Uncovering Prospective Role and Applications of Existing and New Nutraceuticals from Bacterial, Fungal, Algal and Cyanobacterial, and Plant Sources

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Abstract: Nutraceuticals are a category of products more often associated with food but having pharmaceutical properties and characteristics. However, there is still no internationally accepted concept of these food-pharmaceutical properties, and their interpretation can differ from country to country. Nutraceuticals are used as part of dietary supplements in most countries. They can be phytochemicals which are biologically active and have health benefits. These can be supplied as a supplement and/or as a functional food to the customer. For human health and longevity, these materials are likely to play a vital role. Consumption of these items is typical without a therapeutic prescription and/or supervision by the vast majority of the public. The development of nutraceuticals can be achieved through many bioresources and organisms. This review article will discuss the current research on nutraceuticals from different biological sources and their potential use as an agent for improving human health and well-being, as well as the gaps and future perspective of research related to nutraceutical development.

Keywords: medicinal mushroom; microbiota; nutraceutical development; human well-being; phytochemicals

1. Introduction to Nutraceuticals

The term “nutraceutical” has been used since the late 1980s to describe medicinally or nutritionally functional food [1]. A nutraceutical can also be described as an all-natural product that is known to have biological advantages against one or more illnesses. The term “nutraceuticals” is an amalgamation of the words “nutrient” and “ceutical”—where “ceutical” means therapy—and it is referring to food, supplements, and/or products that provide therapeutical medical value besides main nutrients [2]. Generally, nutraceuticals are claimed to possess pharmaceutical and/or anti-ageing properties, be capable of reducing symptoms or prevent the development of some long-term diseases, improve overall...
wellness, or show other specific physiological benefits, such as boosting immunity [3]. Nutraceuticals may be referred to as superfoods, health supplements such as vitamins that are derived from natural sources, phytochemicals, nutrient-rich food such as fortified cereals, dietary supplements such as functional herbal pills, and food from a genetically modified organism that serve other purposes besides nutrition (Figure 1) [4].

**Figure 1.** An overview of different types of nutraceuticals and their uses.

Nutraceuticals could be very useful and effective on the condition that they are used properly or as advised by a physician [5]. Nutraceuticals are generally safe to be consumed with very few reported side effects and contraindication [5]. The daily consumptions of nutraceuticals may help in some diseases to avoid or reduce the intake of traditional medication especially for those to be taken for the whole life [6,7]. Health supplements include products that have micro- and macro-nutrient elements such as organic acids, vitamins, flavonoids, phenolic compounds, glucosinolates, polysaccharides, amino acids and protein, and fibres [8] and are normally classified in the market according to their types of nutritional functions such as dietary fibre, pro- and pre-biotics, and vitamins [9]. It has been proposed that plants, animals, and even mushrooms can be a good source for nutraceuticals/pharmaceutical factories which have proven to be more economically efficient [10]. They are regarded as sources for the avoidance of potentially fatal illnesses such as kidney and gut disorders, as well as prevention of microbial disease [11]. On the other side, the industry has its definition for nutraceuticals as “any nontoxic food component that has potential health benefits (Figure 2) [12]. It depends on each country regulation to define and regulate; for instance, in the United States, the Food and Drug Administration (FDA) regulates nutraceuticals as a dietary supplement, while in Malaysia there is no definition for nutraceuticals, and the National Pharmaceutical Regulatory Agency (NPRA) approves health supplements depending on the claim made by the manufacturer [13].
Figure 2. Flow chart illustrating different sources of potential molecules to be used in nutraceutical applications. Natural nutraceuticals could be obtained from higher plants, fungi, bacteria, and algae.
The industry related to nutraceutical and supplement production earns more than 200 billion USD per year globally, and it is expected to double in the upcoming five years [14,15]. Strict regulation is required for the use of these nutraceuticals supported by evidence that those supplement meet minimum standards of safety and quality before approving the production for that supplement, considering that those product are getting more popular and the potential risk from any possible risk or side effect [16]. For that reason, understanding the information regarding nutraceuticals, their proven benefits, and possible side effects is essential for both the manufacturer and consumers. The prospective of a superfood, supplement products to aid health, and the development of substitute remedies for different illness is supported by relatively many in-depth studies and research; however, the mode of action of the active compound is still unknown in many cases and needs further investigations [17]. The goal of this review article is to introduce, define, and briefly discuss the types of potential molecules that can be used in the production of nutraceuticals that are derived from bacterial, fungal, algal, cyanobacterial, and plant origins while highlighting their potential impacts on the consumers’ health. The food industry has drastically also adjusted to accomplish customers’ necessities with the help of modern food manufacturing technologies. Due to the wide connection between contemporary nourishment and the emergence of a pandemic disease, superfood may be the answer to boost immunity and prevent or treat epidemic as well as pandemic diseases.

