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Review Article

SPECTRA OF ALTERNATIVE THERAPIES OF HYPERCHOLESTEROLEMIA BY DIETARY BIOACTIVES: EMPHASIS ON NUTRIGENOMICS OF POLYPHENOLS

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ABSTRACT

Hypercholesterolemia is a clinical situation characterized by the elevated serum cholesterol and associated with the higher risk of cardiovascular disease, hypertension and stroke. Though current therapeutic strategies of hypercholesterolemia meet the present treatment demand but their efficacy is in question as well as the emergence of medicinal resistance. Demand of new therapeutic strategies is obvious while alternative therapeutic strategies are highly promising. Alternative therapeutic approaches are must in that respect but current experimental findings are still ambiguous and scarce. Several transcription factors playing vital role in cholesterol homeostasis and hypercholesterolemia change their expression profile in response to dietary polyphenols like PPARs, SREBPs, SHP, LXR, FXR etc. Function and expression of a number of proteins considered as therapeutically important regarding hypercholesterolemia like HMG-CoA reductase, CYP7A1, CETP, ABCA1 etc. are modulated by the dietary polyphenols. Experimental paradigm lacks to show the effect of polyphenols in metabolite profile under hypercholesterolemia. Therefore, alternative therapeutic approaches of the hypercholesterolemia under the shade of nutrigenomics by dietary bioactive like polyphenols should be focused and flourished for development of more efficient, highly specific and natural therapeutic approaches.

Keywords: Alternative therapy, Polyphenols, Nutrigenomics, Hypercholesterolemia.

INTRODUCTION:

Cholesterol is an organic molecule that is the major sterol synthesized in the animal. Cholesterol has multiple effects on the physical properties of biological membrane like membrane order (fluidity), phase behavior, thickness, and permeability [1]. It also serves as a precursor for the biosynthesis of steroid hormones, bile acids, and vitamin D [2]. Indeed, cholesterol is a two-edge sword from the view of physiological role. While cholesterol is vital for normal health while hypercholesterolemia, high blood cholesterol level, is considered as a risk factor for cardiovascular diseases like heart disease, stroke and hypertension [3]. The prevalence of elevated cholesterol among patients with a history of hyperlipidemia is associated with country-level economic development and health system indices [4]. However, WHO assign elevated total cholesterol is a major cause of disease burden in both the developed and developing world as a risk factor for Ischemic heart disease and stroke. According to WHO, elevated cholesterol is estimated to cause 2.6 million deaths yearly [5].

Though the loss of life is massive but treatment therapy only based on the preventive measures. Currently, a combination of therapeutic lifestyle modification and medication is recommended as treatment strategies. Being a primary prevention strategy, a therapeutic dietary advice is sufficient for the treatment of mildly elevated cholesterol. Actually such a therapeutic dietary regulation mediates a modest decrease in cholesterol levels [6]. An adaptation of the primary and secondary prevention strategy depends on the risk category classified roughly based on serum LDL levels. Pharmacotherapies that occupy a vital place in both primary and secondary prevention strategies involve medication with statins, fibrates, nicotinic acid, cholestyramine etc. Among these medications, statin is most commonly used medication while others are only recommended when statin is not tolerated [7]. Several studies deny the statin as efficient primary preventive medication [8,9]. Some other study showed satin as disable therapy in case of high-risk category patients while statin resistance is increasing continuously beside side effects of statin [7, 10, 11]. Current situation therefore, emphasizes on an alternative in-depth scientific focus on the pathogenesis and therapeutic intervention toward hypercholesterolemia.

The emergence of alternative treatment by non-nutritious dietary bioactives like phytochemicals is very promising for the treatment of chronic disease. Dissection of the impact of alternative therapy in the view of evidence-based research might open a new venture of therapeutic intervention toward chronic disease like hypercholesterolemia. In this review we therefore first go through the spectra of alternative therapy concerning hypercholesterolemia. Nutrigenomics being a modern, rational therapeutic basis aims at the prevention or protection of chronic disease has made it highly hopeful. Unfortunately, nutrigenomics insights toward alternative therapy of hypercholesterolemia, though promising, are still scarce. Therefore, nutrigenomics concern and insights regarding hypercholesterolemia will be discussed elaborately next. Finally, we will summarize the recent experimental evidences of alternative therapy of hypercholeterolemia and remark with recommendations.

