Hindawi
Advances in Pharmacological Sciences
Volume 2019, Article ID 6908716, 5 pages
https://doi.org/10.1155/2019/6908716

Review Article

Nutraceuticals Inspiring the Current Therapy for Lifestyle Diseases

Silpi Chanda,[1] **Raj Kumar Tiwari**,[2] **Arun Kumar**,[2] **and Kuldeep Singh**[3]

[1]*Pharmacy Institute, NIET, Greater Noida, Uttar Pradesh, India*
[2]*Sanskar College of Pharmacy & Research, Ghaziabad, Uttar Pradesh, India*
[3]*Department of Chemistry, MMEC, Maharishi Markandeshwar (Deemed to be University), Mullana, Haryana, India*

Correspondence should be addressed to Silpi Chanda; only_shilpi@yahoo.com

Received 31 August 2018; Accepted 16 December 2018; Published 14 January 2019

Guest Editor: Azhar Rasul

Nutraceuticals are the pharmaceutically blended products that possess both nutritional as well as the medicinal value. Such a product is designed to improve the physical health, fight against day-to-day challenges such as stress, increase longevity, etc. Nowadays, emphasis is given to those herbs which are used as food and medicine due to its greater acceptance. Due to dynamic action, the popularity of nutraceuticals among people as well as healthcare providers has been increased over medicines and health supplements. This review documents herbs with a wide variety of therapeutic values such as immunity booster, antidiabetic, anticancer, antimicrobial, and gastroprotective. These herbs could be better options to formulate as nutraceuticals. Several nutraceuticals are described based on their availability as food, chemical nature, and mechanism of action.

1. Introduction

Hippocrates (460–377 BC), the father of modern medicine, almost 2500 years back established the relation of food and its importance for the treatment of various ailments in a very classical way optimizing various benefits [1]. Nutraceutical is composed of two words: nutrient and pharmaceutical. It is a food supplement that has a vital role in maintaining the healthy body and provides necessary supplements required for various metabolic processes to regulate body functions and thus prevents the body from diseases [1]. There is a vast cornucopia of herbs and foods which stimulate support and nourish our body system. Some have been used by different traditional systems of several countries and are now being evaluated by modern research. Use of pharmaceutical antibiotic would build up tolerances which make it ineffective in the long run. It is a better way to choose such herbs in our daily life, which would be not only capable of normalizing our body functions (even in disease condition) but also preventive and nutritive, and they also boost our immune system. An herb may not act as precisely as an antibiotic but can act as antibacterial (even antiviral) by boosting our body's own defense mechanism. To feel as a healthy well-being, one of the prominent approaches is to stay away from stress and other lifestyle diseases. The following are some examples of herbs used as food as well as medicine during infection, to boost the immune system or even in several other illnesses.

Astragalus membranaceus (Fabaceae) is a traditional Chinese herb. It is an extremely versatile and powerful immune enhancer antioxidant and also has hepatoprotective activity [2]. It also showed antidiabetic [3] and anticancer activity [4].

Triphala is one of the most revered tonics in Ayurveda. It is a combination of three important herbs, namely, *Terminalia bellerica* (Combretaceae), *Terminalia chebula* (Combretaceae), and *Emblica officinalis* (Phyllanthaceae). All these herbs act as a nutritive tonic. Triphala benefits almost all organs/systems of our body, particularly skin, liver, eyes, and digestive and respiratory system. The most well-known therapeutic uses are immunomodulating, antibacterial, antimutagenic, and adaptogenic, etc., which are well established [5, 6].

The northeast region of India is very rich in flora and fauna. The tribal people of the northeast region follow the

principle of Hippocrates. They use their food as medicine. *Paederia foetida* (Rubiaceae) is one of the tribal plants. A research study established its gastroprotective activity and antioxidant activity [7].