2. Nutraceuticals from Bacterial Origin

Several nonpathogenic microorganisms have demonstrated therapeutic properties that are beneficial for gut and immune health, and they are collectively known as probiotics. A probiotic is known as “valuable live microorganisms”, that benefit to the host when given in suitable amounts. Food industries such as vegetables, milk, meat products are wide applications of probiotic bacteria; to extend their positive effects to the host, they must be taken in sufficient quantities [18], that of $10^6$–$10^9$ CFU/g upon intake. The positive effect of probiotics is linked to a specific strain of bacteria, not species only [19]. These strains of bacterial probiotics are alleged to grant health benefits to the human when consumed adequately [20]. Functional food which carrying probiotic bacteria exhibit determinations in connection with the viability of the bacterial cells, correlating with criteria such as food processing and storage conditions, and the acidity of the food matrix [21,22]. The gut normal flora can be moderated to recover host healthiness through the administration of probiotic organisms [23]. The encapsulation of mRNA, siRNA, and proteins into extracellular vesicles of *Bacillus subtilis*, for instance, could have functional participation in food- and clinical-related therapy through the communication between host and the bacteria, reaching the bloodstream and consequently to the intestine and organs [24]. Examples of daily consumed commercially probiotics that are relatively affordable are *Lactobacillus casei* and *Lactobacillus brevis*, suitable for curing children in 6–12 years old suffering from early carious lesions [25]. In this case, the bacteria slow down the development of cariogenic germs and complete the function of fluoride to provide a better oral habitat, and such food raises the buffer solution and enhances the dental remineralisation [26]. Lactobacillus probiotics have anticolorectal cancer activity, *Lactobacillus plantarum*, *Pediococcus pentosaceus*, and *Lactobacillus rhamnosus* ability to modulate the metabolism and decreasing faecal pH, leading to the elimination of carcinogens and toxins [27]. Yoghurt is the famous example of at-hand’s-reach probiotics, these products usually contain one or a mixture of *Lactobacillus delbrueckii* subsp bulgaricus and *Streptococcus thermophiles*, and some types of additions of *Bifidobacterium* and *Lactobacillus* to enhance health benefits [28,29]. *Lactobacillus reuteri* and *L. rhamnosus* were recently reported for their antioxidant properties with more than 38% scavenging activities [30]. On the other hand, yoghurt consumption is related to β-galactosidase enzyme produced by yoghurt bacteria with the ability to enhance lactose digestion [31]. The Scheers et al. (2016) study on vegetables consumed by humans concluded that iron bioavailability increased in vegetables fermented with *L. plantarum*, when compared to nonfermented groups [32]. Lactic acid bacteria (LAB) are known to be used
for food preservation and safety. Their phytate-degrading ability is of importance in food processing as it digests phytates that are known to inhibit the absorption of some minerals such as iron, calcium, and zinc [33].

Probiotics are potential factors in the handling of obesity, leading to a reduction in body weight, body mass index, and total fat [34]. Quantitative and qualitative disorders in gut microbiota lead to dysbiosis [35]. Studies showed an enhancement of gut morphology leads to productive modification of the GI metabolome [36,37]. Intestinal bacteria have enzymes with the ability of deconjugation, dehydrogenation, dihydroxylation, and sulfation of primary bile acids which control detoxification [38]. To avoid dysbiosis in the gut of humans, it is favourable to consume LAB, Bifidobacteria spp. fermented food. Moreover, compositional alterations to the gut microbiota accompanied by changes in immune or metabolic factors in the host indicate that microbiota can serve as a mediators between health outcomes and consumption of fermented food [39]. An aqueous extract mixed with L. casei culture was co-encapsulated and mixed with inulin, chitosan, and whey protein isolate, with very high encapsulation efficiency for anthocyanins and lactic bacteria with high efficiency of release in the human intestine [40]. Utilizing onion peel fermented with LAB to produce functional food revealed some potential to regulate blood pressure [41].

