



A review on Nutraceuticals as a Therapeutic Agents

U. Ghani^{1*}, S.S.H. Bukhari⁴, S. Ullah², H. Rafeeq¹, M.M. Saeed¹, A. Amjad¹, M. Hussain¹, A. Akmal¹, F.T. Zahra², F. Qasim¹, T. Taufiq¹, S.A. Chand³

¹Department of Biochemistry, University of Agriculture, Faisalabad, 38000, Pakistan

²Department of Biochemistry, Government College University Faisalabad, 38000, Pakistan

³Department of Plant Pathology, University of Agriculture, Faisalabad, 38000, Pakistan

⁴Department of Theriogenology, University of Agriculture, Faisalabad, Pakistan

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Abstract

Nutraceuticals is a broad term derived from nutrition and pharmaceutical. Nutraceuticals are foods or part of foods that play a significant role in maintaining many physiological functions to maintain the human health and in preventing and treating many acute and chronic diseases. Nutraceuticals are divided into three main categories including herbs, nutrients and dietary supplements. Several herbal products are produced from various herbs. Nutrients are substances with established nutritional values such as vitamins, minerals and amino acids which are essential for improving our health. The food products which are used as nutraceuticals are dietary fibers, prebiotics, probiotics, polyunsaturated fatty acids, antioxidants, spices and some other types of types of herbs and natural foods. Probiotics are ingested for their positive advantages in the digestive tract or systemic area like in the liver, brain, vagina or blood stream. Antioxidants are very essential in the treatment of almost all diseases because most chronic diseases occur due to oxidative stress which mostly occurs due to aging and lack of dietary antioxidants. Flavonoids and phytochemicals have antioxidant properties due to which it act as therapeutic agents for various diseases such as anti-cancerous. Omega-3 polyunsaturated fatty acids (PUFAs) are used for lowering the high levels of cholesterol in cardiovascular diseases and many inflammatory diseases. The main focus of this review is on role of nutraceuticals in metabolic pathways for the prevention of various diseases such as diabetes mellitus, cardiovascular diseases, obesity and cancer and osteoporosis.

*Corresponding Author: U. Ghani ✉ casghani555@gmail.com

Introduction

Nutraceuticals are used as therapeutic agents in the treatment and prevention of various diseases such as cardiovascular diseases, cancer, obesity and diabetes mellitus. These nutraceuticals have an important role in different functions of our body and are also useful in lowering the risk of many diseases in humans. These pharmaceutical foods are used for the cure and prevention of many diseases, to develop immunity in body and to manage health. According to recent research it has been scientifically proved that these nutraceuticals are very efficient in preventing and curing many disease situations (Rama *et al.*, 2006).

According to world health organization (WHO) about 17.5 million people died due to various cardiovascular diseases (CVD) that includes angina pectoris, coronary heart diseases (CHD), congestive heart failure (CHF), hypertension, rheumatic heart diseases and acute myocardial infarction (Mehta, 2017). To cure these CVD extracts of green tea are suggested to be consumed as a well-known nutraceutical (Shishikura *et al.*, 2006). Saturated derivatives of stanols and sterols are present in many extracts of plants and absorbed from intestine due to which they act as nutraceutical for lowering the level of cholesterol directly (Ferguson *et al.*, 2016).

Cancer is termed as abnormal cell division in any body part and these cancerous cells also affect our normal cells badly. There are many nutraceuticals that are incorporated in various functional foods that are used for prevention and cure of many types of cancers (Gupta, 2016). Nutraceuticals have many mechanisms of action that are involved in the treatment of cancer such as cell cycle arrest induction, apoptosis, stimulation of host's immune system, elimination of toxins from the reactive agents of chemotherapeutic drugs and intensity of proliferated cells to cytotoxic substances (Kotecha *et al.*, 2016).

Diabetes is most common in people that use saturated fats mostly. By prohibiting the trans and saturated fats the development of diabetes can be delayed. R-lipoic acid act as nutraceutical because it is

an antioxidant natural coenzyme that decrease the pyruvate and serum lactate level in patients of diabetes mellitus (Dubnov *et al.*, 2003).

There are many nutraceuticals such as water soluble dietary fibers, polysaccharides, guar gum and pectin that are extracted from many plants and are involved in lowering glucose absorption by reducing gastric empty rate. Glucosidase inhibitors are also used for the cure and prevention of obesity and diabetes mellitus (Watanabe *et al.*, 1997).

According to WHO investigation and estimation obesity is a major problem in millions of people. There are many disorders such as various heart disorders, respiratory disorders, high blood pressure, osteoarthritis and cancer that are caused due to obesity. In most of people obesity is mainly caused by the use of high energy level diet and excess fats (Mermel, 2004). Many nutraceuticals increases the consumption of energy in our body that can be used for the treatment of obesity. Green tea, ephedrine, caffeine, and chitosan are extracted from plants and acts as nutraceuticals for lowering body weight (Bell and Goodrick, 2002).

The aims of this study are to improve the quality of life with the help of nutraceuticals. Fig 1 shows sketch of nutraceuticals role as therapeutic agents.

There are main three categories in which nutraceuticals are classified such as herbals, nutrients and dietary supplements. Herbals are extracted from natural plant sources such as garlic, ginger and aloe vera. There are various varieties of plants that produce compounds like alkaloids and these compounds are used by humans in prevention from different infections and these compounds are also used for the treatment of many diseases in human beings. Substances which have their balanced nutritional values are known as nutrients including vitamins, minerals and amino acids. These nutraceuticals are the food products extracted from natural sources such as dietary fibers, probiotics, prebiotics, antioxidants, polyunsaturated fatty acids.

Nutraceuticals and its role in diseases

Role of nutraceuticals in cardiovascular diseases

The major cardiovascular diseases (CVD) that cause the death of about 17.5 million people includes, hypertension, congestive heart failure (CHF), angina pectoris, acute myocardial infarction, coronary heart diseases (CHD) and rheumatic heart diseases. This data was proven by world health organization (WHO) (Mehta, 2017).

WHO determined in 2014 that all over the world CVDs are the main cause of death and one in two deaths occur because of the CVDs in western countries. CVDs emerge because of various reasons including diabetes, higher consumption of tobacco, obesity, increased level of low-density lipoprotein (LDL), dropped levels of high-density lipoprotein (HDL), insulin resistance and physical inactivity (Danaei *et al.*, 2009).

Aging, bad food habits, high stress career, an unhealthy lifestyle are the other factors which are involved in the prevalence of CVDs. Deskbound lifestyles with poor dietary habits can cause the CVDs even in those individuals that are even at lower risk of CVDs. Various physiological disease are because of imbalance of nutrients in the diet and their treatment is also done by the therapies that are given through diet. The products that are taken from the natural food resources that contain higher nutritional values with much more nutritional properties are termed as nutraceuticals. Different dietary supplements, cereals, herbal products and beverages are the main components of nutraceuticals (Ferrari *et al.*, 2003).