DIETARY BIOACTIVES

Food or dietary bioactives are extra-nutritional constituents that typically occur naturally in small quantities in foods of plant or animal origin. But plant-based bioactives are of great importance due to their health beneficial effects [12]. Besides epidemiologic data a large number of experimental data suggests that plant-based diets have protective effects against chronic disease like cardiovascular disease (CVD), diabetes and cancer [13]. A large number of bioactive compounds have been discovered yet. These food bioactives include polyphenols, flavonoids and phytoestrogens; lycopene; plant sterols; dietary fibers; saponins, terpenoids etc. The effect of such food bioactives ultimately depends on their molecular targets within the human body.

ANIMAL AND PLANT-DERIVED DIETARY BIOACTIVES

Both animal-derived and plant-derived dietary components are considered as effective alternative therapy.

OILS

Several of our investigations have focused on hyporcholesterolemic effects the animal derived food like the fish oil [14, 15, 16, 17]. In a study we demonstrated the probable higher efficacy of animal

source derived edible oil than that of the plant source derived edible oil. We actually evolved the effects of Hilshailisha fish oil, soybean and palm oils on the lipid profile of experimentally induced hypercholesterolemic rats. The feeding of Hilsha fish oil significantly decreased the serum and liver cholesterol with a concomitant fall in serum LDL-cholesterol, an increase in HDL-cholesterol level and fecal cholesterol level compared to soybean and/or palm oil fed rats. The animal-derived Hilshailisha fish oil was more effective in reducing the serum and liver cholesterol than soybean and palm oil, though both soybean and palm oil are also effective in reducing serum and liver cholesterol [18].

CHITOSAN

Besides the conventional animal derived dietary components, unconventional animal-derived dietary components like animal-derived dietary fibers also demand special focus due to significant hypercholesterolemic effect. For example, chitosan, a polysaccharide deacetylated from chitin, obtained from the exoskeletons of shrimps, lobsters, crabs and other crustaceans are known to have significant hyporchole sperolemic effect. Feeding of chitosan to hypercholesterolemic rats significantly reduced plasma total cholesterol and LDL-cholesterol while increased the HDL-cholesterol. Profiling of the plasma fatty acid clearly indicated a significant increase in the molar ratio of total unsaturated fatty acid (TUFA)/total saturated fatty acid (TSFA). Such a rise always represents the attribute of oxidative insult that repeatedly found to be concerned with hypercholesterolemia [19].

SAPONIN/POLYPHENOL-RICH FRUITS AND VEGETABLES

Plant-derived dietary component include a wide range of grain, vegetable, root and fruit. Recent dietary advice to counter hypercholesterolemia always includes fibrous vegetables and polyphenol and/or saponnin rich fruits. Very recently, we found that the extract of *Raphanus sativus* Linn. (radish) significantly decreases the serum and liver cholesterol at the expense of fecal excretion of cholesterol (yet unpublished). In a previous study, we demonstrated that polyphenols-rich extract of *Syzygium cumini* seed significantly reduced alcohol-induced rise of total serum triacylglycerol (TG) and cholesterol (TC) while increased fecal cholesterol excretion. Such an anti-hypercholesterolemic effect of *Syzygium cumini* seed was associated with improvement of liver functional status also [20]. Interestingly, liver triacylglycerol and cholesterol also were reduced in the *S. cumini* seed extract feed rats.

MUSHROOM

Several recent researches have focused on the edible mushrooms as a promising alternative dietary based alternative therapy against hypercholesterolemia. We investigated the effects of edible oyster mushroom *Pleurotus ostreatus* on plasma and liver lipid profiles previously in experimental hypercholesterolemic rats. The study result showed an excellent and significant reduction of TC, LDL-C and TG in mushroom fed hypercholesterolemia rats by 28%, 55% and 34% respectively compared to their hypercholesterolemic counterparts. The feeding of *P. ostreatus* mushrooms also reduced total liver cholesterol levels by about 30%, with a concurrent increase in HDL–cholesterol concentration of about 20%. Interestingly the profiling of the serum fatty acid analysis showed that the palmitic acid was decreased while oleic acid, linoleic acid and linolenic acid increase in the mushroom fed hypercholesterolemic rats with a total decrease in unsaturation index compared to hypercholesterolemic rats [21]. Our study also demonstrated the hypercholesterolemic effect of commonly cultivated oyster mushrooms in Bangladesh namely *Pleurotus ostreatus, P. sajor-caju,* and *P. florida.* Plasma lipid profiling in the hypercholesterolemia rats fed with oyster mushrooms decrease plasma total cholesterol level by 16-37% compared to hypercholesterolemia controls. Furthermore mushroom feeding was found to decrease LDL/HDL ratio by 41-64% without any interfering influence on the liver and kidney functions [22].