Commercially available L. plantarum fermented juices have adequate antioxidants, antimicrobials, and anti-inflammatory properties [42]. Recently, phylogenetic analysis revealed that strains of Lactobacillus fermentum and L. plantarum, with two strains of Pediococcus acidilactici, exhibited different degrees of cell surface hydrophobicity and cholesterol-lowering activity [42]. Consequently, O22, O24, L. rhamnosus K3, and L. plantarum O20 are four tested strains that revealed the ability to induce anti-inflammatory mediators, balancing between regulatory and pro-inflammatory cytokines, with the potential to improve the host immunity [43].

LAB has shown promising antifungal activities. In vitro study of selected L. plantarum LO3 with the maximum antifungal activity was shown to prevent aflatoxin production and fungal growth [44]. The supernatant of this strain showed the ability to inhibit the growth of aflatoxicogenic mould in tomato without modifying its physical and chemical properties.

The protective effect of milk against cancer with a synergistic combination of Lactobacillus gasseri 505 and melon berry leaf extract that have potential anticancer characteristic against colorectal cancer [45]. L. casei and L. plantarum were utilized as a functional food and ingredient exhibited the most potent anticancer effect on human colon adenocarcinoma by regulating apoptotic proteins [46]. Prebiotics are those molecules/fibres which help probiotics grow in the human gut. Mixing Leuconostoc mesenteroides and Lactobacillus sakei in kimchi fermentation produced variable percentages of mannitol, acetic acid, and lactic acid [47]. Fermentation of pasta with a mixed culture of L. plantarum CRL 1964 and L. plantarum CRL 2107 resulted in increased vitamin B2 and B9 levels and haemoglobin in blood [48]. Previously, it was usual that prebiotics and probiotics used separately, but in the last 30 years, a combination between them increased their activity and efficiency [49]. More future research is needed for modulating prebiotics, probiotics, or symbiotics to treat overweight and other metabolic disorders besides the intestinal degradation of non-digestible carbohydrates. Besides that, more in vitro prebiotic expansion studies with model animals are needed to see the changes in their gut microbiota, before clinical trials. For safety and specific targeting, it is advised to involve bioinformatics approaches for precise probing of the bacterial–probiotic mode of function. Complete analysis and full sequencing for the entire genome are necessary with aggressive quality control that should be carried out before introducing the new strains into the market. Future research could include not only prebiotics restricted to Bifidobacteria species which are common in the gut but also expanding to other prebiotics targeting species in the lung and skin. Poor societies should have the chance to obtain probiotics and bacterial fermented food, to reduce the risk of infections, malnutrition, and diabetes. Some probiotics such as L. casei can interact with receptors on the epithelial cells, stimulating the production of cytokines which play an important role in immune cell activation. Due to the powerful capabilities of probiotic bacteria in various
body systems and immune system stimulation, competition with pathogens may direct future studies for examining the probiotics activity with focus on boosting immune system.

3. Nutraceuticals from Fungal Origin

Certain types of fungi are used as traditional medicine across various parts of the world. For example, in Africa, fungi are consumed as food and medicine, for recreational purposes, and for performing certain rituals [50]. Some popular fungi used by the Chinese in traditional medicine include the Chinese Cordyceps [51] and Ganoderma lucidum [52]. *Ganoderma lucidum* has been touted as having anti-ageing properties in addition to promoting other health benefits, and it is even named as “mannentake” in Japanese, which can be translated into “10,000-year-old mushroom” [52].