The yellow powder (turmeric) from South Asia, a curry ingredient, is well known for its preventive action. It is very active against various types of bacteria, fungus, virus, and also parasite. It is a potent inhibitor of HIV [8, 9]. Asian ginseng, probably the most westernized herb, is used as a tonic. It has been popular to promote immunity [10]. The most well-known ginseng is *Panax* ginseng, and it has protective effects in neurological disorders [11].

According to Ayurveda, garlic, onion, and ginger are the basis of all healing food recipes. Garlic is one of the most widely used natural health products. These are considered as food, spice, and medicine [12].

It has been the subject of intensive study for its possible effects against heart disease and cancer [13–15]. It increases the general immune system activity. Studies have also shown to be effective in treating AIDS and antimicrobial [16–18].

2. Classification of Nutraceuticals

2.1. Nutraceuticals Based on Food Availability

2.1.1. Traditional Nutraceuticals. These classes are generally sourced directly from nature, without any changes in the natural form. Various constituents such as lycopene in tomatoes, omega-3 fatty acids in salmon, or saponins in soy are available and consumed for different health benefits. Further, various types of traditional nutraceuticals are as follows:

(i) Chemical constituents

(a) Nutrients
(b) Herbals
(c) Phytochemicals

(ii) Probiotic microorganisms

(iii) Nutraceutical enzymes

(1) Chemical Constituents

(a) Nutrients

Primary metabolites such as amino acids, various vitamins, and fatty acids had well-defined functions in various metabolic pathways. Plant and animal products along with vitamin have many health benefits and are helpful in curing diseases related to heart, kidney, lungs, etc.

Natural products obtained from plants are beneficial in treating various disorders such as brittle bones and low hemoglobin count, and they provide strength to bones and muscles, help in neuron transmission, and maintain rhythm of heart muscles. Fatty acids, omega-3 PUFAs present in salmon, had influenced the overall inflammatory response and brain function and reduced cholesterol in the arteries.

(b) Herbals

Nutraceuticals along with herbs had an excellent impact on prevention of various chronic diseases to make life better. Salicin present in the willow bark (*Salix nigra*) had been proved for anti-inflammatory, analgesic, antipyretic, astringent, and antiarthritic response clinically. Flavonoids such as psoralen present in parsley (*Petroselinum crispum*) is useful in diuretic, carminative, and antipyretic.

Peppermint (*Mentha piperita*) contains various terpenoids especially menthol, a bioactive constituent, and cures cold and flu. Tannin contents of lavender (*Lavandula angustifolia*) help releasing stress and blood pressure and are useful for lung disorders such as asthma [19].

(c) Phytochemicals

They are mainly classified on the basis of phytochemicals. Carotenoids (isoprenoids) are present in vegetables, enhancing immune system, mainly killer cells accounting for an anticancer response. Legumes (chickpeas and soybeans), grains, and palm oil contain noncarotenoids, which remove cholesterol and are anticarcinogenic.

Flavonoids, a class of secondary metabolites, which are present in most of the plants, having more than 4000 varieties had been proven clinically for preventing various diseases such as cancer, diabetes, heart diseases, and kidney problem through its antioxidant properties and their bioactive components [20].

Phenolic acids are the largest class of secondary metabolites, mainly found in citrus fruits and red wine, and have the antioxidant activity of scavenging the free radicals produced as a result of various metabolic pathways such as protein, carbohydrate, and fat. They also have anticancer and antitumour activity.

One of the classical examples is curcumin (turmeric), used as phytochemicals in most of the kitchen.

(2) Probiotic Microorganisms. Metchnikoff coined the term "probiotic." Its application is well boosted in modern medicine due to its ability of making the intestine more friendly for processes such as absorption and metabolism. Probiotics are very important to make life smoother by removing the toxic flora of the intestine and maintaining a friendly environment, for example, useful consumption of *Bacillus bulgaricus* [21]. Currently various probiotic products are available in the market with adequate nutrients to counter various pathogens so that a number of ailments related to human body can be treated.

