e-ISSN:2320-1215
p-ISSN:2322-0112

Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences

Nutraceuticals: An Imperative to Wellness

Pravin Shende[1,2]*, Drashti Desai[1] and Gaud RS[1]

[1]Department of Chemistry IFM, University of Torino, Italy

[2]SPP-School of Pharmacy and Technology Management, SVKM'S NMIMS, Vile Parle, India

Review Article

Received date: 23/01/2016

Accepted date: 25/03/2016

Published date: 30/03/2016

***For Correspondence**

Pravin Shende, Department of Chemistry IFM and Department of Science and Technology of Pharmaceutics, University of Torino, Via P. Giuria 9, Torino, Italy, Tel: +91-22-42332000.

E-mail: shendepravin94@gmail.com

Keywords: Nutraceutical, cancer, anti-oxidant, proliferation, apoptosis, tumour

Abbreviations: EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid, CSC: Cancer stem cells, EMT: Epithelial mesenchymal transition, EGF-R: Epidermal growth factor receptor, AHCC: Active hexose correlated compound, PEITC: Phenethyl isothiocyanate, NK cells: Natural killer cells, CoQ10: Coenzyme Q10, ROS: Reactive oxidative species, RNS: Reactive nitrogen species, LDL: Low density lipoprotein, COX-2: Cyclo-oxygenase 2, VEGF: Vascular endothelial growth factor, IL: Interleukin, LPO: Lipid peroxidation

ABSTRACT

Nutraceuticals have received considerable attention due to their speculative safety, potential nutritive and therapeutic effects. They are alternative to modern medicines and also provide healthy living. To avoid side effects associated with medicines, live longer expectancy and increase the health value of our diet, nutraceuticals are being preferred. They possess numerous therapeutic benefits like anti-obesity, immune enhancement, natural antioxidant, cardiovascular effects, anti-diabetic, anti-inflammatory effects, etc. Major constituents of nutraceuticals are nutrients, herbals and dietary supplements which help to maintain health, function against various diseases and ensure better quality of life. The aim of this article is to provide the current knowledge about the application of various nutraceuticals in different diseases.

INTRODUCTION

Nutraceuticals have been received considerable attention due to their speculative safety, potential nutritional and therapeutic effects. Present day, exploration and exploitation of disease fighting properties of phytochemicals are found in both food and non-food plants which has created a renaissance in human health and nutrition research. However, it has become a social issue as food composition has been scientifically proven to avoid lifestyle-related diseases. Based on assumptions like, to avoid side effects associated with medicines, live longer and increase the health value of our diet, Nutraceuticals are being preferred [1].

Nutraceutical was derived from the words "nutrition" and "pharmaceutical", by Stephen DeFelice L in 1989. They are sometimes also termed as "functional foods". This term is applicable to the products that range from isolated nutrients, herbal products and dietary supplements, specific diets and processed foods such as beverages, soups and cereals. Functional foods or nutrients are foods that have one or more compounds with biochemical and physiological functions beneficial to individual's

health. When functional food consumed regularly they provide specific health-beneficial effects (i.e. healthier status or lowering the risk of diseases-beyond their nutritional properties). The definition for Nutraceuticals and functional foods are not yet clear. Functional food is defined as "any food or food ingredients that may provide a health benefit beyond the traditional nutrients it contains", by the US Institute of Medicine's Food and Nutrition Board [2,3].

Nutraceuticals are new generation of food or supplements which is a link between drug and food. In addition, Father of medicine, Hippocrates emphasized on the relation between the use of appropriate food for health and their therapeutic benefits about 2000 years ago [4].

