Nutraceuticals

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Nutraceuticals are essential food constituents that provide nutritional benefits as well as medicinal effects. The benefits of these foods are due to the presence of active compounds such as carotenoids, collagen hydrolysate, and dietary fibers.

functional foods anti-cancer anti-inflammation antioxidant activity anti-lipid activity nutraceuticals safety and toxicity

1. Introduction

Nutraceuticals are known as bioactive substances that are present in common food or botanical-based sources that can be delivered in the form of dietary supplements or functional food, supplying beneficial effects in addition to the nutritional essential components [1]. Nutraceuticals comprise a wide range of bioactive derivatives accumulated in edible sources including antioxidants, phytochemicals, fatty acids, amino acids, and probiotics. With either established previously or potential effects, nutraceuticals are well-known for their role of being involved in disease treatment and prevention, anti-aging properties, and malignancy prevention. Consuming probiotics is encouraged due to its significant role in the treatment and prevention of gastroenterological diseases [2]. Garlic, for example, has been suggested as a complementary therapy for high blood pressure and cholesterol [3].

With the presence of side effects induced by some pharmaceutical drugs and the emergence of antimicrobial resistance, nutraceutical compounds have gained attention as an alternative therapeutic and preventive approach alongside the advantages of being more affordable and available. Several studies have significantly shown the beneficial effects of nutraceutical ingredients on immune system functions. Such functions include enhancing the infection response mechanism, boosting immunomodulatory activity, and contributing to reducing the impacts of autoimmune disorders and hypersensitivity. Nutraceuticals have also been shown to exert lipid-lowering, anti-inflammatory, anti-cancer and antioxidant activity [4][5][6][7].

The acknowledgment of the science of nutraceuticals has been growing, with increased interest in finding novel therapeutic options by utilizing new technologies and scientific methods. Although many nutraceuticals have been reported for their effective properties in the immune system, there is a necessity of conducting more high-level, clearly evidenced clinical trials for further investigation regarding the long-term effects and public safety.

2. Types of Nutraceuticals Based on Source, Nature and Application

Nutraceuticals have been classified based on their application into traditional, non-traditional, fortified, recombinant, phytochemical, herbal, functional foods, dietary supplements, probiotics and prebiotics [8][9]. Nutraceuticals with their different classes have a variety of applications and uses depending on their nature. Table 1 summarizes the classes of nutraceuticals with their beneficial effects to health.

Table 1. Summary of types of nutraceuticals and their potential effects on health.

Class/Type of Nutraceutical	Examples	Active Ingredient	Advantages	References
Traditional approaches				
Functional foods	Tomatoes	Lycopene	Anticancer activities, e.g., lung and prostate, reduce blood pressure	[10]
	Salmon	Omega 3	Lower cardiovascular, diabetes disease risk	[11]
	Soy	Saponins	Antioxidant, detoxification of enzymes, stimulate immune response, hormonal metabolism	[12]
	Fermented milk and milk products	*L. acidophilus*, *Bifidobacterium* spp.	Prevent gastrointestinal infections, lower the level of cholesterol	[13]
	Marine algae	Fucoidans	Antioxidant, anticancer, anticoagulant activity	[14]
	Broccoli	Sulforaphane, glucosinolates	Decrease risk of several cancers, antioxidant	[15][16]
	Carrots	β-carotene	Reduce cancer risk, improve immune system	[15][17]
	Aloe	Aloins	Wound healing, antiulcer, anti-inflammatory, immunostimulant, antimicrobial activity, hematopoietic stimulation	[18][19]
	Turmeric	Curcumin	Anti-inflammatory, anticarcinogenic	[18][20]

Class/Type of Nutraceutical	Examples	Active Ingredient	Advantages	References
Traditional approaches				
Dietary supplements	Folic acid		Prevent defect in neural tubes, Red blood cells formation	[18][21]
	Vitamin A		Antioxidant, growth, treat some skin diseases	[22]
	Calcium		Bone, muscles, teeth nerve health, prevent osteoporosis	[23][24]
	Iron		Carry oxygen, produce energy	[22]
	Vitamin D		Bone and teeth health, help in calcium absorption, musculoskeletal health	[25]
Probiotics	*Lactobacillus acidophilus*, *Bifidobacterium* spp., *Streptococci*, *Enterococci*		Gut health, replace diarrhea-causing bacteria, anticancer	[22][26][27]
Prebiotics	Fructo-oligosaccharides		Enhance probiotics growth, *bifidobacteria* growth enhancement	[28]
	Inulin		Enhance immune system, minerals absorption, protect bones	[29][26][30]
Non-conventional approach				
Fortified	Orange juice with calcium	Calcium, ascorbic acid	Glycemic control enhancement, sensitivity to insulin	[31]
	Anthocyanin-fortified bread	Anthocyanin	Reduce digestion rate	[32]
Recombinant	Gold kiwifruit	Ascorbic acid, carotenoids	Immune system enhancement	[8][33]