NUTRIGENOMICS: A DIALOUGE BETWEEN GENE AND DIETARY COMPONENT

Genome-wide effects of foods and food constituents refer to nutrigenomics [23]. Nutrigenomics includes the study of molecular relationships between nutrients and genes (nutrigenetics), how these interactions influence changes in the profile of transcripts (transcriptomics), proteins (proteomics), and metabolites (metabolomics) [24]. In nutrigenomics, food constituents are considered as dietary signals that are detected by the cellular sensory systems and ultimately regulate gene and protein expressions and affect metabolite productions [25]. Such regulation of gene expression by particular nutrients or dietary protocols could produce a specific pattern of gene, protein and metabolite expressions which can be viewed as 'dietary signatures'. Nutrigenomics studies include dietary signatures in specific cells, tissues and organisms. Nutrigenomics researches actually involve two interacted strategies. The first strategy provides deliberate information regarding the interaction between genome and nutrition at the molecular level. The second strategy establishes a variety of physiological condition specific biomarkers that aids in tracking the health of an individual at any time or stage of life [26]. The ultimate goal of nutrigenomics is that of developing genomics-based biomarkers that help in the early detection and prevention of diet-related diseases.

ALTERNATIVE THERAPY: NUTRIGENOMICS CONCERNS

Alternative therapy is the therapeutic approaches other than the conventional therapies. Alternative therapy has either complementary mood when used together with conventional medical treatments or integrative mood when used in combination with evidence-based medicines [27]. However, alternative therapeutic approach covers an appreciable domain in the treatment of hypercholesterolemia. Plant-based alternative treatment of hypercholesterolemia is very popular due to market demand despite of a poor understanding of the efficacy and effects of the treatment. A statistic showed that 1.1% of US adult try alternative medicine as an attempt to treat cholesterol. Various herbal medications may lower average total cholesterol by 10 to 33 percent [28]. Such herbal or plant derived medicinal approaches ultimately depend on the presence of therapeutic components. These dietary components actually act as a signal which has the capacity of cholesterol lowing through single or multiple moods like inhibition of cholesterol absorption, inhibition de novo cholesterol synthesis or augmentation of reverse cholesterol transport etc. Thus, alternative therapies toward hypercholesterolemia possess an implicative but deem nutrigenomics aspect.

POLYPHENOLS: EFFECT ON TRANSCRIPTION FACTOR PROFILE

The phytochemicals present in the food can alter and/ or regulate the expression of the genetic information [23]. This change in the gene expression can be either directly or indirectly [29, 30]. Phytochemicals may directly act as a ligand for a transcription factor. In case of indirect mood, phytochemical or any of its metabolic intermediate of primary or secondary pathway can be involved in cell signaling that ultimately alternate existing gene regulation or signal transduction pathways.

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor superfamily [31]. Three types of PPARs have been identified in mammal encoded by separate gene: PPARα, PPARδ, and PPARγ. All of these PPARs form a heterodimeric complex with the retinoid X receptor (RXR) that binds to peroxisome proliferator hormone response elements occur in the promoter region of a target gene [32]. The expression pattern of each of PPAR is specific with PPARα and PPARγ predominantly in the liver and adipose tissue, respectively, and PPARδ in many tissues. PPARγ acts to regulate adipocyte differentiation as well as promoting lipid storage in mature adipocytes while PPARα enhances fatty acid combustion in the liver by upregulating genes encoding enzymes in β-oxidation [33]. Endogenous ligands for the activation of PPARs include eicosanoids, fatty acids and fatty acid derivatives [31]. Upon activation, it can modulate hypolipidemic effect by enhancing

catabolism of triglyceride-rich particles and reduced secretion of VLDL particles. PPARs are also known to be involved in the upregulation of HDL are apo A-I and apo A-II while the vasculature apo A-I interacts with the ATP-binding cassette transporter, ABCA1 and extracts cholesterol from cells like macrophage [34].