Nutraceuticals can be classified [5] as follows:

A) On the basis of natural source:

Products can be obtained from-

1. Plants- e.g. Indole-3-carbinol(cabbage), lycopene (tomatoes)
2. Animals- e.g. EPA and DHA (fish oil)
3. Minerals- e.g. selenium, iodine
4. Microbes- e.g. Phycocyanobilin (Spirulina), lactobacillus (yogurt)

B) On the basis of pharmacological conditions, or as per chemical constituents of the products

C) Nutraceuticals on basis of below properties:

1. Potential Nutraceuticals (plant-foods polyphenols for diabetes)
2. Established Nutraceuticals (polyvitamins, omega-3 fatty acids)

Most widely used food sources as Nutraceuticals are of natural sources and can be categorized as follows:

1. Dietary fibre- e.g. beans, fruits
2. Probiotics- e.g. yogurt, dark chocolate
3. Prebiotics- e.g. Asparagus, almonds, apples
4. Polyunsaturated fatty acids- e.g. olive oil, walnuts
5. Antioxidants vitamins- e.g. vitamin C, vitamin E
6. Polyphenols- e.g. tea, coffee, spinach
1. Spices- e.g. garlic, turmeric

Nutraceuticals in cancer treatment

Among adults, the leading cause of death is cancer. Treatment of cancer involves expensive and traumatic use of drugs, surgery and irradiation. By change in lifestyle, reduction in the rates of cancer has been observed in recent times. Nutrition and foods are related to 30% of cancers. A deficiency of any of the 40 nutrients essential for life increases the risk of cancer has been proven in animal study [6].

A large subset of organ-specific subtypes are often too unique, histologically and genomically is represented in human cancers. One of the biggest challenges is the absence of validated therapeutic target(s), especially when evaluating the activity of natural agents (Nutraceuticals) for effective clinical management of human cancers [7].

Nutraceuticals have the ability to control and regulate the DNA damaging factors in cancer cells and DNA transcription in tumours. They possess numerous therapeutic benefits like anti-obesity, immunity enhancement, natural antioxidant, cardiovascular, Antidiabetic, and anti-inflammatory effects [8].

The possibility always exists for herbal-based dietary supplements (or Nutraceuticals) to antagonize therapy. The recent research has revealed that certain natural compounds of phytochemical origin has the potential to interfere with the late-stage cancer and altering the metastatic spread of cancer [9]. Certain foods or supplements has shown direct effect on cancer causing genes and make it harder for them to trigger cancer growth while others work to suppress cancer from developing by directly strengthening those genes [10].

A wide-range of phytochemicals has been acquired by plants to protect themselves for their own defence mechanism and from highly reactive oxygen species. In recent years, the demand for food products or supplements containing bioactive compounds and non-food products (i.e. dietetics and pharmaceuticals) has increased. There has been vast growth in the Nutraceutical industries to yield large number of phytochemicals containing Nutraceuticals with diverse composition and health claim due to increased application of phytochemicals in cancer care. Now to develop dietary supplements that can help to prevent

or delay the onset of nutrition-related diseases in a specific population groups is a big challenge. This will be possible when effective understanding of the molecular basis for the ways in which these components affect human health is studied [11].

Numerous Nutraceuticals have shown to regulate specific tumour suppressor genes and cancer driving genes. By utilizing a daily diet of Nutraceuticals specific to the entire possible gene combinations found in your particular form of cancer we can inhibit the over-expressed oncogenes unique to that form of cancer [10]. There are many cellular mediators involved to be manipulated from initial development of a single cell, to invasion, angiogenesis, proliferation and metastasis [12].

Promises of Nutraceuticals in cancer research:

1) Pleiotropic activity
2) Target Classical signaling Pathways (NF-kappa B, EGFR, AKT, etc.)
3) Target CSCs, miRNAs, EMT and deregulate epigenetic programing
4) Sensitize tumour cells to chemo/radio- therapy
5) Generally well tolerated
6) Parent structure usable for design of novel synthetic analogues for improving efficacy

Challenges of Nutraceuticals in cancer research:

1) Bioavailability: metabolized effectively, high systemic concentrations difficult to achieve
2) Insufficient pre-clinical data to advance combinational multi-agent therapy in clinical setting
3) Lower priority by pharmaceutical industry as they may not be patented **(Table 1).**

Table 1. Nutraceuticals which as widely used in cancer therapy.