In recent years, modern science has uncovered fungi as rich sources of nutraceuticals [53]. Mushrooms are rich in various types of bioactive compounds with functional properties as antioxidants [54,55], anticancer compounds [56], antibiotics [57], immunomodulators [58], hypcholesterolemic [59], and hypoglycemic [60]. The *Cordyceps* fungi that were used as traditional medicine contain many bioactive molecules, with cordycepin considered the most important due to its beneficial potentials [61]. Cordycepin is known for various nutraceutical abilities, such as fighting diabetic, cancer cardiovascular-related diseases which makes it a valued remedial mushroom [62]. Other fungi like *Ganoderma* are usually used as a traditional medicine and are now one of the main components in the nutraceutical and pharmaceutical industries, recently characterised by spectroscopy and mass spectrometry, showing that it has multiple bioactive compounds important for biological reactions [63]. *Ganoderma* was also shown to be very active in preventing and treating various kidney diseases [64]. A recent study also showed that certain medicinal mushrooms-derived metabolites are potential candidates for easing neurological disorders such as ataxia and mental dysfunction (dementia) [65]. *Ophiocordyceps sinensis* cultured mycelia showed antibacterial potential when the extracts were tested against a group of pathogenic bacteria. These antibacterial properties highlight the potential utilisation of fungi for use in therapeutics and the nutraceutical industry [66]. One of the common components used in the nutraceutical industry, beta-glucans, is found in many fungal species. Beta-glucan is a natural polysaccharide that can be found in plant cell walls such as barley and oats [67]. It is also present in yeast cells, generally fungal cell walls, and some other microorganisms. The biological activity of this molecule depends on the molecular weight, bond frequency, and changes in structure. It is known to lower cholesterol levels in the blood by binding cholesterol molecules in the intestines [68] and promoting beneficial metabolic effects in high-fat diet individuals [69]. Beta-glucans were also shown to promote apoptosis in certain cancer cell lines [70]. It is also known to be an immunostimulant by binding to specific receptors such as CR3 and Dectin-1, which activates macrophages [71]. Beta-glucan extracted from yeast used as supplements have shown antidiabetic properties, reducing insulin resistance, and regulating gut microbiota in patients, to the extent of potentially ameliorating neuronal damage in brain tissue [72,73]. Apart from polysaccharides such as beta-glucans, other macromolecules found in fungi also contribute to the advantages of fungi as a source for nutraceutical products [74]. Extracellular polysaccharopeptides from Sanghuang mushrooms in Eastern Asia showed antioxidant and anti-inflammatory activities in inhibiting ulcerative colitis (UC) when tested in mice, possessing the potential to be developed as nutraceuticals or incorporated in functional food development [75].

Prospects of Fungi for Novel Nutraceutical Discovery

The vast diversity of fungi on Earth can be taken advantage of as a potential source for novel discoveries. It is reported that many fungal species are yet to be discovered, and only less than 7% are screened for bioactive compounds [76]. Even with fungi residing in residential properties, a crowdsourcing program found fungal strains with anticancer metabolites [77]. Another study that screened more than 10,000 fungi for bioactive com-
pounds found that 1526 of those fungi extracts had certain biological activity against developing zebrafish [78]. Efforts have been made to search for novel fungi living in marine environments [79] and the Antarctic [80], which could lead to new potential fungal nutraceuticals. Recent surveys in the Arctic and Antarctic discovered that potential lichen-forming fungi within the Parmeliaceae family produced a wide array of metabolites and proteins with promising nutraceutical activities [81]. This further enunciates the potential for discovering novel nutraceuticals and bioactive compounds from fungi living in remote or extreme ecological areas. Fungi are also known to adapt rapidly to environmental changes and can produce a variety of secondary metabolites in response to different ecological interactions such as protection from invertebrates; the explanation for this adaptation lies in the complexity of their biochemical pathways and the richness of gene clusters [82].

Future research could highlight nutraceuticals from traditional remedies and allows the modern pharmaceutical/nutraceuticals industry to reintroduce those metabolites as new health supplements [83].

4. Nutraceuticals from the Algal and Cyanobacterial Origin

Seaweed bioactive metabolites have been consumed for many years in different cuisines [84]. Technologies that may improve the production of seaweed molecules are also previously discussed [85]. The brown seaweed polysaccharide fucoidan has immunomodulatory properties by modulating T cells and decreasing cytokines like interleukin 6 (IL6) [86]. A promising functional drink product from the brown seaweed *Sargassum binderi* tea contains fucoidan exhibits antioxidant activity [87]. Fucoidan from other species like wakame *Undaria pinnatifida* showed anticancer and antioxidant properties [88], anticoagulant [88], and antioxidant properties [89]. Generally, seaweed is known as a great source of some essential elements like iron and iodine [90]. High concentrations of minerals such as iron, cadmium, and zinc were found in a group of different Mediterranean seaweed species like *Gracilaria verrucosa*, *Codium tomentosum*, and *Sargassum linifolium* with high potential to be used in the nutritional supplement industry [91]. However, the content of those minerals depends not only on the species but also on the geographical distributions and environmental conditions [92]; therefore, the assessment of the content and potential human toxicity should be a routine procedure for those species selected for health supplements and the food processing industry. Brown seaweed *Dictyota friabilis* showed potential antiviral properties against HIV [93]. Besides *Dictyota* spp., *Turbinaria decurrens* using an in vitro metabolomics study also revealed anti-HIV activity for polysaccharides extracted from these species [94]. *Dictyota menstrualis* showed inhibition activity against Zika virus in Brazil [95]. This property of antiviral activity of the seaweed extracts/products related to bioactive secondary metabolites has promising applications to fight different viruses, making these different species of seaweeds a target for the supplement/drug development process and thus increasing their values.