The therapeutic and preventive potential is the reason due to which nutraceuticals are used against different physiological disorders (hypercholesterolemia, periodontal disease, neurodegenerative diseases, hyperglycemia, osteoarthritis and cancer) by incorporating in dietary supplements. Nowadays our regime is moved from traditional carbohydrate and high fiber diet to the completely processed and packed diet completely consists of fats. The change in lifestyle and also the

decrease in physical activities increase the risk of CVDs. Every individual should be aware that which food in our diet must be avoided and which one is necessary to maintain a healthy heart (Spoorthi *et al.*, 2017).

The adaptable risk factor of CVDs is the low-density lipoprotein (LDL) cholesterol, studies shows that risk of CVDs decreases by lowering the LDL level (silverman *et al.*, 2018). Recently in individuals suffering from hypercholesterolemia with high level of cholesterol in blood are treated with the nutraceuticals and other functional food as national therapies. While the process through which nutraceuticals lowers the cholesterol level is still unknown, most of the nutraceuticals are utilized for the cure of cardiovascular diseases. By inhibition of intestinal absorption of cholesterol and also the hindrance in the synthesis of cholesterol nutraceutical decreases the cholesterol level Figure 2 (Cicero *et al.*, 2017).

Through the reversible inhibition of hepatic enzyme that results in the reduction in synthesis of a cholesterol (3-hydroxy-3-methylglutaryl-coenzyme A reductase) the nutraceuticals like garlic, monacolin and green tea used to treat the CVDs. Various medicinal plants (*Hydrastis canadensis*, *Berberis vulgaris*, *Berberis aquifolium*, *Coptis chinensis*, *Berberis aristata*) contain natural alkaloid berberineis. Berberineis has low oral bioavailability. The metabolism of this substance is done by the liver and excreted out after glucuronidation through the bile. This protein work by facilitating the separation of the hepatic LDL receptor from the cell surface to the lysosomes. The degradation of this protein in lysosomes cause the maintenance of half-life of receptor which furthered take-up more cholesterol from the blood stream which is then sent to the bile for further disposal Figure 3 (Cicero *et al.*, 2015).

Numerous nutraceuticals act to inhibit the cholesterol absorption from the intestine and enhance the cholesterol secretion. There are various nutraceuticals which act as inhibitors of cholesterol

absorption from intestine and also enhance the excretion of cholesterol. There are some nutraceuticals such as Gamma-oryzanol which is extracted from rice bran causes the lowering of cholesterol by inhibiting the absorption of cholesterol present in the diet in the intestine. Bergamot is a

nutraceutical which is a derivative of polyphenols have many beneficial effects for the lowering of cholesterol by decreasing the concentration of many receptors such as phosphor PKB, malondialdehyde and oxyLDL receptor.

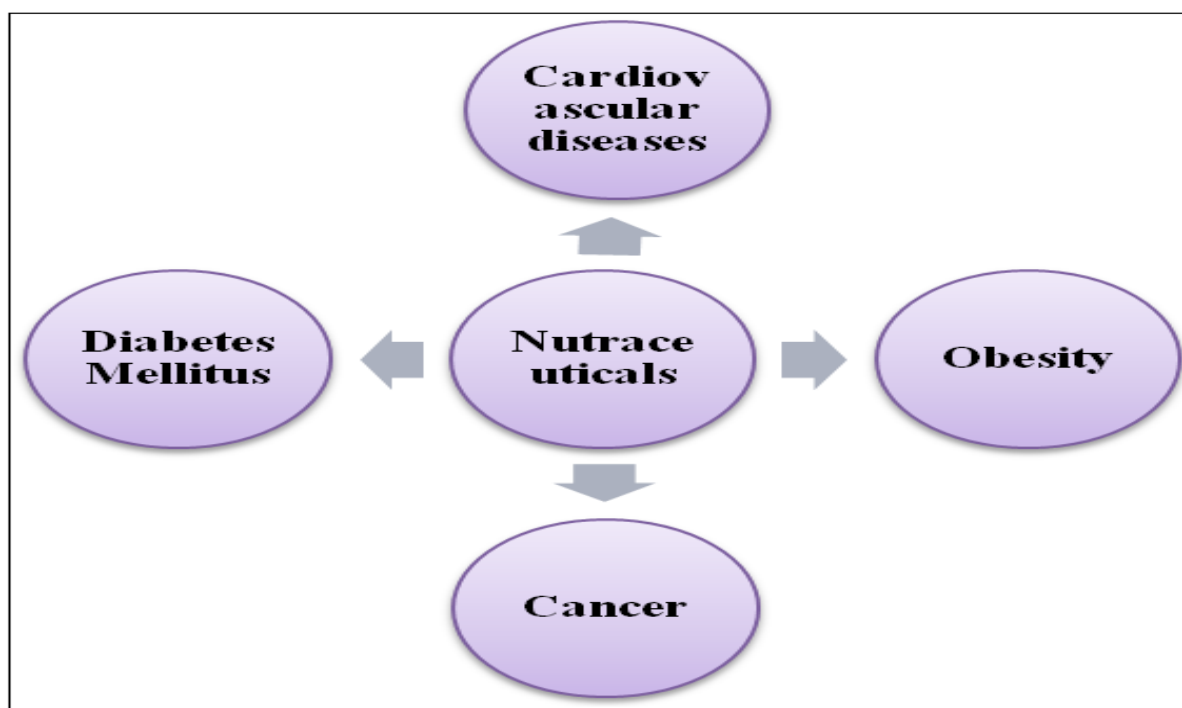


Fig. 1. Nutraceuticals as therapeutic agents.

There is a transporter known as NPC1L1 which is responsible for the absorption of cholesterol in the enterocytes present in the jejunum. It is also responsible for the transportation of cholesterol into the enterocytes from lumen. Acyl-CoA cholesterol acyltransferase present in the intestine is responsible for the conversion of cholesterol into the cholesterol ester (CE) when it enters into the enterocyte cells. Cholesterol ester surrounded by the chylomicron by microsomal triacylglycerol transport protein. CM is transported into the blood through the lymphatic system (Altmann *et al.*, 2004). In the enterocytes the remaining amount of cholesterol which is not absorbed, transported again into the lumen by the ATP-binding cassette transporters so that this cholesterol can be excreted from the body. Dietary phytosterols and curcumin are the competitors of NPC1L1 because the structure of cholesterol is similar to those competitors (Plat and Mensink, 2005).