Sr.no	Bioactive compound	Source	Mechanism	Ref. no.
	Eugenol	Cloves, basil, cinnamon	Inhibition of cell proliferation and suppression of NFκβ	9
	6-gingerol	Ginger	Acts as anti-inflammatory and as 5-HT3 receptor antagonist	9
	Diosgenin	Fenugreek	Supresses proliferation of cancerous cells and inhibits NFκβ activity	9
	Piperine	Pepper	Inhibition of cell proliferation	9
	AHCC	Mushroom	Immunomodulation and antitumor effects, strengthens and optimizes the capacity of the immune system, stimulates the immune surveillance system, inhibits the immune-suppressive factors produced by the cancer cells, stimulating the activity of the killer cells and increasing production of the cells that attack cancer.	13
	Astaxanthin	Salmon	Induces apoptosis and inhibits tumour invasion by decreasing extracellular matrix production.	14
	Caffeine Theophylline	Cacao, tea, coffee	It has the ability of offsetting the immunosuppressive activity of tumour-produced adenosine	13
	Limonene	Citrus oils from orange, lemon, mandarin, lime, and grapefruit	Has inhibitory effect on cell migration on cancerous cell, acts by inhibiting the activity of ornithine decarboxylase and causes anti-proliferation activity	15
	Allicin	Garlic	Induces apoptosis	15
	Indole-3-carbinol	Cabbage	It helps detox estrogen into favourable metabolite for some period of time. It induces apoptosis and cancer cell death at doses >400 µm and repress cancer cell growth at lower doses of about <200 µm.	14, 15,16
	Isothiocyanates Sulforaphane	Broccoli	It constitutes of PEITC that helps to prevent cancer.	15
	Beta-carotene, lycopene	Tomatoes	Induces apoptosis	15
	Epigallocatechin-3-gallate	Green tea	Inhibits proliferation of tumour cells, inhibits NFκβ , inhibits EGFR, inhibiting Her-2 receptor phosphorylation in breast carcinoma cells, induces apoptosis in estrogen receptor-(ER-) independent breast cancer cells, inhibits proteasome formation and glucose-regulated protein (GRP78) activity and insulin-like growth factor-I receptor (IGF-IR) and preventing invasion of tumours by inducing HMG-box transcription factor 1 (HBP1) transcriptional repressor.	9,15
	Quercetin	Black tea	Induces apoptosis	15
	Curcumin	Turmeric	It inhibits neurotensin-mediated interleukin-8 production and migration of HCT116 and affects cox-2 and IL-1, IL-6	9,14