Another group of brown seaweeds showed their ability to be a source of functional food and nutraceuticals products such as fucoidan, laminarin, and alginate [96]. Carrageenan production from red/brown seaweed showed promising abilities to contribute as nutraceuticals in many food industry applications [97]. It also shows some medical applications against obesity in mice by interaction and affecting lipid metabolism, which could potentially use carrageenan as healthy additives in the food industry [98]. *Alaria esculenta* and *Saccharina latissima* are brown seaweed algal species with high nutritional value for the food and feed industry value [99]. Both species can be a good natural source of iron and iodine in the food industry [100,101]. *Pyropia vietnamensis* showed a high value of protein content which also could be a good substitute for protein sources for vegetarian and vegan diets [102].

*Spirulina* or Arthrospira is a blue-green alga considered one of the famous examples of beneficial cyanobacteria, with many products already in the market for many years now [103]. This alga and its extracts are believed to have many functions as antioxidant and anti-inflammatory properties [104]. Many *Spirulina* products, now available as super-
food/herbal supplements to reduce cholesterol concentration by reducing triacylglycerols level [105], through research on rabbit confirm this characteristic [106], while more recent research on a human claim no changes were made after consuming Spirulina on cholesterol profile [107]. More research on human lipid profile behaviour after spirulina consumption is highly recommended. Chlorella, on the other hand, is another group of microalgae that is widely known for producing nutraceutical compounds with potential used in nutraceutical/pharmaceuticals applications [108].

Seaweed, cyanobacteria, and other algal sources of these food supplements and additives draw the attention of researchers pharma/nutraceuticals manufacturers in recent years [109]. Chlorella and Spirulina have been relatively well studied compared to other algae in terms of their antioxidant, anticancer, and anti-hyperlipidemia properties besides being natural sources of many macro- and micro-nutrients. Despite some reports related to a possible side effect of its related products [110], the seaweed industry is expanding tremendously [111]. Algae, and to be specific seaweed, is considered a good source of multivitamins [112]. Saccharina latissima (sugar kelp) for instance is considered a good source of vitamin C in its dried and fermented form [113,114]. Undaria pinnatifida and Porphyra purpurea have high contents of vitamin A besides having the known activity of lowering the bad cholesterol (LDL) and being a good natural source of proteins and carbohydrates [115]. Red seaweeds Gracilaria spp. (Gracilaria edulis and Gracilaria corticata) revealed multivitamin contents including different forms of vitamin B and vitamin C in addition to their content of minerals, polysaccharides, and fibre [116]. Considering the number of market shares of these algae and the increased popularity of their related products, more targeted researches should be encouraged to focus on (1) understanding the algal and cyanobacterial mode of action in exhibiting their nutraceutical properties and clinical verification of the claims related to their health benefits and (2) exploring and identifying more potential bioactive compounds from different underutilized species of algae and cyanobacteria.