Cholesterol is similar to phytosterols in their structure due to which it not only competes with NPC1L1 but also poorly absorbed into the intestine in very low percentages. While on the other hand the absorption of cholesterol is above from 50%. The difference in the absorption rates in the intestine of cholesterol and phytosterols is due to the ACAT present in the enterocytes because it prefers the esterification of cholesterol more as compared to phytosterols. To avoid from the deposition of phytosterols in the enterocytes they are transported back by the ABCG5/8 into the lumen so that they can be excreted from the body. Phytosterols are the nutraceuticals that are incorporated into the vegetable oils, margarine and fats as an important constituent for lowering the level of cholesterol from the body. Increase in the intake of phytosterols present in the diet can decrease the level of total cholesterol in the serum and also decrease the level of

LDL (Graf *et al.*, 2002).

Plant sterols and stanols: Plant sterols are naturally present in almost all plant sources such as oils extracted from different vegetables, in seeds, nuts, and also in legumes. These plant sterols act as nutraceuticals and have structures identical to cholesterol but their side chains are different from them. The difference in their side chains is due to the presence of ethyl group or methyl group or at C22 there may be the presence of double bond. Plant sterols are the saturated derivatives of many plant extracts such as stigmasterol, beta-sitosterol and campestanol (Devaraj and Jialal, 2006).

Both stanols and plant sterols can decrease the absorption of cholesterol from the intestine and also lower the concentration of LDL cholesterol and leads to formation of micelles which are solubilized. These micelles facilitate the transportation of plant sterols from the lumen of intestine with the help of NPC1L1 transporter and also by reacting with the membrane. In this way the amount of cholesterol in the intestine increases and excreted through the feces.

The expression of a transporter ABCA1 can be exaggerated by stanols and plant sterols as a result of which an enzyme ACAT is inhibited which decreases the absorption of cholesterol (Ferguson *et al.*, 2016).

Green tea extracts: Green tea is a known nutraceutical and consumption of green tea extracts are suggested to be used for the cure of CVD. It is also known as cardio preventive extracts due to the presence of large amount of antioxidants like polyphenols. Flavan-3-ols and catechins are the main and large portion of polyphenols in the green tea (Shishikura *et al.*, 2006). EGCG is another compound which is recognized due to the presence of cardio preventive and also antioxidant properties. Green tea has antioxidant effects and these are the derivatives of polyphenols and are used to decrease the process of lipid peroxidation. It also inhibits the absorption of cholesterol and solubilization of micelles. The extracts of green tea are inhibitors of an enzyme HMG-CoA

reductase and these are also the initiator of AMP-activated protein kinase and encourage the process of lipogenesis. Catechins dropping the absorption of bile acids again by prohibiting the sodium-dependent bile acid transporter as a result of which the expression of LDL-R in liver increase due to which the amount of biliary secretion of cholesterol increases from the body (Way *et al.*, 2009).

Garlic: There is a nutraceutical known as garlic (*Allium sativum*) which is recognized for its multiple health properties. In garlic, allicin is an important constituent and it is synthesized by the nonproteinogenic amino acid. This process is mainly catalyzed by an enzyme known as alliinase. In garlic the allicin constituent is mainly involved in the mechanism which causes the decrease in concentration of lipids in the body (Borlinghaus *et al.*, 2014).

The Allicin compound is also an inhibitor of many enzymes such as monooxygenase, squalene, acetyl-CoA synthetase and HMG-CoA reductase which are responsible for synthesis of cholesterol. A thiol group is also present in the allicin compound due to which it causes the reduction of acetyl-CoA by reacting with non-acetylated-CoA enzyme as a result of which the synthesis of cholesterol stops. Inhibitions of cholesterol absorption from diet and increase in the elimination of bile acids from the body are the important functions which are performed by the garlic (Ried, 2016). **Polyunsaturated n-3 fatty acids:** Omega 3 fatty acids are known as polyunsaturated fatty acids (PUFAs) containing a double bond in position 3 at the end of the carbon chain. Animals and plants both are the natural sources of omega 3 fatty acids. Daily 2g intake of DHA and EPA is responsible for the regulating the normal levels of TG in the blood. Reducing the activity of enzymes that are responsible for the synthesis of TG, by lowering the synthesis of hepatic VLDL, by enhancing the process of beta oxidation of fatty acids and increasing the synthesis of phospholipids are the mechanisms due to which omega 3 fatty acids can decrease the level of TGs (Harris and Bulchandani, 2006).

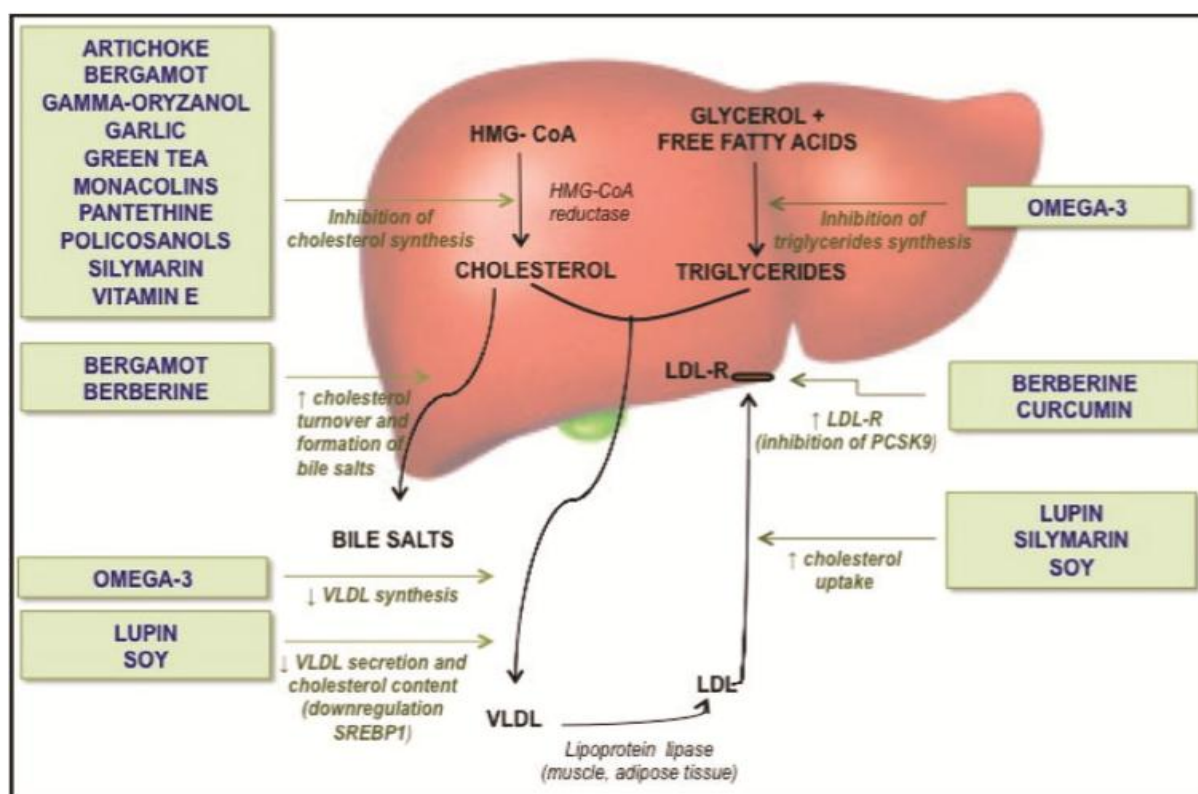


Fig. 2. Nutraceuticals acting as inhibitors of liver cholesterol synthesis.