3. Classification of Nutraceuticals Based on Modes of Action

3.1. Anti-Cancer Activity

The use of nutraceuticals as chemo-preventative agents has been studied, and promising results were obtained as per their ability to prevent and treat cancer. Nutraceuticals of different origins have been shown to exhibit anti-cancer activity. Table 2 summarizes anti-cancer modes of action.

Table 2. Selected anti-cancer modes of action classified based on cancer type and nutraceutical.

Type of Cancer	Mode of Action	Nutraceutical	References
Prostate cancer	Antiproliferation, cell cycle inhibition, angiogenesis inhibition and promotion of apoptosis	Vitamin D	[34]
	Antioxidation, antiproliferation, and promotion of apoptosis	Catechins in green tea	[35][36]
Colon cancer	Tumor marker suppression, promotion of apoptosis, metastasis inhibition, and antiproliferation	Polyphenols	[37][38]
	Antioxidant, antiproliferation, promotion of apoptosis, inflammatory protein inhibition	Terpenoids	[39][40]
	Autophagy induction and promotion of apoptosis	Alkaloids	[41][42][43]
	Induction of DNA hypomethylation, promotion of apoptosis, and antiproliferation	Micronutrients	[44][45]
Breast cancer	Antiproliferation, angiogenesis inhibition, and promotion of apoptosis	Allicin in garlic	[46][47][48]
	Antiproliferation and promotion of apoptosis	Curcumin	[49]
	Cell cycle inhibition, promotion of apoptosis, and inhibition of metastasis	Vitamin D	[50][51]
Oral cancer	Prevent tumor initiation	Strawberry	[44]
	Antioxidation	Rosemary	[45]
	Antiproliferation, promotion of apoptosis, and angiogenesis inhibition	Geraniol	[52]

3.2. Anti-Inflammatory Activity

Nutraceuticals exert anti-inflammatory activities which help in the prevention and treatment of chronic inflammation-associated diseases [53]. Another benefit of nutraceuticals as anti-inflammatory agents is that they can be used as a complementary alternative to anti-inflammatory therapeutic drugs, which leads to a reduction in drug dosage, and

therefore reducing side effects [54]. Chronic inflammation is the major cause of chronic diseases such as cardiovascular diseases, pulmonary diseases, diabetes, and cancer [53]. Table 3 summarizes anti-inflammatory modes of action.

Table 3. Selected anti-inflammatory modes of action classified based on nutraceutical and benefits.

Mode of Action	Nutraceutical	Benefits	Reference
Reduce nitric oxide synthase (iNOS), tumor necrosis factor-α (TNF-α), production of nitric oxide (NO), interleukin-1β (IL-1β), nuclear factor kappa B (NF-κB)	Resveratrol	Neuroprotective	[55]
Inhibit the activation of NF-κB and limits the inflammatory response, such as ICAM-1, MCP-1, Cox-2, TNF-α, IL-1β, and IL-6	Baicalin	Improvement of trinitrobenzene sulphonic acid (TNBS) induced colitis	[56]
Reduce the expression of TNF-α, COX-2, 5-LOX, and IL-6 and increase IL-10 levels	Flavocoxid	Protects from sepsis	[57]
Reduces the expression of TNFα, IL-1β and reduces myeloperoxidase (MPO) activity	Curcumin	Improve dextran sulfate sodium (DSS)-induced colitis	[58]
Decreases the expression of iNOS and COX-2	6-Gingerol	Protects from carbon tetrachloride (CCl4)-induced liver fibrosis	[59]
Inhibits the expression of TLR4 and NF-κB and suppress iNOS, COX-2, TNF-α, IL-6, and IL-1β	Apigenin	Protects against blood-brain barrier disruption	[60]
Reduced the expression of TNF-α, IL-1β, and IL-6 and increases IL-10 expression. Decreases TLR-2 and TLR-4 expression Inhibits phosphorylation of I-κB, p65, p38, ERK, and JNK	Piperine	Reduces inflammatory injury in *Staphylococcus aureus* endometritis.	[61]
Suppresses the activity of renal MPO	Naringin	Decreases neutrophil infiltration in the kidneys.	[62]
Reduces NF-kappa B p65 subunit activation which decreases inflammatory cells and reduces cytokine secretion	Eucalyptol	Potential agent in the treatment of cigarette smoke-induced acute lung inflammation.	[63]
Suppresses NF-kB and p38 and reduces the level of TNF-α and IL-1β levels	**Ortho-eugenol**	Treatment of pain and inflammation.	[64]