5. Nutraceuticals from Plant Origin

Medicinal plants have an ancient history of usage as local remedies for many illnesses. Today, this principle is the same as using those plant molecules as nutraceuticals and pharmaceuticals for human well-being [117]. The nutraceutical industry has continued supply from nature with the vast majority of registered products in the US FDA from natural sources [118]. Traditional plant-based nutraceutical is considered the source of nutritional elements, phytochemicals, and functional food to more than three quarters of the world’s population [119]. The most universally known plant-based nutraceuticals are vitamins [120]. Phytonutrients are considered as a source of a bioactive raw unprocessed compound which can be counted as a primitive form of nutraceuticals [121]. For instance, fruits and vegetables give us a group of nutrients such as vitamins, minerals, dietary fibre, water, and healthful phytochemicals [122]. Amongst known phytochemicals are flavonoids, isothiocyanate, carotenoids, polyphenols, anthocyanidins, allyl sulfides, and catechins [123]. It is believed that grains, fruit, and vegetables contain more than 4000 phytochemicals with potential nutraceutical application [124]. In addition to the macronutrients such as proteins, fats, carbohydrates, necessary for normal metabolism, and plant-based micronutrients such as trace elements, vitamins also have significant importance in health improvement [125,126]. Several nutraceuticals bioactive peptides, vitamins, are proposed to be able to prevent against microbial bowel diseases [127]. Anthocyanidins, for instance, are promising anti-inflammatory and antioxidant flavonoids. A previous study demonstrated that ulcerative colitis patients who were giving an anthocyanidin extract daily for 9 weeks show high improvement [128]. Epigallocatechin gallate (present in green tea, nuts, pomegranates, and berries) has shown anti-inflammatory against microbial bowel disease and gut microbiome revival abilities [129,130]. Resveratrol has also been shown to have a protecting role in gastric inflammation and reduce the progression to colorectal cancer. Few species of Lamiaceae, have been linked with a reduction of in-
flammatory bowel disease [131]. The anti-inflammatory effect of Lavender was exerted through the nuclear kappa factor signalling pathway [131,132]. Moringa is one of the well-studied plants with a big number of identified phytochemicals, vitamins, minerals (sodium, potassium, magnesium, phosphorus, iron, zinc, copper, calcium, and manganese), proteins, and amino acids [133]. *Moringa oleifera* leaves contain plenty of antimicrobial molecules natural antioxidant with more moringa based-supplements available in the market [134]. A recent study used in silico-peptide docking with phytochemicals extracted from *M. oleifera*, proposed that hydroxychloroquine, kaempferol, and anthraquinone can be used in clinical trials as effective antiviral agents against COVID-19 [135]. Basil leave callus on the other hand revealed recently antioxidant activity linked to the production of chicoric acid and rosmarinic acid by the inhibition of reactive oxygen species (ROS) [136]. Cinnamon has been used to relieve many disease complications of humans [137]. Recent works show cinnamon’s ability to produce compounds with root canal disinfection capabilities in dental applications [138]. Recent research proposed antiviral phytochemicals compounds extracted from Cinnamon against the main protease enzyme of COVID-19 and to reveal the in silico activity against the virus [139]. However, in vitro studies have to be achieved performed 1st to build upon such claims [140]. Garlic and its phyto-components strongly inhibit angiotensin-converting enzyme activity as well as alter the production of Prostaglandin E2 and thromboxane to alter the vascular function to control blood pressure [141]. Also, garlic was shown to display strong anti-inflammatory and antioxidant activities thereby lowering the vascular oxidative stress and exhibiting antihypertensive activity [142,143]. Recent investigation on active compounds found in garlic essential oil was identified by mass spectrometry analysis with potential coronavirus resistance specifically against Angiotensin-converting enzyme protein and the main protease PDB6LU7 of COVID-19 [144]. One of the commonly phenolic acids present in a wide variety of plants such as coffee caffeic acid [145]. A recent study indicates that there is a powerful in vitro antagonist activity between human coronavirus NL63 and caffeic acid resulting in stopping the interaction of the virus with human angiotensin-converting enzyme 2 [146]. Research on the antioxidant activity of equisetum debile extracts ethyl acetate extract was suggested as the most attractive ingredients for functional food and nutraceuticals because of the high inhibitory activity against IL-6 secretion, 5α-reductase, and lipid peroxidation inhibition [147]. A study on the plant data revealed the presence of beneficial individual phenolic and sugar compounds. Antioxidants such as caffeicacid, gallic acid, and 3-coumaric acid were present. Surpassingly, not many nutraceuticals/supplement products developed yet from the plant [148]. Therefore, as high antioxidant and promising nutritional components, *Phoenix dactylifera* can be well adopted as source of nutraceuticals product which will have respective share of their market value [149]. *Citrus sinensis* (sweet orange) contains fats, proteins, carbohydrates (soluble sugars) [150]. Other active ingredients include carotenoids, and flavanones and hesperidin [151]. In sweet orange, there more than 60 mg of hesperidin in 100 mL of fruit juice [152]. Recent research showed interestingly antiviral activity for hesperidin against viral protease. Despite coronavirus sequence variations, the main protease backbone structure and active site conformation are conserved, it is proposed that the inhibitory effect of hesperidin previously detected in SARS virus can be confirmed also in SARS-CoV-2 [153].