Role of nutraceuticals in cancer

Abnormal cell division of cells in our body is known as cancer. This abnormal growth can also disturb the growth of normal cells. These abnormal cells accumulate in any part of the body which causes the formation of tumors (Naeem *et al.*, 2019). All types of tumors cannot cause cancer and the tumors which cause cancer are malignant in nature. Every year a lot of people are dying due to cancer (Ingole *et al.*, 2016). There are many kinds of nutraceuticals which are present in natural food sources like flavonoids, polysterols and carotenoids. There are various types of nutraceuticals which are used for the cure and prevention of many cancers and these nutraceuticals are incorporated in many functional foods. According to the many biological factors and their chemical structures nutraceuticals are different from each other (Gupta, 2016).

In fruits, vegetables, grains and natural foods these nutraceuticals are present naturally and can be used from their natural sources. Nutraceuticals are different in their structure and their molar masses also vary from one another. All these properties

including their functional groups have a great effect on the reactivity of these nutraceuticals (McClements, 2015). In addition to it some nutraceuticals are isolated from their natural sources and added into many adjuvants. Many of the dietary supplements contain these additives which have many beneficial effects in the prevention and cure of many disorders. There are many nutraceuticals which are used against various forms of cancer due to their anticancer activities including tea polyphenols, resveratrol, flavonoids and curcumin (Arvanitoyannis & van Houwelingen-Koukaliaroglou, 2005).

The exhibition of very low side effects is the most important advantage of nutraceuticals, due to the presence of this property these are used for the cure and inhibition of cancer, while the administration of pharmaceutical products have many side effects on the body when they are used for longer time. There are many mechanisms of action of these nutraceutical for the cure of cancer and these mechanisms may include the process of apoptosis, cell cycle arrest induction, stimulation of immune system of host, intensity of proliferated cells to cytotoxic substances

and removal of toxins from the reactive agents of drugs used in chemotherapy (Kotecha *et al.*, 2016). Several important anticancer nutraceuticals are used for the cure and prevention of various cancers.

Curcumin: Curcumin is present in the turmeric which is a polyphenol and related to the family of ginger

(Joe *et al.*, 2004). Curcumin stops the mechanism of cell cycle induction and initiates the process of apoptosis in cancer cells and stops the proliferation of cancer cells. These processes also alters many cancer targets like tumor necrosis factor (TNF), nuclear factor kappa B (NF- κ B) and cyclooxygenase 2 (COX-2) (Perrone *et al.*, 2015).

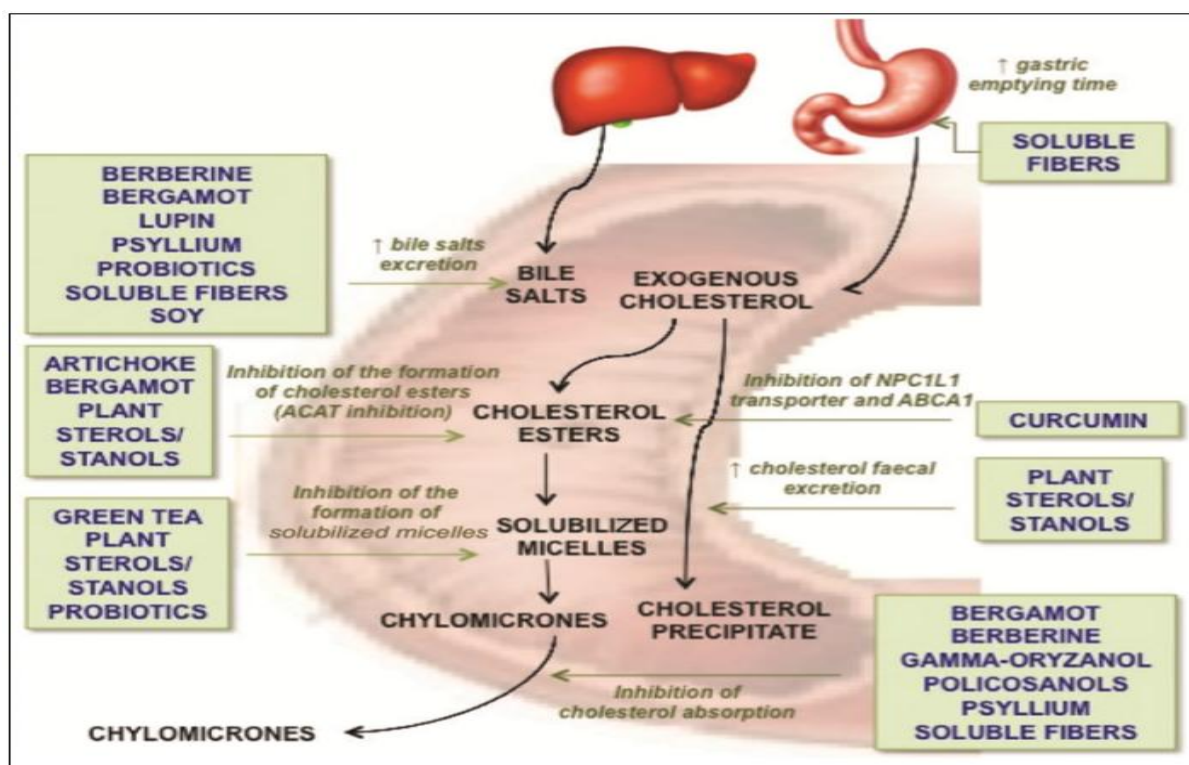


Fig. 3. Nutraceuticals acting as inhibitors of intestinal cholesterol absorption and enhancers of cholesterol excretion.