The antimicrobial property usually had an altering impact on the microflora, making the epithelial tissues more grounded and making a situation for the supplements for better retention, which is required by the body. Moreover, probiotics are very useful in lactose intolerance by the production of related enzymes (*ß*-galactosidase) and hydrolyzing lactose into its sugar components [22].

(3) Nutraceutical Enzymes. Enzymes are proteinous in structure, are produced by the cell, and act as a biocatalyst. It eases the metabolic rate and fastens the life process. The medical problem mainly related to the GIT whether GERD (gastroesophageal reflux disease) or constipation or diarrhoea or ulcerative colitis could be treated with enzyme supplements. The enzyme could be a better option for diabetic patients. Nowadays, enzyme therapies are used for

Table 1: Natural nutraceuticals along with mechanism.

Nutraceuticals	Mechanism/activity
Proanthocyanidin (chestnut fruits)	Inhibit IL-8 secretion by impairing NF-kappa-B signaling [24]
Fish-based diet	Severe osteoarthritis and hip and elbow dysplasia [25]
Curcuma extract	Decrease the level of PSA for prostate cancer [26]
Supplementation of live yeast fostered	Regulate inflammation and epithelial barrier in the rumen and express DFEB1 coding for an antimicrobial peptide [27]
Inulin-type friction dietary fiber	Immune responses against hepatitis-B [28]
Bovine milk-derived oligosaccharide and *B. lactis*	Modulate gut microbiota and immune system [29]
Lipid-based nutrient supplements	Prevent growth faltering in infants [30]
Partially hydrolyzed cow's milk proteins	Cow's milk allergy in children [31]
Lactic acid bacteria (LAB) probiotic	Endometrial inflammation and infection [32]
Lipid-based nutrient supplement (LNS)	Moderate acute malnutrition (MAM) [33]
Vitamin D supplementation	Extraskeletal benefits [34]
Neutral amino acid supplements	Optimize neurocognitive function [35]
Myo-inositol	Gestational diabetes [36]
Lactobacillus fermentum CRL1446	Enhances metabolism and oxidative parameters [37]
Dehydrozingerone and its dimer	Counteract the inflammation and oxidative stress [38]
25-Hydroxy vitamin D	Cognitive status in older adults [39]
Malic acid, a precursor of citrate	Antioxidant activity [40]
Combined omega-3 fatty acids	Prevents atrophy in AD-related brain [41]
Lactobacillus rhamnosus SP1	Insulin signaling and improves adult acne [42]
Omega-3 fatty acid ethyl esters	Breast cancer [43]
CoQ10 supplementation	Propofol inhibition on complex [44]
Omega-3 fatty acids and high-dose cholecalciferol	Type 1 diabetes [45]
Large neutral amino acid supplementation	Phenylketonuria (PKU) [46]
Low-fat yoghurt supplemented with a rooster comb extract	Muscle and joint function [47]
Lipid-based nutrient supplements	Home fortification in poor settings [48]
Cholecalciferol supplementation (HYPODD)	Arterial hypertension [49]
Omega-3 polyunsaturated fatty acid supplementation	Postmenopausal vascular disease [50]
Omega-3 fatty acids	Breast cancer prevention [51]
Myo-inositol supplementation	Gestational diabetes in obese pregnant women [52]

several rare diseases such as Gaucher disease, Hunter syndrome, Fabry disease, and Pompe disease. Although enzymes are produced by their own cells, microbial sources are preferred more over plant and animal sources as they are more economical.

2.1.2. Nontraditional Nutraceuticals. They are foods enriched with supplements or biotechnologically designed crops to boost the nutrients; for example, rice and broccoli are rich in β-carotene and vitamins, respectively. Food samples contain bioactive components which are engineered to produce products for human wellness. They are arranged as follows:

(1) Fortified Nutraceuticals. These types of nutraceuticals include breeding at the agriculture level or addition of compatible nutrients to the main ingredients such as minerals added to cereals, flour fortified with calcium, iron, and folic acid, and milk fortified with cholecalciferol commonly used for vitamin D deficiency [23].

