gallic acid derivatives\textsuperscript{34} Catechin flavanols appear to account for more than 80% of the total antioxidant activity of green tea but less than 60% of that of black tea.\textsuperscript{126} The radical-quenching ability of green tea has been shown to be more than 20% more effective than that of black tea in both aqueous and lipophilic systems. In tea extracts, the strongest antioxidant and H2O2-scavenging activity is due to phenols, with 3 –OH groups bonded to the aromatic ring, adjacent to each other.\textsuperscript{127} Epigallocatechin, which has 3 adjacent –OH substitutions on the B ring, has the highest antioxidant activity. These polyphenolic flavonoids are particularly effective free radical scavengers (Lien and others 2008).\textsuperscript{132}

The primary catechin polyphenol [\((\text{-}1)\text{-epigallocatechin-3-gallate}]\) is also the primary peroxyl-radical-scavenging compound in tea extracts,\textsuperscript{128,129} In terms of free radical-scavenging ability, epicatechin gallate > epigallocatechin > epicatechin.\textsuperscript{130} Mitsumoto and others (2005).\textsuperscript{131} found that adding tea catechins to raw beef (200 or 400 mg/kg) inhibited (P < 0.05) lipid oxidation to a greater extent than vitamin C (200 or 400 mg/kg). Chen and others (1998).\textsuperscript{132} reported that green tea catechin extract, consisting primarily of 4 epicatechin isomers, was much more antioxidative than rosemary extract when added to canola oil, pork lard, and chicken fat. In maize (corn) oil triglycerides, Huang and Frankel (1997).\textsuperscript{133} found that epigallocatechin (140 M), epigallocatechin gallate, and epicatechin gallate were better antioxidants than either epicatechin or catechin. The improved antioxidant activity of tea catechins in liposomes, compared with emulsions, may be due to the greater affinity of the polar catechins toward the polar surface of the lecithin bilayers, thus affording better protection.\textsuperscript{134} In a model system mixture of the flavanols,
the antioxidant potential has been shown with no apparent synergism or antagonism occurring.\textsuperscript{[126]} Alkyl compounds with double bond(s), such as 3,7-dimethyl-1,6-octadien-3-ol in green tea extracts and heterocyclic compounds (furfural) in roasted green tea extracts, are major volatile constituents that also exhibit some antioxidative activity (Yanagimoto and others 2003).\textsuperscript{[136]}

2.21 Grape seed extract
Because red wines are produced from red grapes, the antioxidant capacity and chemical composition are related to the grapes. The antioxidant activity of red wines is associated with the content of polyphenols such as flavonoids, phenolic acids, stilbenes, coumarmines, and lignoids (Radovanovic and others 2009).\textsuperscript{[137]} The phenolic composition varies greatly due to grape variety, environmental and climate conditions, soil type, degree of ripeness, and winemaking process.\textsuperscript{[17, 134, 138-141]} Touns and others (2009).\textsuperscript{[142]} reported wide variations in the contents of total phenols (122 to 441 mg GAE/g), flavonoids 17 to 48 mc epicatechin [EC]/g, and tannins (15 to 37 mc EC/g) in the methanolic extracts from seeds of 3 varieties of grapes. Phenolic compounds in grape seeds and skins include catechins, epicatechins, epicatechin-3-O-gallate, phenolic acids, caffeicacid, quercetin, myricetin, proanthocyanidins, andresveratrol.\textsuperscript{[134, 138]} Resveratrol, quercetin, and rutin are generally found in grape skin extracts, while catechin and epicatechin are found in the seeds. The phenolic content of grape seeds defatted with hexane then extracted with methanol and dried under vacuum has been reported to be about 5 mg/100 g, while the anthocyanin content is between 0.14 and 0.68 g/100 g (Rababah and others 2008).\textsuperscript{[140]} Iacopini and others (2008).\textsuperscript{[17]} assessed the antioxidant activity of the extracts and pure compounds using 2 different in vitro tests: scavenging of the stable DPPH radical and of authentic peroxynitrite (ONOO\textsuperscript{−}). Monophenols, quercetin, rutin, and resveratrol may act either synergistically or antagonistically depending on their concentrations and the reaction temperature. Grape seed extract has been shown to inhibit both lipid hydroperoxide and propanal formation in an emulsion system(Hu and Skibsted 2002).\textsuperscript{[143]}