Curcumin is mainly used for the cure of colorectal cancer as a chemo therapeutic agent because it is present in the colonic mucosa more preferably as compared to other organs. Poor bioavailability is the most important factor that limited the bio efficiency of curcumin. (Bar-Sela *et al.*, 2010). To improve the efficiency and availability of curcumin many delivery systems are used which includes many drug delivery systems by modifying them, liposomes, nanoemulsions based on organ gel, nanoparticles containing chitosan and liposomes (Ting *et al.*, 2014). Such as nanoparticles in which curcumin is encapsulated polylactide coglycolide suppress the development of cancer cells by initiating the process of apoptosis in the cell. In the model of hepatocellular carcinoma the structures related to pathology can also

be improved. But if the same concentration of curcumin is present in its free form it has no effect on the body (Ghosh *et al.*, 2012).

Resveratrol: Resveratrol naturally present in plant extracts, blueberries, peanuts, raspberries and fruits. According to recent studies resveratrol is a polyphenol and have many beneficial effects for the cure of cancer such as it interfere with many stages of carcinogenesis and cure various types of cancer including cancer related to pancreas, breast cancer, skin cancer, cancer of colon and prostate (Shukla and Singh, 2011). The patients suffering from breast cancer are more preferably treated with resveratrol due to its anticancer effects. According to recent research the supplementation of resveratrol for about

twelve weeks causes the decline in the methylation of four genes related to cancer which are present in women in mammary tissues and these genes are associated with an increase in the threat of breast cancer. In the treatment of prostate cancer if curcumin and resveratrol both are encapsulated in the same liposome it will increase their effects (Zhu *et al.*, 2012).

Teapolyphenols: Tea polyphenols are naturally present in the tea plant extracts including epicatechin-3-gallate and epigallocatechin-3-gallate. These EGCG and ECG are strong antioxidants and are used in lowering the concentration of reactive oxygen species to protect DNA from damage. Due to its antioxidant properties it mainly used to stop the progression of cancer in normal cells. These polyphenols are involved in the regulation of many pathways involved in the signaling of cell as a result of which angiogenesis is suppressed. It also cause the activation of detoxifying enzymes related to phase II and also cause changes in immune system. According to recent research tea polyphenols are involved in the cure and prevention of various cancer types such as cancer related to lung and liver, bladder cancer and oral leukoplakia (Yang *et al.*, 2013).

Flavonoids: Flavonoids are naturally present in vegetables, fruits and in various plants. These flavonoids are major class of polyphenols related to the plant secondary metabolites and have many beneficial effects to inhibit various types of cancers in humans. Recent studies shows that diets which are rich in flavonoids have many minute chances of different types of cancer such as breast cancer, cancer of colon and prostate. There are various types of flavonoids which are categorized on the bases of their structures such as flavanols, flavones and antocyanins. Flavonoids are involved in the cure of many cancers by inhibiting various mechanisms like it inhibits the progression of cancer cells, initiates the process of apoptosis in cancer cells, it also target many mechanisms related to signaling pathways in cancer cells and also involved in the suppression of tumor angiogenesis (Batra and Sharma, 2013).

Quercetin is a well-known flavone and it is naturally present in apples and onions abundantly. Quercetin due to its anticancer properties is used for the cure of various types of cancers in humans like in breast cancer, lung cancer, liver cancer, and cancer of cervical and colon (Yang *et al.*, 2015). Due to low absorption quercetin normally shows poor oral bioavailability. To avoid from it nanoparticles are used to increase the effect of quercetin. A microencapsulation method is used for the reduction of the oxidative damage and reducing inflammation due to increased absorption (Guazelli *et al.*, 2013).

Role of Nutraceuticals in Diabetes Mellitus

The complex disorder of the metabolism is called Diabetes Mellitus. In diabetes several changes occur e.g. impairment in oxidative stress, lipid and glucose metabolism, insulin signaling and β -cell. The quantity of diabetes patient is increasing from 171 million in 2000 to the 366 million day by day (Evans and Goldfine, 2016).

Diabetes Mellitus is divided into type 1 and type 2. Diabetes mellitus type 1 occurs in people of young age with poor health. In this type of diabetes pancreas fails to produce insulin hormone. It is an autoimmune disorder caused by the damage of beta cells of pancreas due to oxidative stress. Type 2 diabetes usually present in the people of older age above than 40. Type 2 diabetes is a genetic disorder and inherited in families from one generation to the other and associated with relative insulin deficiency. In both type 1 and 2 diabetes fundamental cause of diabetic complications is the chronic elevation of blood glucose level, which affects multiple organs of the body (Kaiser *et al.*, 2003).

Nutraceuticals and glucose metabolism in diabetes: Although, many dangerous factors are responsible for the diabetes type 2 but diet is the major one. Phytochemicals, antioxidants and polyphenolic compounds are responsible for lowering the diabetes (Montonen *et al.*, 2004). Diabetes with complications could be treated by nutraceuticals which have many medical and health benefits. Nutraceuticals are

functionally natural as well as medical foods. They promote health as well as prevent the prevalence of several diseases (Perera and Li, 2012).

Occurrence of diabetes is large in those people which are mostly using saturated fatty acids. The development of diabetes could be slowed down by the prohibition of saturated as well as trans fats. Diabetes might be treated by daily exercise, weight loss as well as by nutritious food (Dubnov *et al.*, 2003). In diabetic patients, level of serum lactate and pyruvate decrease by R-lipoic acid (nutraceutical), natural coenzyme and antioxidant. Diabetic neuropathy is treated by activating the insulin signaling pathway. Glucose metabolism could be increased by R-LA which speeds up the uptake of glucose; it helps in the oxidation of glucose (Korotchikina *et al.*, 2004).

Diabetes mellitus relates to the oxidative stress only in the conditions of hyperglycemia and hyperlipidemia. Inflammatory immune response and oxidative stress reactions are produced as a result of hyperglycemia, increased level of fatty acids, TAG-rich as well as modeled lipoproteins. Additionally, free radicals are also generated that are the main cause of cardiovascular diseases, obesity and type 2 diabetes (Baynes and Thorpe, 1999).

In diabetes there is a significant decrease in antioxidants like carotene, retinol, ascorbic acid, and tocopherol in the plasma. This decrease in the amount of antioxidants causes many disorders like atherosclerosis and disturbance in the function of endothelial cells. The presence of very low amount of antioxidants in the plasma is very prominent in elder people of diabetes. The use of antioxidants as therapeutic agents is very beneficial for the cure of diabetes and other disorders related to it. There are many nutraceuticals which have antioxidant properties and are used for the cure of diabetes such as ascorbic acid, carotenoids, tocopherols and flavonoids (Pietta, 2000).