(2) Recombinant Nutraceuticals. Biotechnology tools have been well applied through a fermentation process in various food materials such as cheese and bread to extract the enzyme useful for providing necessary nutrients at an optimum level.

2.2. Classification Based on Mechanism of Action. Nutraceuticals has been further classified in regard to specific therapeutic properties accounting for antimicrobial, anti-inflammatory, and antioxidant properties.

2.3. Classification Based on Chemical Nature. These types are classified depending upon their primary and secondary metabolite sources such as isoprenoid derivatives, phenolic substances, fatty acids, carbohydrates, and amino acid-based substances.

Different types of nutraceutical constituents of natural origin are described in Table 1. All the nutraceuticals are the resources of nature.

3. Conclusions

Natural products have been known for their therapeutic values for centuries. In the modern era, these substances have been used as an immunity booster; antidiabetic, anticancer, antimicrobial, and gastroprotective agents; and so

on. Therefore, these herbs could be better options to be formulated as nutraceuticals.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] C. Yapijakis, "Hippocrates of Kos, the father of clinical medicine, and Asclepiades of Bithynia, the father of molecular medicine. Review," *In Vivo*, vol. 23, no. 4, pp. 507–514, 2009.

[2] K. S. Zhao, C. Mancini, and G. Doria, "Enhancement of the immune response in mice by *Astragalus membranaceus* extracts," *Immunopharmacology*, vol. 20, no. 3, pp. 225–233, 1990.

[3] K. Agyemang, L. Han, E. Liu, Y. Zhang, T. Wang, and X. Gao, "Recent advances in *Astragalus membranaceus* anti-diabetic research: pharmacological effects of its phytochemical constituents," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 654643, 9 pages, 2013.

[4] C. Y. Wu, Y. Ke, Y. F. Zeng, Y. W. Zhang, and H. J. Yu, "Anticancer activity of Astragalus polysaccharide in human non-small cell lung cancer cells," *Cancer Cell International*, vol. 17, no. 1, p. 115, 2017.

[5] C. T. Peterson, K. Denniston, and D. Chopra, "Therapeutic uses of triphala in Ayurvedic medicine," *The Journal of Alternative and Complementary Medicine*, vol. 23, no. 8, pp. 607–614, 2017.

[6] P. Belapurkar, P. Goyal, and P. Tiwari-Barua, "Immunomodulatory effects of triphala and its individual constituents: a review," *Indian Journal of Pharmaceutical Sciences*, vol. 76, no. 6, pp. 467–475, 2014.

[7] S. Chanda, L. Deb, R. K. Tiwari, K. Singh, and S. Ahmad, "Gastroprotective mechanism of *Paederia foetida* Linn. (Rubiaceae)--a popular edible plant used by the tribal community of North-East India," *BMC Complementary and Alternative Medicine*, vol. 15, no. 1, p. 304, 2015.

[8] S. Z. Moghadamtousi, H. A. Kadir, P. Hassandarvish, H. Tajik, S. Abubakar, and K. Zandi, "A review on antibacterial, antiviral, and antifungal activity of curcumin," *BioMed Research International*, vol. 2014, Article ID 186864, 12 pages, 2014.

[9] S. Prasad and A. K. Tyagi, "Curcumin and its analogues: a potential natural compound against HIV infection and AIDS," *Food and Function*, vol. 6, no. 11, pp. 3412–3419, 2015.

[10] S.-W. Kang and H.-Y. Min, "Ginseng, the 'immunity boost': the effects of *Panax* ginseng on immune system," *Journal of Ginseng Research*, vol. 36, no. 4, pp. 354–368, 2012.

[11] W. Y. Ong, T. Farooqui, H. L. Koh, A. A. Farooqui, and E. A. Ling, "Protective effects of ginseng on neurological disorders," *Frontiers in Aging Neuroscience*, vol. 7, p. 129, 2015.