Dietary isoflavone activate PPARs by doubling PPARα-directed gene expression while increases PPARγ-directed gene expression 200-400% in obese rat [35]. Several researches have established genistein as a ligand of the PPAR-γ receptor. Genistein causes PPARα-directed enhancement of fatty acid catabolism genes in HepG2 [36]. Genistein supplementation in mice with diet-induced obesity markedly altered in the expression of 107 genes of which 97 transcripts were altered in the HFD-fed group and 84 genes were normalized by genistein supplementation [37]. Quercetin inhibited the activation of all three isoforms of PPAR where as its metabolites unregulated PPAR-γ expression [38, 39]. On the other hand a supplementary study demonstrates PPAR-γ as a potential molecular target of resveratrol, a naturally occurring polyphenol present in red wine, peanuts, and grapes [40].

Sterol regulatory element-binding proteins (SREBPs) belong to the basic helix-loop-helix leucine zipper family of transcription factors [41]. Sterol regulatory element-binding proteins (SREBPs) actually regulate enzymes responsible for the synthesis of cholesterol, fatty acids, and the low density lipoprotein receptor (LDLr) [42]. SREBPs are of two types SREBP1 and SREBP2 encoded by SREBF1 and SREBF2 gene respectively. Generally, SREBP-1 seems to be involved in energy metabolism including fatty acid and glucose/insulin metabolism, whereas SREBP-2 is specific to cholesterol synthesis [43]. However, SREBP-1a is the predominant SREBP-1 isoform expressed in cell lines that activates the genes involved in both cholesterol and fatty acid metabolism. Another isoform of SREBP-1 is SREBP-1c which predomintes in primary cell cultures and intact tissues and preferentially regulates genes involved in sterol biosynthesis [44]. In mammalian liver, SREBP-1c and SREBP-2 are the major isoforms of SREBP expressed [45].

Naringenin, a citrus flavonoid, induced PI3K-dependent increases in cytosolic and nuclear SREBP-1 and more specifically SREBP-1a. Such a PI3K-dependent activation of SREBP-1 by naringenin converges to increased LDLr expression where as the removal of LDL cholesterol from the blood is mainly mediated by LDLr [46]. The study of Murase et al., also showed the dietary supplementation of coffee polyphenols suppresses diet-induced body fat accumulation by suppressing SREBP-1c in high fat-fed mice. There was a concomitant decrease in the mRNA level of acetyl-CoA carboxylase-1 and -2, stearoyl-CoA desaturase-1, and pyruvate dehydrogenase kinase-4 in the liver coffee polyphenols-fed mice than that of high-fat control-fed mice [47]. *Hibiscus sabdariffa* polyphenols causes the reduction of SREBP-1, thus inhibiting the expression of fatty acid synthase and HMG-CoA reductase with a concomitant increase of LDLr in HepG2 cells. The polyphenol profile of hibiscus extracts like hydroxybenzoic acids, caffeoylquinic acids, flavonols, and anthocyanins overlaps with dietary polyphenols [48, 49].

Small heterodimer partner (SHP) is an orphan nuclear receptor lacking a DNA binding domain and consists only of putative ligand binding domain [50]. It is a member of the nuclear receptor family of intracellular transcription factors encoded by NR0B2 gene [51]. Small heterodimer partner exerts its effect by forming a non-productive heterodimers with other nuclear receptors. To date, a number of nuclear receptors are known to repress by SHP including Retinoid X receptor (RXR), Thyroid hormone receptor, Constitutive androstane receptor (mCAR), Estrogen receptor (ER), HNF4α, androgen receptor, ER related receptor γ (ERRγ), Liver receptor homolog-1 (LRH-1), Liver X receptor (LXR), Glucocorticoid receptor (GR), Pregnane X receptor, Retinoid X receptor alpha (RXR-α) [52, 53, 54]. SHP plays a pivotal role in the regulation of cholesterol homeostasis via repressing the expression cholesterol 7-α-hydroxylase (CYP7A1). CYP7A1, the rate-limiting enzyme in the natural pathway of bile acid biosynthesis is also under feedback-inhibited of hydrophobic bile acids [55, 56].