Resveratrol produced primarily in the grapevine, is present in various parts of the grape, including the skin. It has strong antioxidant activity exceeding that of propyl gallate, vanillin, phenol, BHT, and α-tocopherol (Murcia and Martínez-Tome 2001).\textsuperscript{[144]} Resveratrol inhibits peroxidation in a concentration-dependent manner. However, it does not scavenge hydroxyl radicals or does it react with H2O2, making it an inefficient catalyst of
subsequent oxidation (Murcia and MartinezTome 2001).[144,145,146]

3. CURRENT TRENDS OF HERBAL AND NATURAL ANTIOXIDANTS

3.1 Current Market Share

Not only the Nutraceuticals have become the biggest trend now-a-days but it is growing in importance every year and has become the key driver of innovation in health everywhere. People buy benefits, not ingredients. Nowadays, consumers are driven by benefits. Ingredients only take off when consumers see the benefit that the ingredient brings as being credible and relevant to their lifestyles. The message that a food or food ingredient has a natural and intrinsic health benefit is one of the most compelling for many people.[148]

The rise of the nutraceuticals can be seen in our own Indian markets and this is because these nutraceuticals offer “Naturally healthy” products with some intrinsic health benefit. Nowadays consumers have a perception in their minds that natural products are more beneficial than processed food. Moreover they connect to the other big trends or enable you to create a product that makes the connection and very importantly there’s a secure supply chain that can make these ingredients widely and reliably available.[148] Due to rising awareness about health, fitness and changing lifestyle, India's nutraceuticals market is likely to touch USD 6.1 billion by 2020 from the current level of USD 2.8 billion, growing at compounded annual growth rate (CAGR) of 17 per cent, a study showed. Nutraceutical product is a food or fortified food product that not only supplements the diet but also assists in treating or preventing diseases (apart from anaemia), providing medical benefits. India accounts for around 1.5 per cent of the global market, which is anticipated to increase owing to country's large population base, increasing urban belt and awareness, noted the study. Nutraceuticals, herbal and functional foods in India are covered under the definition of food as per Section 22 of Food Safety & Standards Act, 2006. These food products have been categorised as non-standardised/special food products.

It added that government should provide special incentives and subsidies to companies for faster growth of the nutraceuticals market in India.[149] Financial support will also help Indian talent to innovate cost effective nutraceuticals. The products available in the market are majorly targeted to upper-middle class leaving a vast potential. To catch the masses, nutraceuticals for all should be the target concept.[150]
The trend towards preventive healthcare has seen Pharma Companies such as
Novartis, GlaxoSmithKline, and Cadila Healthcare has diversified into the production of
nutraceutical. Then there are fast moving companies like Cadbury India and Dabur that
have had a presence in the market with a slew of supplements & additives. On the other end
of the spectrum companies that specialize in Ayurvedic/ herbal health care products like
the Himalaya Drug Company. The Indian Nutraceutical Market is dominated by
pharmaceutical and fast-moving consumer goods (FMCG) giants. While Dietary
supplements such as Vitamin and Mineral Supplements have been captured by
Pharmaceutical companies, functional food and beverages are now being brought to the
market by FMCG companies. However, certain segments like dietetic supplements are
now being catered to by pure-play nutraceutical companies, apart from their
pharmaceutical and FMCG counterparts. The Indian Nutraceutical market was valued
at $1480 million in 2011. Dietary supplements were the largest category accounting for
64 percent of the Nutraceutical market, driven primarily by the pharmaceutical sector in the
form of Vitamin and Mineral supplements.[10]