[12] S. Chanda, S. Kushwaha, and R. K. Tiwari, "Garlic as food, spice and medicine: as prospective," *Journal of Pharmacy Research*, vol. 4, no. 6, pp. 1857–1860, 2011.

[13] S. K. Banerjee and S. K. Maulik, "Effect of garlic on cardiovascular disorders: a review," *Nutrition Journal*, vol. 1, no. 1, 2002.

[14] H. L. Nicastro, S. A. Ross, and J. A. Milner, "Garlic and onions: their cancer prevention properties," *Cancer Prevention Research*, vol. 8, no. 3, pp. 181–189, 2015.

[15] A. Tsubura, Y.-C. Lai, M. Kuwata, N. Uehara, and K. Yoshizawa, "Anticancer effects of garlic and garlic-derived compounds for breast cancer control," *Anti-Cancer Agents in Medicinal Chemistry*, vol. 11, no. 3, pp. 249–253, 2011.

[16] G. Schäfer and C. Kaschula, "The immunomodulation and anti-inflammatory effects of garlic organosulfur compounds in cancer chemoprevention," *Anti-Cancer Agents in Medicinal Chemistry*, vol. 14, no. 2, pp. 233–240, 2014.

[17] C. Liu, C. Wang, E. Robison et al., "Short-term garlic supplementation and highly active antiretroviral treatment adherence, CD4+ cell counts, and human immunodeficiency virus viral load," *Alternative Therapies in Health and Medicine*, vol. 18, no. 1, pp. 18–22, 2012.

[18] S. Ankri and D. Mirelman, "Antimicrobial properties of allicin from garlic," *Microbes and Infection*, vol. 1, no. 2, pp. 125–129, 1999.

[19] S. D. Ehrlich, *(Willow Bark), Private Practice Specializing in Complementary and Alternative Medicine, Review*, VeriMed Healthcare Network, Phoenix, AZ, USA, 2008.

[20] S. D. Ehrlich, *Peppermint (Mentha Piperita), Private Practice Specializing in Complementary and Alternative Medicine, Review*, VeriMed Healthcare Network, Phoenix, AZ, USA, 2009.

[21] W. H. Holzapfel, P. Haberer, R. Geisen, J. Björkroth, and U. Schillinger, "Taxonomy and important features of probiotic microorganisms in food and nutrition," *The American Journal of Clinical Nutrition*, vol. 73, no. 2, pp. 365S–373S, 2001.

[22] M. Pineiro and C. Stanton, "Probiotic bacteria: legislative framework-requirements to evidence basis," *The Journal of Nutrition*, vol. 137, no. 3, pp. 850S–853S, 2007.

[23] C. F. Casey, D. C. Slawson, and L. R. Neal, "Vitamin D supplementation in infants, children, and adolescents," *American Family Physician*, vol. 81, no. 6, pp. 745–748, 2010.

[24] E. Sangiovanni, S. Piazza, U. Vrhovsek et al., "A bio-guided approach for the development of a chestnut-based proanthocyanidin-enriched nutraceutical with potential anti-gastritis properties," *Pharmacological Research*, vol. 134, pp. 145–155, 2018.

[25] S. Manfredi, F. Di Ianni, N. Di Girolamo et al., "Effect of a commercially available fish-based dog food enriched with nutraceuticals on hip and elbow dysplasia in growing Labrador retrievers," *Canadian Journal of Veterinary Research*, vol. 82, no. 2, pp. 154–158, 2018.

[26] A. Fabiani, C. Morosetti, A. Filosa et al., "Effect on prostatic specific antigen by a short time treatment with a Curcuma extract: a real life experience and implications for prostate biopsy," *Archivio Italiano di Urologia e Andrologia*, vol. 90, no. 2, pp. 107–111, 2018.

[27] A. Bach, I. Guasch, G. Elcoso et al., "Changes in gene expression in the rumen and colon epithelia during the dry period through lactation of dairy cows and effects of live yeast supplementation," *Journal of Dairy Science*, vol. 101, no. 3, pp. 2631–2640, 2018.