These antioxidants are used to inhibit the production of reactive oxygen species (ROS) by inhibiting several

enzymes that produce ROS such as NADH oxidase, monooxygenase, xanthine oxidase, lipoxygenase, and mitochondrial succinoxidase. To superoxide anion or other radicals, these antioxidants donate an electron or hydrogen atom and defend many proteins, DNA molecules, and lipoproteins from damage caused by oxidative stress. In the patients of diabetes more utilization of vegetables and fruits can decrease the threat of heart disorders (Dembinska-Kiec *et al.*, 2008).

In our body there are many regulatory mechanisms which are used to regulate the level of glucose, level of stored energy and also lipid homeostasis. These pathways involved the control of metabolism of energy in different cells and tissues (Chertow, 2004). There are many different types of cells present in mammals that can identify the level of various macromolecules such as of mammalian cells that can sense changes directly in the levels of various macronutrients such as glucose, fatty acids and amino acids and also in the levels of the related enzymes involved in catabolism, such as mammalian target of rapamycin (mTOR), protein kinase, Per-Arnt-Sin (PAS) kinase, AMP-activated protein kinase (AMPK) hexosamine synthetic pathway flux (HBP) (insulin sensing), or NAD⁺-dependent protein deacetylase SIRT2 (McCue *et al.*, 2005).

There are some most important mechanism such as decrease in the passage of glucose through the intestine, prohibition of digestion of starch in regulation of glucose, and postponing the rate of gastric emptying can decrease the threat of diabetes type 2. For the regulation of hyperglycemia plant sterols are very beneficial by the prohibition of glucosidase and amylase activity along with the prohibition of sodium glucose cotransporter present in the intestine. Prohibition of sucrose and amylase activity can be done by the plant sterols and tea extracts which leads to a decrease in postprandial glycemia (Kobayashi *et al.*, 2000).

There are many nutraceuticals like polyphenols like epigallocatechin, catechin, epicatechingallate,

isoflavones extracted from soyabeans and tannic acid can drop the level of S-Glut-1 can regulate the transportation of glucose in the intestine.

From stomach to the small intestine the transportation of glucose can be decreased by another compound saponins (Francis *et al.*, 2002). There are some other nutraceuticals such as guar gum, pectins, polysaccharides and water soluble dietary fibers extracted from the plants are recognized for decreasing the absorption of glucose by slowing the gastric emptying rate. For the cure of diabetes and obesity inhibitors of glucosidase are used (Watanabe *et al.*, 1997).

Obesity and diabetes type 2 can be cured and prevented by the use of many nutraceuticals like polyphenols, anthocyanins present in bilberries and some other berries. Anthocyanins which are extracted from various sources have many beneficial effects in the secretion and action of glucose, metabolism of lipids and absorption of glucose. During digestion by decreasing the release of glucose these nutraceuticals can also decrease the absorption of glucose (Jayaprakasam *et al.*, 2005).

The extracts of blueberry are very beneficial in the prohibition of maltase and glycosidase activity and also strongly prohibited the digestion of starch as compared to the extracts which are obtained from raspberry and strawberry. In the presence of insulin the intake of glucose increases by cells present in muscles can be increase by the extracts obtained from blueberry. These also have important role in the protection of cells of neurons from the harmful effects of high amount of glucose. Recent studies on the cells of pancreas have shown that pure extracts of anthocyanins such as delphinidylglucosides, cyanidingalactosides and cyanidin glycosides can increase the excretion of insulin in primary cell cultures (Martineau *et al.*, 2006). Glycemia and lipidemia are controlled by the leave extracts of *Gymnema sylvestre*. It increased the endogenous secretion of insulin in the IDDM patients when given for 10-12 months (Young *et al.*, 2002).

Role of nutraceuticals in obesity

Unhealthy amount of fats in the body or use of excess amount of calories in the body is usually known as obesity. There are several disorders which are commonly caused by obesity like respiratory disorders, cancer, osteoarthritis, high blood pressure and many heart disorders. According to the estimation of investigation of WHO millions of people are suffering from it. Use of excess fats and diets with high energy levels are the major causes of obesity in many people (Mermel, 2004).

Consumption of trans-saturated fats, extreme utilization of diets that are rich in energy like drinks, modified foods and snacks are the main causes of gaining weight. Obesity can be managed by regulating some mechanisms such as by using diet with low calories and increasing physical activities to reduce the excess fats of body. There are many nutraceuticals which are used are for the cure of obesity because these compounds increase the expenditure of energy.

There are also some nutraceuticals which are extracted from plants such as caffeine, chitosan, ephedrine and green tea which are used for lowering the weight of body (Bell and Goodrick 2002).

Seed of Buckwheat act in a similar way as natural fibers and these are very beneficial for the cure of obesity and for reducing the excess weight of body green tea extracts and 5-hydroxytryptophan are also used. There are also some other nutraceuticals which are present in dietary supplements such as vitamin C, chitosan and glucomannan and these nutraceuticals increase the loss of extra fats from the body resulting in decrease in the body fat. Nutraceuticals like capaicin, conjugated linoleic acid (CLA), and *Momordica Charantia* (MC) are used as therapeutic agents for the cure of obesity (Amariles *et al.*, 2006).

Conjugated linoleic acid (CLA): Conjugated linoleic acid is naturally present in the oils extracted from fish and nuts sources, seeds of flax, and in eggs. The main beneficial effects of these nutraceutical products are the regulation of quantities of high density

lipoproteins and low density lipoproteins in the blood. The main function of these nutraceuticals is dropping the levels of triacylglycerols in the plasma by lipoprotein (Chan *et al.*, 2003).

According to recent studies utilization of CLA supplementation can reduced amount of fats in the body. While it can be used in its original form in salads or it can be used in therapeutic dosage but it cannot be used in its cooked form because it shows sensitivity to temperature (Blankson *et al.*, 2000).

There are several mechanisms through which these specific types of oils are used in the reduction of excess fats of the body such as by regulating the expression of certain genes coding adipocytokines. Due to this the process of progression of cells and their differentiation decreases.

There are some factors like peroxisome proliferator activated receptor (PPAR), CCAAT, and enhancer binding protein and some other genes related to adipose cells are included in the regulation of obesity.

There is another mechanism which is related to melatonin hormone that controls the obesity is related to hormone melatonin.

The hormone Melatonin (MLT) mainly controls circadian rhythm in human body. The ingestion of fatty acids is lowered when rodents are administered with MLT, CLA and EPA (Dauchy *et al.*, 2003). As a result of this the production of cyclic amp (c-amp) is inhibited and it allows the body to use fats already present in the body as the main source of energy.