In a study by Bas et al. found that Procyanidins, the most abundant polyphenols in red wine, increase the mRNA levels of small heterodimer partner, CYP7A1 in rat [57]. Procyanidin also down regulates several lipogenic genes in mouse liver. The striking event is that, transcription factors of the liver are also modulated by procyanidine supplementation like steroid response element binding protein 1c (SREBP-1c) in a SHP-dependent manner [58].

As a result of supplementation of apple polyphenols expression of farnesoid X receptor (FXR) was up-regulated 1.5 times in the apple polyphenols-fed rats than those of the control rats [59]. In human monocytes-derived macrophage, resveratrol induced LXR-alpha expression [60]. Interestingly, naringenin, flavone, catechin, and quercetin, display in vitro agonist properties on the aryl hydrocarbon receptor (AhR) [61]. These, discreet study actually suggests the probable effect of dietary polyphenols of other transcription factors like FXR, LXR, AhR etc.

Table 1: Dietary polyphenols with target transcription factors and molecular signature.

Dietary Polyphenols	Target Transcription Factor	Summary Molecular Signature	References
Dietary isoflavone, Genistein, Quercetin, Resveratrol	PPARs: PPARα, PPARδ, and PPARγ	PPRAs gene induction; PPARs-induced gene expression upregulation or downregulation	26, 27, 29, 30, 31
Naringenin, Coffee polyphenols, Flavonols, Anthocyanins	SREBPs: SREBP-1, SREBP-1c, SREBP-2	SREBPs gene induction; SREBPs-induced gene expression upregulation or downregulation	37, 38, 39, 40
Procyanidins	SHP	SHP gene expression induction	48, 49
Apple polyphenols	FXR	FXR gene expression upregulation	50
Resveratrol	LXR-alpha	Inductive effect	51
Naringenin, Flavone, Catechin, Quercetin	AhR	Agonistic effect	52

POLYPHENOLS: EFFECT ON PROTEIN PROFILE

Apolipoproteins:

Apolipoproteins are polypeptide that binds to hydrophobic lipids of the human plasma like cholesterol, cholesteryl esters, triglycerides, and phospholipids to form spherical macromolecular complexes of lipid and apolipoprotin called lipoproteins. To date six classes (A, B, C, D, E & H) of apolipoprotin have been identified with the predominating role of three class of in lipid metabolism assigned as apo A, apo B, apo C [62]. In general, apolipoproteins maintain the structural integrity and solubility of lipoproteins.

Apolipoprotein A (Apo A) has two major forms apo AI and apo AII. Apo A-I is the major apolipoprotein associated with HDL-C and largely responsible for determining the plasma level of HDL [63]. Apo A-I is a cofactor for lecithin cholesterol acyl transferase (LCAT) involved in reverse cholesterol transport and also a ligand for the ATP-binding cassette (ABC) protein, ABCA1 involved in the docking procedure by which excess cholesterol in peripheral cells is externalized to HDL [64, 65]. Apo A-II inhibits hepatic and lipoprotein lipase (LL) activity [66]. Apolipoprotein B (Apo B) exists in two forms, apo B-48 and apo B-100. Apo B-48 is synthesized in the intestine and found to be present in chylomicron and its

remnants. Apo B-100 is synthesized in the liver and is present in LDL, IDL and VLDL particles. Apo B acts as a ligand for the LDLr and thus allows the internalization of LDL as well as absorbed cholesterol [67]. Apolipoprotein C (Apo C) is also associated with chylomicrons, VLDL-C and HDL-C [68]. Three major subtypes are found to be involved in lipid metabolism each of which are synthesized in the liver but have distinct functions. Both of apo C-I and apoC-III function as inhibitors for lipoprotein-receptor interactions and thus interfere with the clearance TG-rich lipoprotein (LDL, VLDL) from the circulation. Aporotein C-I (Apo-C) is a plasma inhibitor of cholesteryl ester transfer protein (CETP) but apo C-III inhibits LL while apo C-II is a major activator of LL [69, 70, 71]. Apolipoprotein E (Apo E) is a constituent of VLDL, IDL and chylomicrons. Apo E is involved in receptor recognition of intermediate density lipoprotein and chylomicron remnant by the liver. It is essential for the normal catabolism of triglyceride-rich lipoprotein constituents [72].