	Capsaicin	Chilli peppers	Induces apoptosis by mediating TRPV6 by KB cells pathway	15
	Ellagic acid	Black berries, raspberry	It acts on NPC-BM1 cells and inhibits NF- kappB activation	15
	Gallic acid	Promegranate, nuts	It reduces cell proliferation and act on HTB-35 cells	15
	Pterostilbene	Blueberries and grapes	Helpful in breast cancer by inducing apoptosis.	15
	Resveratrol	Almonds, blueberries, grapes	It induces apoptosis and also reduces cell proliferation, supresses the growth of new blood vessels which leads to tumour growth	14,15
	Daidzein Genistein	Soy	Possess weak estrogen like activity and bind to ER- β receptors	9,15
	EPA (eicosapnetaenoic acid) and DHA (docosahexaenoic acid)	Fish Oil/ Omega 3	Tends to slow growth of tumour and shows a suppressive effect of fish oil on angiogenesis and decreases the expression of a key receptor in endothelial cells that makes them responsive to VEGF and also the potential to antagonize the role of Cox-2 by decreasing the production of Cox-2-derived prostanoids in cancer cells in angiogenic process. Fish oil has the ability to prevent cachexia.	13
	Boswellic acids	Salai Guggul	Inhibitors of the enzyme 5-LPO-and act on cancer growth factors by suppressing the production of leukotrienes	13
	Proteases (proteolytic enzymes), a digestive enzymes papain bromelain	Found in the stomach juices, pancreatic juices, and intestinal juices Papayas pineapples	They digest proteins and aiding digestion, proteolytic enzymes have analgesic, anti-inflammatory, antithrombotic, fibrinolytic, immune-modulating, and edema-reducing properties.	13
	Silymarin Silibinin	Milk thistle	Silymarin is a strong antioxidant, inhibits proliferation and causes apoptosis. Silibinin has the ability to suppress the NF-kappa B signalling pathway and reduces function of the epidermal growth factor receptor (EGF-R)	13
	Phycocyanobilin	Spirulina	It is a potent inhibitor of specific enzyme complex and acts by reducing oxidative stress and contains cell wall polysaccharides that stimulate immune-supportive dendritic cells. It also interferes with the angiogenic process.	13
	Cimetidine	antiulcer	It acts as immuno-supportive agent. It can reduce the risk of metastasis in many cancers. It also has immuno-stimulant activity for natural killer cells and cytotoxic T-cells.	13
	Coenzyme Q10	Meat, fish, eggs	It is a fat-soluble substance that possesses vitamin-like properties. It acts as an antioxidant by scavenging free radicals. CoQ10 defends against the onset of cancer and destroys existing cancer.	13
	Melatonin	Pineapples, bananas, oranges	It is an immuno-supportive agent and also stimulates the immune surveillance system. Its immuno-stimulant effect boosts the activity of natural killer cells and cytotoxic T-cells, they amplify their capacity to stimulate natural killer cells and cytotoxic T-cells. Melatonin boosts the ability of dendritic cells to produce interleukin-2, which helps cancer-attacking immune cells reach maturity.	13
	Salsalate	salicylic acid	It acts by supressing the signalling pathways activated by either NK-kappaB or Cox-2. High-dose salicylic acid are more likely to reflect inhibition of NF-kappB activation. Salicylic acid binds to and inhibits an enzyme that is usually required for NF-kappaB activation.	13
	Selenium	Oysters, Tuna fish	It is an immuno-supportive agent. It acts by increasing the capacity of stimulated NK cells and cytotoxic T-cells to express receptors for interleukin-2.	13
	Probiotics	Lactobacilli Bifidobacteria	They are immuno-supportive agents. These are enterically-coated capsules which introduce live healthy bacteria into the gastrointestinal tract. The bacteria that are chosen for this supplement include special strains of Lactobacilli and Bifidobacteria. They stimulate the immune system and activate NK cells and cytotoxic T-cells.	13

Nutraceuticals as anti-inflammatory

Nutraceuticals possessing anti-inflammatory activity are widely used as a complementary therapy for rheumatoid arthritis. Rheumatoid arthritis is a chronic inflammatory disease in which oxidative stress and inflammatory biomarkers are elevated. Synthetic drugs recommended for its treatment has severe side effects due to which new and safer approaches are being adopted for its treatment. Phenolic compounds, polyunsaturated fatty acids, phytosterols, tocopherols and carotenoids are rice sources of food containing anti-inflammatory activity. Examples of food containing those constituents are fish oil, fenugreek, coriander, tomato, carrot, green tea, walnut, etc [17].

Nutraceuticals acts as anti-inflammatory by numerous mechanisms like inhibiting the activation of NK-kappa B, down regulation of the overexpression of CAMs and enzymes like COX-2, phospholipase A2, etc, it also blocks the cover expression of pro-inflammatory cytokines such as IL-1, IL-6, and had the ability to scavenging ROS. The mechanism of as anti-inflammatory

nutraceuticals and non-steroidal anti-inflammatory drugs shares a common molecular targets. Both has the ability to inhibit the metastatic processes which lead to inflammation by activation of NK-kappa B, induction and up regulation of pro-inflammatory cytokines, production of ROS [18].