[28] L. M. Vogt, M. E. Elderman, T. Borghuis, B. J. De Haan, M. M. Faas, and P. De Vos, "Chain length-dependent effects of inulin-type fructan dietary fiber on human systemic immune responses against hepatitis-B," *Molecular Nutrition & Food Research*, vol. 61, no. 10, article 1700171, 2017.

[29] M. Radke, J.-C. Picaud, A. Loui et al., "Starter formula enriched in prebiotics and probiotics ensures normal growth of infants and promotes gut health: a randomized clinical trial," *Pediatric Research*, vol. 81, no. 4, pp. 622–631, 2016.

[30] T. M. Matsungo, H. S. Kruger, C. M. Smuts, and M. Faber, "Lipid-based nutrient supplements and linear growth in

children under 2 years: a review," in *Proceedings of the Nutrition Society*, vol. 76, no. 4, pp. 580–588, 2017.

[31] M. B. G. Kiewiet, B. Van Esch, J. Garssen, M. M. Faas, and P. De Vos, "Partially hydrolyzed whey proteins prevent clinical symptoms in a cow's milk allergy mouse model and enhance regulatory T and B cell frequencies," *Molecular Nutrition & Food Research*, vol. 61, no. 11, article 1700340, 2017.

[32] S. Genís, A. Sánchez-Chardi, À. Bach, F. Fàbregas, and A. Arís, "A combination of lactic acid bacteria regulates *Escherichia coli* infection and inflammation of the bovine endometrium," *Journal of Dairy Science*, vol. 100, no. 1, pp. 479–492, 2017.

[33] C. Fabiansen, C. W. Yaméogo, A.-S. Iuel-Brockdorf et al., "Effectiveness of food supplements in increasing fat-free tissue accretion in children with moderate acute malnutrition: a randomised 2 × 2 × 3 factorial trial in Burkina Faso," *PLoS Medicine*, vol. 14, no. 9, article e1002387, 2017.

[34] M. Caprio, M. Infante, M. Calanchini, C. Mammi, and A. Fabbri, "Vitamin D: not just the bone. Evidence for beneficial pleiotropic extraskeletal effects," *Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity*, vol. 22, no. 1, pp. 27–41, 2016.

[35] D. van Vliet, V. M. Bruinenberg, P. N. Mazzola et al., "Therapeutic brain modulation with targeted large neutral amino acid supplements in the Pah-enu2 phenylketonuria mouse model," *The American Journal of Clinical Nutrition*, vol. 104, no. 5, pp. 1292–1300, 2016.

[36] A. Santamaria, A. Di Benedetto, E. Petrella et al., "Myo-inositol may prevent gestational diabetes onset in overweight women: a randomized, controlled trial," *The Journal of Maternal-Fetal & Neonatal Medicine*, vol. 29, no. 14, pp. 2245–2247, 2016.

[37] M. Russo, E. Fabersani, M. C. Abeijon-Mukdsi et al., "Lactobacillus fermentum CRL1446 ameliorates oxidative and metabolic parameters by increasing intestinal feruloyl esterase activity and modulating microbiota in caloric-restricted mice," *Nutrients*, vol. 8, no. 7, 415 pages, 2016.

[38] E. Profumo, B. Buttari, D. D'arcangelo et al., "The nutraceutical dehydrozingerone and its dimer counteract inflammation- and oxidative stress-induced dysfunction of in vitro cultured human endothelial cells: a novel perspective for the prevention and therapy of atherosclerosis," *Oxidative Medicine and Cellular Longevity*, vol. 2016, Article ID 1246485, 12 pages, 2016.

[39] C. Manzo, A. Castagna, E. Palummeri et al., "[Relationship between 25-hydroxy vitamin D and cognitive status in older adults: the COGNIDAGE study]," *Recenti Progressi in Medicina*, vol. 107, no. 2, pp. 75–83, 2016.