Hence it is clear that the combination of CLA with melatonin play a major role in reducing the weight of animal's body, and it also play similar function in humans as well. CLA also have a significant effect on the improvement of insulin resistance which occurs due to obesity. According to recent studies it is proved that the administration of high fat diet along with CLA in rodents can prevent them from muscle insulin resistance which is induced (Lavigne *et al.*, 2001).

Conclusion

Diseases like metabolic syndromes can be prevented by changing the life style. Lifestyle can be changed by changing our diet. There are some important issues about nutraceuticals such as formation of standard scientific assessment for the prevention of diseases, use of these assessment systems for disease prevention of human trials. The predicted effect of nutraceuticals for the prevention of diseases is very complex because it is the combination of several components, not a single component due to which it is essential to compare the complex action and preventive effects of these components present in that product.

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References

- Ferrari CKB, Torres EAFDS.** 2003. Biochemical pharmacology of functional foods and prevention of chronic diseases of aging. *Biomedicine & Pharmacotherapy* **57(5-6)**, 251-260.
- Altmann SW, Davis HR, Zhu LJ, Yao X, Hoos LM, Tetzloff G, Wang L.** 2004. Niemann-Pick C1 like 1 protein is critical for intestinal cholesterol absorption. *Science* **303(5661)**, 1201-1204.
- Amariles P, González LI, Giraldo NA.** 2006. Prevalence of self-treatment with complementary products and therapies for weight Loss: A randomized, cross-sectional study in overweight and obese patients in Colombia. *Current therapeutic research* **67(1)**, 66-78.
- Arvanitoyannis IS, Van Houwelingen-Koukaliaroglou M.** 2005. Functional foods: a survey of health claims, pros and cons, and current legislation. *Critical reviews in food science and*

nutrition **45(5)**, 385-404.

Bar-Sela G, Epelbaum R, Schaffer M. 2010. Curcumin as an anti-cancer agent: review of the gap between basic and clinical applications. *Current medicinal chemistry* **17(3)**, 190-197.

Batra P, Sharma AK. 2013. Anti-cancer potential of flavonoids: recent trends and future perspectives. *3 Biotech* **3(6)**, 439-459.

Baynes JW, Thorpe SR. 1999. Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. *Diabetes* **48(1)**, 1-9.

Bell SJ, Goodrick GK. 2002. A functional food product for the management of weight. *Critical reviews in food science and nutrition* **42(2)**, 163-178.

Blankson H, Stakkestad JA, Fagertun H, Thom E, Wadstein J, Gudmundsen O. 2000. Conjugated linoleic acid reduces body fat mass in overweight and obese humans. *The Journal of nutrition* **130(12)**, 2943-2948.

Borlinghaus J, Albrecht F, Gruhlk MC, Nwachukwu ID, Slusarenko AJ. 2014. Allicin: chemistry and biological properties. *Molecules* **19(8)**, 12591-12618.

Chan DC, Watt GF, Mori TA, Barrett PHR, Redgrave TG, Beilin LJ. 2003. Randomized controlled trial of the effect of n-3 fatty acid supplementation on the metabolism of apolipoprotein B-100 and chylomicron remnants in men with visceral obesity. *The American journal of clinical nutrition* **77(2)**, 300-307.

Chertow B. 2004. Advances in diabetes for the millennium: vitamins and oxidant stress in diabetes and its complications. *Medscape general medicine* **6(3)**.

Cicero AF, Colletti A, Bajraktari G, Descamps O, Djuric DM, Ezhov M, Panagiotakos DB.

2017. Lipid-lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. *Nutrition reviews* **75(9)**, 731-767.

Cicero AF, Parini A, Rosticci M. 2015. Nutraceuticals and cholesterol-lowering action. *International Journal of Cardiology Metabolic & Endocrine* **6**, 1-4.

Da Costa JP. 2017. A current look at nutraceuticals—key concepts and future prospects. *Trends in Food Science & Technology* **62**, 68-78.

Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehman J, Murray CJ, Ezzati M. 2009. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. *PLoS medicine* **6(4)**, e1000058.

Dauchy RT, Blask DE, Sauer LA, Davidson LK, Krause JA, Smith LC, Dauchy EM. 2003. Physiologic melatonin concentration, omega-3 fatty acids, and conjugated linoleic acid inhibit fatty acid transport in rodent hind limb skeletal muscle in vivo. *Comparative medicine* **53(2)**, 186-190.

Dembinska-Kiec A, Mykkänen O, Kiec-Wilk B, Mykkänen H. 2008. Antioxidant phytochemicals against type 2 diabetes. *British Journal of Nutrition* **99(E-S1)**, ES109-ES117.

Devaraj S, Jialal I. 2006. The role of dietary supplementation with plant sterols and stanols in the prevention of cardiovascular disease. *Nutrition reviews* **64(7)**, 348-354.

Dubnov G, Brzezinski A, Berry EM. 2003. Weight control and the management of obesity after menopause: the role of physical activity. *Maturitas* **44(2)**, 89-101.

Evans JL, Goldfine ID. 2016. A new road for treating the vascular complications of diabetes: so let's step on the gas. *Diabetes* **65(2)**, 346-348.