3.2 NUTRACEUTICALS AVAILABLE IN MARKET[151,152]

<table>
<thead>
<tr>
<th>BRAND</th>
<th>COMPONENTS</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betatene</td>
<td>Carotenoids</td>
<td>Immune system</td>
</tr>
<tr>
<td>Soylife</td>
<td>Soyabean phytoestrogen</td>
<td>Bone Health</td>
</tr>
<tr>
<td>Lipoec</td>
<td>α-lipoic acid</td>
<td>Potent Antioxidant</td>
</tr>
<tr>
<td>Generol</td>
<td>Phstoler</td>
<td>CHD Reduction</td>
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<tr>
<td>Probiotics</td>
<td>Probiotics</td>
<td>Intestinal Disorder</td>
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<tr>
<td>Xangold</td>
<td>Lutein Esters</td>
<td>Eye Health</td>
</tr>
<tr>
<td>Z-trim</td>
<td>Wheat</td>
<td>Zero calorie fat replacer</td>
</tr>
<tr>
<td>Linumlife</td>
<td>Lignan extracr flax</td>
<td>Prostate health</td>
</tr>
<tr>
<td>Fenulife</td>
<td>Fenugreek galactomannon</td>
<td>Controls blood sugar</td>
</tr>
<tr>
<td>Teamax</td>
<td>Green tea extract</td>
<td>Potent antioxidant</td>
</tr>
<tr>
<td>Marinol</td>
<td>Omega 3 FA, DHA, EPA</td>
<td>Heart health protection</td>
</tr>
<tr>
<td>Clarinol</td>
<td>CLA</td>
<td>For Weight loss</td>
</tr>
<tr>
<td>Cholestaid</td>
<td>Saponin</td>
<td>Reduce Cholesterol</td>
</tr>
<tr>
<td>Eternex</td>
<td>Melatonin</td>
<td>Skin &amp; Bone health</td>
</tr>
</tbody>
</table>

3.3 REGULATORY GUIDELINES FOR THE NUTRACEUTICALS[149,150,153,164]

Counterfeit and un-registered/un-approved products should be called-off from the
market as these products bring bad name to the industry. Small committees should be built
at block levels to check the counterfeit products in the market and immediately discard
them. All products, before reaching the market should go through rigorous testing and it should not be compromised at any cost. An exponential growth has been noticed the number of food testing labs. The government should also provide special incentives and subsidies to emerging companies for the industry growth. The funding will help companies to use improved process technology and come up with quality nutraceuticals.

At present, India does not have any kind of regulatory guidelines for the approval or monitoring of the products under this segment. The nutraceutical products are regulated under the guidelines of FSSA, 2006 amended in 2011 for registration, licensing, approval, labeling & packaging, import, marketing & distribution, laboratory testing like conventional food products. One or more of the following can be covered under nutraceuticals:

- Plants or botanicals or their parts in the form of powder, concentrate or extract in water, ethyl alcohol or hydro alcoholic extract, single or combination.
- Minerals or vitamins or proteins or metals or their compounds or amino acids (in amounts not exceeding the Recommended Daily Allowance (RDA) for Indians) or enzymes with permissible limits
- Substances of animal origin.
- Dietary substances for use by human beings to supplement the diet by increasing the total dietary intake