Nutraceuticals as antioxidants

Antioxidants are the substances that act on free radicals or their actions. It has been proven that higher intake of foods/ compounds with antioxidant can reduce various human mortalities. Some compounds that possess antioxidant activities are onion, garlic, turmeric, basil, etc [19].

Antioxidants (nutraceuticals) play a major role in neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, etc. Major components that possess antioxidant activities are flavonoid polyphenols - green tea, apples, non-flavonoid polyphenols- turmeric, grapes, phenolic acids or phenolic diterpenes- rosemary, organ sulfur compounds- broccoli, garlic, etc. They act by directly scavenging free radicals or increasing endogenous cellular antioxidant defenses. They act on ROS and RNS. It also prevents the formation of oxidized LDL [20].

Newer approaches include gene therapy that will produce more antioxidant in body and use of functional foods and novel biomolecules.

Nutraceuticals as anti-aging

In current scenario, there are increased cases of age related degenerative diseases and people are keener to shift towards better quality of life. Hence, the combination of cosmetics and food supplements is a new approach used to provide skin care treatment. It was assumed by Denham Harman in 1th 1950s that aging is a consequence of excessive production of free radicals. This results to cause damage to human body and even oxidative damage to DNA. Nutraceuticals useful as anti-aging acts similar as antioxidants. They also affect the processes that stimulate the production of reactive species; ROS, RON, etc.

Right selection of nutrients plays a vital role in the treatment of various diseases which can be achieved by proper diet containing intake of food supplements rich in vitamin E, folic acid, vitamin B12, iron, etc. main food sources includes egg yolk, green leafed vegetables, beans, nuts, etc [21].

Nutraceuticals as anti-obesity

Obesity is a common chronic disease and a major underline reason for metabolic syndrome which arises when there is an imbalance between energy intake and energy expenditure. Some components widely used as nutraceuticals in obesity are curcumin, bottle guard, black gram, green tea, etc. They secrete leptin and other cytokines like IL-1, IL-6 that are critically involved in obesity and chronic inflammation. They also help in reducing LDL and total cholesterol. Some act by limiting overall food daily intake. Nutraceuticals have ability to affect weight loss and have huge potential to reverse the development of overweight and obesity-related comorbidities [22,23].

Nutraceuticals as anti-diabetic

Diabetes is a metabolic syndrome where a person suffers from high blood glucose. It is caused due to lack of insulin production or the body cells do not respond properly to insulin or both. Some nutraceuticals used to treat and prevent diabetes are *Emblica officinalis*, fenugreek, green tea, etc. It also includes anti-oxidant vitamins like vitamin C and E and minerals like magnesium and chromium. They generally act by affecting insulin sensitivity and also prevent insulin resistance. Some act by increasing hepatic glycogen concentration and decreasing the concentration of glycogen phosphorylase and glyconeogenic enzymes [22-24] **(Table 2).**

Table 2. Various nutraceuticals used against different diseases.

Sr.no.	Disease	Examples	Ref. no.
1	Alzheimer	Vitamin E and C, alpha- lipoic acid	1
2	Cardiovascular	Flavonoids (onion, black grapes)	1
3	Parkinson	Vitamin E	1
4	Obesity	Chitosan, fenugreek, vitamin C	1
5	Diabetes	Calcium, vitamin D, Emblica officinalis	1
6	Osteoarthritis	Glucosamine, chondroitin sulfate	1
7	Constipation	Buck wheat	3
8	Vision improving	Carrot, mangoes, spinach, kiwi, egg yolk	3
9	Antioxidant	Oats, fruits, carrots	3
10	Anti-inflammatory	Turmeric	3
11	Hypertension	Curry leaf, green tea	22
12	Hyperlipidemia	*Emblica officinalis*	22

CONCLUSION

Nutraceuticals have been emerged as an alternative to modern medicines and have proven health benefits. Most dietary

supplements are derived from plants and some from animals. Nutraceuticals has disease prevention capability with good nutritional value and food ingredients with additional health benefits. They are widely accepted by all age groups due to their higher quality, purity, safety and efficacy, promoting health and help to cure diseases. The latest trend is moved towards nutragenomics and nutraceuticals has led to new era of medicine and health.