Several studies showed that dietary polyphenols can significantly modulate the expression as well as the function of several apolipoproteins while other study can be taken into advantage to explore the probable effect of polyphenols on the apolipoprotein expression. The study of Yasuda et al. suggest that cacao polyphenols namely (-)-epicatechin, (+)-catechin, procyanidin B2, procyanidin C1, and cinnamtannin A2 can unregulated the expression of apo A-I and apo B in both HepG2 cells and intestinal Caco2 cell lines probably through sterol regulatory element binding proteins (SREBPs)-dependant manner [73]. Red wine polyphenolics such as resveratrol (a stilbene, with estrogen-like activity), and the flavonoids, catechin, epicatechin, quercetin and phenolic acids such as gallic acid can suppress the secretion of apo B100 from human HepG2 cells [74].The study of a Kurowska et al. showed that polymethoxylated flavone from citrus fruits, tangeretin, marckedly reduce the apo B secretion in human hepatoma cell-line HepG2 [75]. In another supplementary study suggest an increase of apo A-I secretion concomitantly with the decrease of apo B in HepG2 cells as a result of taxifolin, a plant flavonoid, treatment [76].

Table 1: Dietary polyphenols with target protein and molecular signature

Dietary Polyphenols	Target Protein	Molecular Signature	References
Procyanidin B2, Procyanidin C1, Cinnamtannin A2, Resveratrol, Catechin, Epicatechin, Quercetin, Gallic acid, Tangeretin, Taxifolin	apo A-I, apo B, apo B100	Increase expression and secretion	64, 65, 66, 67
Catechin, Naringenin, Hesperetin, Gossypin, Eriocitrin, Red grape juice polyphenols	LDLr	Increase expression	69, 70, 71, 72, 73
Red grape juice polyphenols, Red wine polyphenolics, Resveratrol, Gossypin	HMG-CoA reductase	Increase or decrease expression	72, 74
Catechin, Resveratrol	CYP7A1	Expression upregulation	75, 76, 77
Resveratrol, Anthocyanin	CETP	Expression upregulation	78, 79
Olive oil polyphenols, Quercetin, Kaempferol, Curcumin	ABCA1	Expression upregulation	80, 81, 82

LDL-Receptor:

The Low-Density Lipoprotein Receptor (LDLr) is a transmembrane polypeptide that is 839 amino acids in length that can broadly be divided into 5 domains. The extracellular domain of LDLr can recognize apo B-100 embedded on LDL particle and apo E embedded on LDL and particles, Chylomicron remnants and VLDL remnants (IDL). The intracellular domain is responsible for the clustering of LDL receptors into regions of the plasma membrane termed coated pits. Once LDL binds the receptor, the complexes are rapidly endocytosed. It is the primary pathway for removal of cholesterol from the circulation. The function of LDLr also contributes to the intracellular cholesterol levels also [77].

Red grape juice (RGJ) polyphenols increases both the activity and cell surface expression of the LDLr and mRNA levels of LDLr in HepG2 [78]. Dealcoholized red wine contains a panel of polyphenols increases LDLr gene expression in HepG2 cells [74]. Catechin from the extract of green tea can up regulate the hepatic low-density lipoprotein receptor in rats [79]. The citrus flavonoids naringenin and hesperetin was found to increase the mRNA level of LDLr 5-fold and 7-fold respectively in HepG2 cell Line [80]. Lu et al., demonstrate that gossypin, a*glucosyl flavone*, up-regulates LDLr expression. This upregulation of LDLr was independent of SREBP-2 but is dependent on ERK activation [81]. Eriocitrin (eriodictyol 7-*O*-β-rutinoside) is the main flavonoid in lemon fruit that enhanced hepatic mRNA levels of LDLr in comparison with the control group [82].

Cholesterol metabolizing enzymes and others

A panel of enzymes and proteins participate in cholesterol metabolism is therapeutically considered as very important including HMG-CoA reductase, cholesterol 7α-hydroxylase (CYP7A1). Beside these, ATP-binding cassette transporter ABCA1 (ABCA1) and Cholesterol ester transfer protein (CETP) also plays an important role in case of reverse cholesterol transport.

HMG-CoA reductase mediates the rate-limiting reaction of the cholesterol biosynthetic pathway. Dietary polyphenols can upregulate or downregulate HMG. Such as red grape juice polyphenols and red wine polyphenolics increase the levels of HMG-CoA reductase levels in HepG2 cell lines. But rosovasterol can attenuate expression of HMG-CoA reductase mRNA in hamsters while Gossypin treatment remain HMG- CoA reductase as unaffected [83, 81].

Cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting enzyme in the natural pathway of bile acid biosynthesis that is also under feedback-inhibited of hydrophobic bile acids [81, 82]. Appraisal study supports that CYP7A1 is a good therapeutic target for the hypocholesterolemic effect of dietary polyphenols [84]. Green tea catechin enhances cholesterol 7α-hydroxylase gene expression at both mRNA level and promoter activity in a dose-dependent manner in HepG2 cells [85]. Resveratrol significantly increased liver expression of CYP7A1 mRNA and protein and CYP7A1 enzyme activity. Furthermore, rosovasterol treatment upregulates CYP7A1 expression and induced liver X receptor alpha (LXRα) activation in a time and dose dependent manner in HepG2 cells [86].

Cholesterol ester transfer protein (CETP) is a plasma protein secreted primarily from the liver. It facilitates the exchange of cholesteryl esters from HDL for triglycerides from LDL and VLDL. Several studies rise hope that the CETP expression could be under the influence of dietary polyphenols. Resveratrol can inhibit CETP activity in hamsters fed a high fat diet. The mass and activity of plasma CETP were decreased by anthocyanin supplementation in human HepG2 cells [87, 83]. But the study of Lam et al., suggest probable null effect of dietary polyphenols on CEPT expression [88].

ATP-binding cassette transporter-A1 (ABCA1) is a protein that transfers cellular cholesterol and phospholipids to HDL that is ultimately attributed to reverse cholesterol transport. Olive oil polyphenols has been reported to enhance the expression of cholesterol efflux related genes ABCA1, scavenger receptor class B type 1 in white blood cells [89]. Quercetin and kaempferol, two major polyphenols of aqueous extracts of Welsh onion green leaves showed an inductive effect on the ABCA1 in macrophages [90]. Furthermore, in curcumin induced apoptosis resistant M14 melanoma ATP-binding cassette transporter ABCA1 is over-expressed as a result of curcumin treatment, a naturally occurring polyphenol of the rhizome of turmeric [91].

POLYPHENOLS: EFFECT ON METABOLITE PROFILE

The abnormalities of cholesterol metabolism are closely associated with hypercholesterolemia. Hepatic cholesterol synthesis, lypolysis in adipose tissue, exogenous cholesterol absorption and distribution, reverse cholesterol transport, bile synthesis pathways and intracellular cholesterol pool play intricate role to maintain the plasma cholesterol levels. All these pathways actually contribute to the entire cholesterol metabolism. A set of the metabolite is involved in cholesterol metabolism. But most of the study deals with the hypocholesterolemic effect of a particular dietary polyphenols only focus on the ultimate end product of these metabolic pathways.

CONCLUDING REMARKS

Dietary polyphenols, as a signaling molecule, have the capacity to modulate the gene expression. A panel of transcription factors like PPAR, SREBPS, SHP, LXR, FXR play vital role in the molecular regulation of genes involved in cholesterol metabolism as well as hypercholesterolemia. According to current experimental evidence several of these transcription factors are either directly or indirectly influenced by dietary polyphenols. Current researches are not enough to pasteurize the complete dietary signature of dietary polyphenols on transcription factors. Therefore, further researches are recommended to explore the effect of polyphenols from different dietary sources on different transcription factors associated with tissue or cell specific cholesterol metabolism and/or hypercholesterolemia.

At the molecular level proteins execute the ultimate effect of gene expression modulation by the dietary polyphenols. A number of proteins are known as therapeutically important regarding hypercholesterolemia like HMG-CoA reductase, CYP7A1, CETP, ABCA1 etc. These protein expression and functions are also known to be modified by the dietary polyphenols. But, current findings of such modulation are still ambiguous and elusive. Unfortunately, no clear evidence exists in support of the metabolite profile regarding cholesterol metabolism and/ or hypercholesterolemia under the influence of dietary polyphenols. Therefore, alternative therapeutic approach toward hypercholesterolemia by dietary bioactive like polyphenols urge further researches on proteom and metabolom regarding hypercholesterolemia.

CONFLICT OF INTEREST

The author declares that there is no conflict of any competing interests.

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