- Ferguson JJ, Stojanovski E, MacDonald-Wicks L, Garg ML.** 2016. Fat type in phytosterol products influence their cholesterol-lowering potential: a systematic review and meta-analysis of RCTs. *Progress in lipid research* **64**, 16-29.
- Francis G, Kerem Z, Makkar HP, Becker K.** 2002. The biological action of saponins in animal systems: a review. *British journal of Nutrition* **88(6)**, 587-605.
- Ghosh D, Choudhury ST, Ghosh S, Mandal AK, Sarkar S, Ghosh A, Das N.** 2012. Nanocapsulated curcumin: oral chemopreventive formulation against diethylnitrosamine induced hepatocellular carcinoma in rat. *Chemico-biological interactions* **195(3)**, 206-214.
- Graf GA, Li WP, Gerard RD, Gelissen I, White A, Cohen JC, Hobbs HH.** 2002. Coexpression of ATP-binding cassette proteins ABCG5 and ABCG8 permits their transport to the apical surface. *The Journal of clinical investigation* **110(5)**, 659-669.
- Guazelli CF, Fattori V, Colombo BB, Georgetti SR, Vicentini FT, Casagrande R, Verri Jr WA.** 2013. Quercetin-loaded microcapsules ameliorate experimental colitis in mice by anti-inflammatory and antioxidant mechanisms. *Journal of natural products* **76(2)**, 200-208.
- Gupta RC.** 2016. *Nutraceuticals: Efficacy, Safety and Toxicity* London, U.K.: Academic 944 Press.
- Harris WS, Bulchandani D.** 2006. Why do omega-3 fatty acids lower serum triglycerides?. *Current opinion in lipidology* **17(4)**, 387-393.
- Ingole SP, Kakde AU, Bonde PB.** 2016. A Review on Statistics of Cancer in India. *Journal. Environ. Science. Toxicol. Food Technol* **10(7)**, 107-116.
- Jayaprakasam B, Vareed SK, Olson LK, Nair MG.** 2005. Insulin secretion by bioactive anthocyanins and anthocyanidins present in fruits. *Journal of Agricultural and Food Chemistry* **53(1)**, 28-31.
- Kaiser N, Leibowitz G, Nesher R.** 2003. Glucotoxicity and β -cell failure in type 2 diabetes mellitus. *Journal of Pediatric Endocrinology and Metabolism* **16(1)**, 5-22.
- Kobayashi K, Saito Y, Nakazawa I, Yoshizaki F.** 2000. Screening of crude drugs for influence on amylase activity and postprandial blood glucose in mouse plasma. *Biological and Pharmaceutical Bulletin* **23(10)**, 1250-1253.
- Korotchikina LG, Sidhu S, Patel MS.** 2004. R-lipoic acid inhibits mammalian pyruvate dehydrogenase kinase. *Free radical research* **38(10)**, 1083-1092.
- Kotecha R, Takami A, Espinoza JL.** 2016. Dietary phytochemicals and cancer chemoprevention: a review of the clinical evidence. *Oncotarget* **7(32)**, 52517.
- Lavigne C, Tremblay F, Asselin G, Jacques H, Marette A.** 2001. Prevention of skeletal muscle insulin resistance by dietary cod protein in high fat-fed rats. *American Journal of Physiology-Endocrinology and Metabolism* **281(1)**, E62-E71.
- Martineau LC, Couture A, Spoor D, Benhaddou-Andaloussi A, Harris C, Meddah B, Prentki M.** 2006. Anti-diabetic properties of the Canadian lowbush blueberry *Vaccinium angustifolium* Ait. *Phytomedicine* **13(9-10)**, 612-623.
- McClements DJ.** 2014. *Nanoparticle- and microparticle-based delivery systems: Encapsulation, protection and release of active compounds.* CRC Press.
- McCue P, Kwon YI, Shetty K.** 2005. Anti-diabetic and anti-hypertensive potential of sprouted and solid-state bioprocessed soybean. *Asia pacific Journal of*

clinical nutrition **14(2)**, 145.

Mehta D. 2017. Integrative medicine and cardiovascular disorders. Primary Care: Clinics in Office Practice **44(2)**, 351-367.

Mermel VL. 2004. Old paths new directions: the use of functional foods in the treatment of obesity. Trends in food science & technology **15(11)**, 532-540.

Montonen J, Knekt P, Järvinen R, Reunanen A. 2004. Dietary antioxidant intake and risk of type 2 diabetes. Diabetes Care **27(2)**, 362-366.

Naeem M, Hayat M, Qamar SA, Mehmood T, Munir A, Ahmad G, Azmi UR, Faryad MA, Talib MZ, Irfan M, Hussain A, Hayder MA, Ghani U, Mehmood F. 2019. Risk factors, genetic mutations and prevention of breast cancer. Int. J. Biosci. **14(4)**, 492-496,

Perera PK, Li Y. 2012. Functional herbal food ingredients used in type 2 diabetes mellitus. Pharmacognosy reviews **6(11)**, 37.

Perrone D, Ardito F, Giannatempo G, Dioguardi M, Troiano G, Lo Russo L, Lo Muzio L. 2015. Biological and therapeutic activities, and anticancer properties of curcumin. Experimental and therapeutic medicine **10(5)**, 1615-1623.

Pietta PG. 2000. Flavonoids as antioxidants. Journal of natural products **63(7)**, 1035-1042.

Plat J, Mensink RP. 2005. Plant stanol and sterol esters in the control of blood cholesterol levels: mechanism and safety aspects. The American journal of cardiology **96(1)**, 15-22.

Ried K. 2016. Garlic Lowers Blood Pressure in Hypertensive Individuals, Regulates Serum Cholesterol, and Stimulates Immunity: An Updated Meta-analysis and Review, 2. The Journal of nutrition **146(2)**, 389S-396S.

Shishikura Y, Khokhar S, Murra BS. 2006. Effects of tea polyphenols on emulsification of olive oil in a small intestine model system. Journal of agricultural and food chemistry **54(5)**, 1906-1913.

Shukla Y, Singh R. 2011. Resveratrol and cellular mechanisms of cancer prevention. Annals of the New York Academy of Sciences **1215(1)**, 1-8.

Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, Sabatine MS. 2016. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. Jama **316(12)**, 1289-1297.

Spoorthi BC, Gautham SA, More SS, Maiti AK. 2018. Nutraceuticals: Potential therapeutic agents for the treatment and prevention of cardiovascular diseases. Journal of Pharmacy Research **12(2)**, 231.

Ting Y, Jiang Y, Ho CT, Huang Q. 2014. Common delivery systems for enhancing in vivo bioavailability and biological efficacy of nutraceuticals. Journal of Functional Foods **7**, 112-128.

Watanabe J, Kawabata J, Kurihara H, Niki R. 1997. Isolation and identification of α -glucosidase inhibitors from tochu-cha (Eucommia ulmoides). Bioscience, biotechnology, and biochemistry **61(1)**, 177-178.

Way TD, Lin HY, Kuo DH, Tsai SJ, Shieh JC, Wu JC, Li JK. 2009. Pu-erh tea attenuates hyperlipogenesis and induces hepatoma cells growth arrest through activating AMP-activated protein kinase (AMPK) in human HepG2 cells. Journal of agricultural and food chemistry **57(12)**, 5257-5264.

Yang CS, Li G, Yang Z, Guan F, Chen A, Ju J. 2013. Cancer prevention by tocopherols and tea polyphenols. Cancer letters **334(1)**, 79-85.

Yang F, Song L, Wang H, Wang J, Xu Z, Xing N. 2015. Quercetin in prostate cancer: Chemotherapeutic and chemopreventive effects, mechanisms and clinical application potential. *Oncology reports* **33(6)**, 2659-2668.

Young JF, Dragsted LO, Haraldsdottir J, Daneshvar B, Kall MA, Loft S, Huynh-Ba T. 2002. Green tea extract only affects markers of

oxidative status postprandially: lasting antioxidant effect of flavonoid-free diet. *British Journal of Nutrition* **87(4)**,

Zhu W, Qin W, Zhang K, Rottinghaus GE, Chen YC, Kliethermes B, Sauter ER. 2012. Trans-resveratrol alters mammary promoter hypermethylation in women at increased risk for breast cancer. *Nutrition and cancer* **64(3)**, 393-400.