A study showed that the use of polyphenol extracted from *Camellia sinensis* (Black tea) results in increased Bacteroidetes compared to Firmicutes in a simulated intestinal microbiota [154]. Cardamom showed anti-inflammatory ability by acting as a cytokines inhibition agent [155,156]. *Curcuma longa* root (Turmeric) is excessively used as a major condiment in Asian food as well as a traditional therapy in Indian and Chinese traditional medicine. Curcuminoids are metabolized by colonic normal flora, changing bacterial populations and their metabolic activity [157]. Piperine that present in *Piper nigrum* L. (black pepper) is considered a high bioactive compound with anti-inflammatory, antibacterial, and antioxidant properties, also composed of 40% nutritional fibre; these characteristics make this species a considerable prebiotic candidate [158]. Low molecular weight phenolic
metabolism of white bran catalyzed by the contents of gut microbiota, such as *Eubacterium* spp., *Lactobacillus* spp., *Escherichia coli*, *Bacteroides* spp., and *Bifidobacterium* spp., which may exhibit health effects on the host [159]. Sago starch is one of the remarkable sources of functional foods, that extracted from *Metroxylon sagu* (palm) which is considered a Southeast Asia indigenous [160]. It is called “lemantak” in its native form and resistant starches compose about 60% of its contents. In vivo and in vitro studies have proved the significance of sago starch to increase numbers of *Bifidobacterium* and *Lactobacillus* spp. with a high potential to develop gut health supplements [161]. The role of resistant starch as a functional food had been demonstrated due to its effects on insulin responses, glycaemic index, and satiety [162]. Lentils are another proposed prebiotic crop that grown abundantly in Asia, especially in India, because 13% of its content is nondigestible carbohydrate [163]. Some plants can be utilized both as whole foods added to the diet with monitoring the potential prebiotic activity and a source of prebiotic compounds. Kiwifruit is considered a rich source of insoluble and soluble fibre, composed of cellulose, polysaccharides, and hemicellulose [164,165]. Many in vivo and in vitro studies detected the capability of the whole, fresh kiwifruit to generate metabolites such as short-chain fatty acids (SCFA) and the modulation of the colonic microbiota [166,167]. Similarly, β-glucan, a nonstarch water-soluble polysaccharide found in cereal plants such as barley and oats, exerts resistance to digestion in the upper mammalian gastrointestinal tract and then is fermented in the large intestine by gut microbiota. β-glucan comprised 2–20% and 3–8% in barley and oats respectively while barley β-glucan contain lower water-soluble fraction (65%) compared with oats (80%) [168]. High solubility levels make oats bran a preferred source of β-glucan for gastrointestinal microbiota fermentation. In vivo and in vitro studies suggest that oat β-glucan could selectively enhance the growth of bifidobacteria and lactobacilli, causing the production of lactic and acetic acids [169]. These characteristics qualify oats as a candidate for prebiotic development [170]. Ginger is a famous plant with its medicinal value that has been used for a long time as a therapeutic plant, metabolites isolate from ginger revealed antioxidant, antimicrobial, and anticancer which were discussed in detail recently [171].

**Future Prospects of Nutraceuticals Derived from Plants**

Plant-derived molecules have been recognized based on the presence of different biological characteristics which contribute to their positive effect on human health. Classes of phytochemicals such as saponins, flavonoids, alkaloids, tannins, terpenoids, steroids, and glycosides are frequently isolated from different plant organs with an important role in the maintenance of human health hence they can be used in functional food and supplement development. Plant-derived nutraceuticals could be further used to improve human health, treating chronic diseases, and support other human metabolomics activities. The interest in plant nutraceuticals-related research gaining more attention due to the therapeutic effects especially in the pandemic era considering the supplement manufacturer’s interest to replace the synthetic component with natural plant-based molecules due to the high demand for natural products. Increasing research in the field of safety and effectiveness of these novel products encourages further investment in the application and technology. Promising molecular biology technologies such as nutrigenomics, nutriproteomics, and nutrigenetics are highly encouraged in nutraceutical development research. The innovation in plant-based industries technology might also participate in the further progress in developing food products that can enhance optimum human health.