[40] R. Manfredini, A. De Giorgi, A. Storari, and F. Fabbian, "Pears and renal stones: possible weapon for prevention? A comprehensive narrative review," *European Review for Medical and Pharmacological Sciences*, vol. 20, no. 3, pp. 414–425, 2016.

[41] T. Köbe, A. V. Witte, A. Schnelle et al., "Combined omega-3 fatty acids, aerobic exercise and cognitive stimulation prevents decline in gray matter volume of the frontal, parietal and cingulate cortex in patients with mild cognitive impairment," *Neuroimage*, vol. 131, pp. 226–238, 2016.

[42] G. Fabbrocini, M. Bertona, Ó. Picazo, H. Pareja-Galeano, G. Monfrecola, and E. Emanuele, "Supplementation with Lactobacillus rhamnosus SP1 normalises skin expression of genes implicated in insulin signalling and improves adult acne," *Beneficial Microbes*, vol. 7, no. 5, pp. 625–630, 2016.

[43] C. H. Chen, C. Fabian, S. Hursting, L. A. Degraffenried, and L. A. deGraffenried, "Breast cancer genetic and molecular subtype impacts response to omega-3 fatty acid ethyl esters," *Nutrition and Cancer*, vol. 68, no. 6, pp. 1021–1033, 2016.

[44] C. Bergamini, N. Moruzzi, F. Volta et al., "Role of mitochondrial complex I and protective effect of CoQ10 supplementation in propofol induced cytotoxicity," *Journal of Bioenergetics and Biomembranes*, vol. 48, no. 4, pp. 413–423, 2016.

[45] D. A. Baidal, C. Ricordi, M. Garcia-Contreras, A. Sonnino, and A. Fabbri, "Combination high-dose omega-3 fatty acids and high-dose cholecalciferol in new onset type 1 diabetes: a potential role in preservation of beta-cell mass," *European Review for Medical and Pharmacological Sciences*, vol. 20, no. 15, pp. 3313–3318, 2016.

[46] D. van Vliet, V. M. Bruinenberg, P. N. Mazzola et al., "Large neutral amino acid supplementation exerts its effect through three synergistic mechanisms: proof of principle in phenylketonuria mice," *PLoS One*, vol. 10, no. 12, Article ID e0143833, 2015.

[47] R. Solà, R.-M. Valls, I. Martorell et al., "A low-fat yoghurt supplemented with a rooster comb extract on muscle joint function in adults with mild knee pain: a randomized, double blind, parallel, placebo-controlled, clinical trial of efficacy," *Food and Function*, vol. 6, no. 11, pp. 3531–3539, 2015.

[48] M. Rothman, C. Berti, C. M. Smuts, M. Faber, and N. Covic, "Acceptability of novel small-quantity lipid-based nutrient supplements for complementary feeding in a peri-urban South African community," *Food and Nutrition Bulletin*, vol. 36, no. 4, pp. 455–466, 2015.

[49] D. Rendina, R. Ippolito, L. D'Elia et al., "Hypovitaminosis D and organ damage in patients with arterial hypertension: a multicenter double blind randomised controlled trial of cholecalciferol supplementation (HYPODD)," *High Blood Pressure and Cardiovascular Prevention*, vol. 22, no. 2, pp. 135–142, 2015.

[50] P. Losurdo, A. Grillo, E. Panizon et al., "Baroreflex sensitivity and central hemodynamics after omega-3 polyunsaturated fatty acids supplementation in an animal model of menopause," *Vascular Pharmacology*, vol. 71, pp. 65–69, 2015.

[51] C. J. Fabian, B. F. Kimler, and S. D. Hursting, "Omega-3 fatty acids for breast cancer prevention and survivorship," *Breast Cancer Research*, vol. 17, no. 1, 2015.

[52] R. D'anna, A. Di Benedetto, A. Scilipoti et al., "Myo-inositol supplementation for prevention of gestational diabetes in obese pregnant women: a randomized controlled trial," *Obstetrics & Gynecology*, vol. 126, no. 2, pp. 310–315, 2015.