3.4 FSSAI: The new ray of hope!

Food Safety and Security (FSS) Act was passed by the parliament in 2006. In 2008, Food Safety and Standard Authority of India (FSSAI) came into existence. The FSSAI has prepared the draft rules and regulations for implementation of FSS Act 2006 The FSSAI will make rules and frame standards to regulate nutraceuticals as outlined in the Food Safety Act, 2006. Food Safety and Standard Act 2006 consists of 12 chapters and chapter IV article 22 of the Act addresses nutraceutical, functional food, dietary supplements and need to regulate these products such that anyone can manufacture, sell or distribute or import these products. These products include novel foods, genetically modified article of food, irradiated food, organic food, and food for special dietary uses, functional food, nutraceuticals and health supplements. Article 23 and 24 address the packaging and labeling of food and restriction of advertisement regarding foods. A product that is labeled as “food for special dietary uses” functional food or nutraceutical dietary supplements which is not represented for use as conventional food and whereby such products may be formulated in
the form of powders, granules, tablets, capsules, liquids, jelly and other dosage forms but not parenterals, and are meant for oral administration. Nutraceutical products do not claim to cure or mitigate any specific disease, disorder or condition (except for certain health benefit or such promotion claims) as may be permitted by the regulations made under this Act; It does not include a narcotic drug or a psychotropic substance as defined in the Schedule of the Narcotic Drugs and Psychotropic Substances Act, 1985 and rules made there under and substances listed in Schedules E and EI of the Drugs and Cosmetics Rules, 1945; It also includes "genetically engineered or modified food which means food and food ingredients composed of or containing genetically modified or engineered organisms obtained through modern biotechnology, or food and food ingredients produced from but not containing genetically modified or engineered organisms obtained through modern biotechnology; "organic food" means food products that have been produced in accordance with specified organic production standards; Under the new rule each state will have a food safety commissioner who would be the implementing agency.

Rules and regulation under the new regime will be exhaustive to control quality and claims and their implementation should be expedited. The industries recognise list of nutritional ingredients with proven health benefits and define the list of permitted health claims. They should form a Regulatory Framework and thereby increasing collaboration among Indian manufacturers on R&D and also Standardizing the Manufacturing Process, Validation and Intellectual property protection.

4. LICENSING AND REGULATORY REQUIREMENTS

4.1 Regulatory requirements for India entry

As the nutraceutical regulation is evolving in India, with FSSA getting recently implemented there is a possibility that some of the content is conflicting/confusing, but for Indian industry to take a shape, these have to be streamlined. In order to enter Indian nutraceutical market, some of the very important areas to focus include product evaluation, actual product analysis, procuring licenses and developing India specific health and label claims.

4.1.1. Product evaluation

In Indian conditions, the formulations behave very funnily and get mixed up in classifications. Hence, the due-diligence in terms of carving a specific amount for each
ingredient and the combination of ingredients becomes very crucial. In order to perform product assessment as per Indian regulatory definition, it is of utmost importance to examine each active ingredient and additive in the context of permissibility, standards and dosage of vitamins/minerals allowed as per the Therapeutic, Prophylactic or Recommended Daily Allowance for Indians. Also manufacturers are unclear whether their products will be classified as food or food supplement or drug in the context of the Prevention of Food Adulteration Act, 1954 and Rules, 1955, Food Safety and Standards Act, 2006 and Drugs and Cosmetics Act, 1940 and Rules, 1945. The Food Safety and Standards Rules, 2011 highlights regulatory enforcement structure and procedures which Central Government proposes to make. The structure has a hierarchy from commissioner of Food Safety to number of officers like designated officer, food safety officer, food analyst, etc. who will be involved in the product analysis process at different points.

The various steps in the product analysis include developing extracts of documents and authenticating them by concerned authority, sample collection (in the presence of witnesses), sample dispatch to concerned authority (different process for bulk package and single package), food analysis. And if analysis is not complete within stipulated period of time, further action plan by designated officer and thereby adjudication proceedings (holding enquiry, appeal procedure, hearing, etc.)

4.1.2 Licenses

Though new FSSA promises to simplify Licensing and Registration processes for nutraceuticals, the actual process vary depending on number of parameter. To get the product registered in India, number of licenses (almost 4-5) will be required depending on the actual product status like if company wants to sell bulk drug or finished formulation or import. Also if the company has packaging license or manufacturing license or marketing license. Number of documents will have to be furnished by the food importer to the government authority along with registration application dossiers like import licensing, manufacturing licensing, marketing licensing and other State and national level clearances.

4.1.3 Health and label claims

Developing health and label claims specific to Indian regulatory guidelines is the major element to be focused while entering Indian market. International as well as national clients have number of questions about Indian labeling and packaging requirements,
Packing of consignment, Need for sample material and declaration for registration, Composition of consignment and approach for the same, Label contend and Structure-function claim and label claim. Based on the results of regulatory assessment of the product, India specific label content and claims are developed.

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