**6. Improving the Yields of Nutraceuticals Using Fungal Elicitors**

A common issue in the production of natural compounds—nutraceuticals included—is production time and costs. Extraction of nutraceuticals is usually resource-intensive due to multiple solvent extraction processes. This problem can be greatly alleviated by the employment of genetic and metabolic engineering techniques [172]. While plants are also sources of nutraceuticals, it was found that plant cell cultures have increased yields after coculturing with their respective native endophytic fungi. Therefore, besides fungi
being the source of the nutraceutical and therapeutical products, fungi can also be used as elicitors that can influence metabolic changes in other organisms for enhancing the yields of the intended target product. For example, the production of paclitaxel increased when plant cell cultures of *Taxus chinensis* were cocultured with *Aspergillus niger* [173]. Other fungal elicitors have been studied in the production of other compounds such as glycyrrhizin [174] and ajmalicine [175]. A more recent example related to nutraceutical elicitors is the use of fungal suspension homogenate of the pathogenic fungi, *Alternaria panax* Whetz. as an elicitor for the mass and rapid production of *Panax ginseng* [176]. Fungal elicitors have also been studied to increase the *P. ginseng* root’s growth. In a recent study, *Penicillium* sp. YJM-2013 activated the expression of transcription factors and by this promoted the increment in ginsenosides production [177]. From this observation, it is important to take into consideration the role of fungi that is not only commonly used as a source of nutraceutical products but also as a mediator in eliciting nutraceutical production in plants.

7. Issues in Nutraceutical Efficacy

Concerns have been raised regarding the efficacy of nutraceuticals. While nutraceuticals are found in many commonly consumed foods, their beneficial effects may not translate to any meaningful effect. This includes nutraceuticals that have been sold as a supplement. Optimising dosage and delivery systems is vital for the efficacy of nutraceuticals. More studies need to be carried out specifically to find out whether long-term, frequent dosing of nutraceuticals has an actual positive health impact. Due to the chemical complexity of those supplements, it can be difficult to pinpoint the exact nutrient responsible for the acclaimed health benefits. It is also possible that certain health benefits are garnered not by one single nutrient but by a group of nutrients with intertwining interactions.

8. Conclusions and Future Perspective of Nutraceuticals Development

The rapid population growth and the growth in health challenges due to the rising of different diseases made the availability of health-related nutraceuticals or supplements from natural sources an urgent necessity. The need for nutraceuticals may further increase with the changing in the demographic with an elevated trend in an ageing population which will lead to higher incidences of chronic diseases. It is also projected that the workforce will consist of more and more people above the age of 60 [178]. Common diseases associated with ageing are hypertension, congestive heart failure, dementia, osteoporosis, breathing problems, cataract, diabetes, and pathologies associated with decreased immunity [179]. Invertebrate models have shown that certain nutraceuticals can be beneficial in promoting healthy ageing, reducing cancer incidence, and reducing inflammation [180]. The field of nutraceuticals can be advanced from many perspectives. Production-wise, the costs and time can be greatly reduced through enzyme engineering, coupled with gene/protein discovery and characterisation to avoid purely synthetic supplement manufacturing [181]. The advancement in DNA sequencing and gene-editing technologies also opens up avenues for biosynthetic pathway engineering, reducing the number of steps for the synthesis of nutraceuticals [182]. For peptide- and protein-based nutraceuticals, better artificial intelligence and deep-learning technologies can help better understand protein-folding mechanisms in engineering more potent nutraceuticals [183]. Increasing the bioavailability of nutraceuticals is also an active area of research. Due to the diverse chemical nature of nutraceuticals, their bioavailability profiles differ due to the difference in composition and chemical structure [184]. Developing better delivery systems for nutraceuticals to survive the harsh acidic environments of the stomach and to increase absorption through the intestinal wall is one way to increase bioavailability. Specialised nanodelivery systems have been used for the delivery of nutraceuticals for cancer treatment [185]. These function by increasing the cellular uptake of nutraceuticals through mediated endocytosis and other similar mechanisms [186].
Author Contributions: Conceptualization, J.R.A.-O.; writing—original draft preparation J.R.A.-O., E.I.A.-K., K.H.A., B.S.A.-T., D.H.-S.W., H.H., N.N.J. and N.S.A.; figures conceptualization and preparation, J.R.A.-O. and E.I.A.-K. All authors have read and agreed to the published version of the manuscript.

Funding: This work received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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