REFERENCES

1. Chintale AG, et al. Role of Nutraceuticals in various diseases: A Comprehensive Review. IJRPC. 2013;3:290-299.
2. Brower V. A Nutraceutical a day may keep the doctor away. EMBO reports. 2005;6:708-711.
3. Khan RA, et al. Nutraceuticals: In the treatment and prevention of diseases- an overview. Tha Pharma Innovation. 2014;3:147-150.
4. Angel NM, et al. Role of Nutraceuticals in Cancer. Int J Pharm Pharm Sci. 2012;4:415-420.
5. Chauhan B, et al. Current concepts and prospects of herbal Nutraceutical: A review. 2013;4:4-8.
6. Watson RR. Functional Foods & Nutraceuticals in Cancer Prevention. (1stedn), Iowa State Press. 2003.
7. Ahmad A, et al. Molecular Targets of Naturopathy in Cancer Research: Bridge to Modern Medicine. Nutrients. 2015;7:321-334.
8. Kuppusamy P, et al. Nutraceuticals as potential therapeutic agents for colon cancer: a review. Acta Pharmaceutica Sinica B. 2014;4:173-181.
9. Wargovich MJ, et al. Nutraceutical use in late-stage cancer. NIH Public Access. 2010;29:503-510.
10. http://www.ctoam.com/
11. Ranzato E, et al. Role of Nutraceuticals in Cancer Therapy. J Food Res. 2014;3:18-25.
12. Burns, KM. Therapeutic Foods and Nutraceuticals in Cancer Therapy. Veterinary Technician. 2010; E1-E7.
13. Brower V. Nutraceuticals: poised for a healthy slice of the healthcare market, Nat Biotechnol 1998;16:728-731.
14. Saldanha SN and Tollefsbol TO. The Role of Nutraceuticals in Chemoprevention and Chemotherapy and Their Clinical Outcomes. J Oncol. 2012;1-23.
15. Zeisel SH. Regulation of Nutraceuticals Science. 1999;285:185-186
16. Benkouider C. Functional Foods and Nutraceuticals. 2005;44: 8-11
17. Alokbi SY. Nutraceuticals of anti-inflammatory activity as complementary therapy for rheumatoid arthritis. Pub/med.gov. 2014;30:734-749.
18. Huang MT, et al. Inflammatory Process and molecular targets for anti-inflammatory Nutraceuticals. Comprehensive Reviews in Food Science and Food Safety. 2006;3:127-139.
19. Kaur S, et al. Free radicals and antioxidants (Nutraceuticals): Boom to human health. International Journal of Natural Product Science. 2012;1:175.
20. Kelsey NA, et al. Nutraceutical Antioxidants as novel Neuroprotective agents. Molecules, 2010;15:7792-7814.
21. Dariji VB. The role of nutraceuticals in anti-aging medicine. Acta Clin Croat. 2010;49:537-544.
22. Kaur G, et al. Nutraceuticals in the Management and Prevention of Metabolic Syndrome. Austin J Pharmacol Ther. 2015;3:1-6.
23. Conroy KP, et al. Pathogenic obesity and nutraceuticals. Proc Nutr Soc. 2011;70:426-436.
24. Davi G, et al. Nutraceuticals in diabetes and metabolic syndrome. Cardiovasc Ther. 2010;28:216-226.