3.3. Antioxidant Activity

The main sources of antioxidants are food, vitamins, and supplements. Foods such as fruits and vegetables are considered a great source of antioxidants due to their high levels of vitamins and phytochemicals [65]. Beetroot contains betalain and phenolic compounds which cause an increase in the resistance of low-density lipoproteins (LDLs) to oxidation [66], protect the liver from damage [67], and decrease blood pressure [68]. Dried fruits are a good source of antioxidants and have health benefits to humans. They can reduce glucose levels in the blood in addition to reducing risk factors associated with heart disease [69].

3.4. Anti-Lipid Activity

The application of nutraceuticals as hypolipidemic agents has shown great potential in lowering total cholesterol (TC) and low-density lipoprotein (LDL) concentrations. Lipid-lowering nutraceuticals can be classified into three groups based on their mechanism of action. Such mechanisms include the inhibition of cholesterol absorption, inhibition of cholesterol synthesis, and excretion of LDL [70]. Plant sterol foods or supplements have displayed effectiveness in lowering lipid profiles. It has been established that plant sterols modify lipid profiles by decreasing the intestinal absorption of cholesterol [71]. It has been found that the intake of plant sterols demonstrated an effect on lipid profiles by lowering the concentrations of triglycerides and LDL in individuals at risk or suffering from type-2 diabetes mellitus [72]. Red yeast rice (RYR) exhibited potent effects on lowering lipid profiles in patients suffering from cardiovascular disease and dyslipidemia [73][74][75]. The consumption of dietary fibers is considered an effective approach in modulating lipid profiles. Dietary fibers are divided into soluble and insoluble fibers. Soluble fibers are more beneficial because they are fermented by the microbiota of the large intestine [76].

In summary, many nutraceuticals and functional foods have been proven for their ability in regulating lipid profiles. Owing to their mechanism of action, nutraceuticals can either inhibit cholesterol synthesis, inhibit cholesterol absorption, or enhance cholesterol excretion.

4. Nutraceuticals' Safety on Consumers

The majority of nutraceuticals on the market are safe for human consumption and only in some instances may cause harm because some nutraceuticals have toxic effects on human health. Studies have shown that some widely consumed nutraceuticals possess many health benefits with very minimal toxicity when used in correct controllable amounts. Nutraceuticals such as anthocyanins, polyphenols, and catechins are widely used and are safe for human consumption on controlled use. There have been very few studies that have indicated how these substances are harmful to human health.

Nevertheless, studies on nutraceuticals have shown that benefits of use outweigh the risk, and they are widely approved for human use within the correct amounts and dosages [70]. However, misuse and overuse of these products may pose health risks to humans. The safety of these nutraceuticals on consumers basically depends on the type, time, and the quantity used. Use of some nutraceuticals, especially when one is under medication, can

result in interactions between the drug and the nutraceutical compounds causing very harmful effects on the body [77]. Thus, for safe usage, they should be used only when prescribed by qualified personnel at the right quantity, the correct quality, and timing.

5. Summary

Nutraceuticals embody a novel and exhilarating research field for the discovery of innovative health products with tremendous potentials of health benefits including safety, efficacy, and economy. Globally, researchers have realized the fact that proper nutrition and dietary supplements can prevent and cure chronic diseases. This research area has major attractions both for academia and pharmaceutical/food industries. A few pharma-industries including Ranbaxy and Abbot have taken the initiative of synthesizing a range of nutraceutical products for different age consumers. The preventive role of these products is uncovered by researchers to a great extent; therefore, further extensive research both from academia as well as the pharmaceutical sector is necessary regarding their safety and efficacy. Furthermore, use of advanced and high-throughput technologies can help us understand the underlying mechanisms of action and develop this exciting area of research to new horizons for the betterment of humanity, both in terms of economic benefits as well as health outcomes.

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