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Functional food ingredients for the management of obesity and associated co-morbidities – A review

Ritesh K. Baboota[a], *Mahendra Bishnoi*[a], *Padma Ambalam*[b], *Kanthi Kiran Kondepudi*[a,*], *Siddhartha M. Sarma*[a], *Ravneet K. Boparai*[c], *Koteswaraiah Podili*[d]

[a]*National Agri-Food Biotechnology Institute (NABI), S. A. S. Nagar, Punjab, India*
[b]*Department of Biotechnology, Christ College "Vidya Niketan", Saurashtra University, Rajkot, Gujarat, India*
[c]*Department of Biochemistry, Panjab University, Chandigarh, Punjab, India*
[d]*School of BioSciences and Technology, VIT University, Vellore, Tamil Nadu, India*

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ABSTRACT

Worldwide obesity has reached a pandemic proportion. World Health Organization (WHO) estimates that by 2020, two thirds of the global disease burden will be attributable to obesity and obesity associated complications. Existing anti-obesity drugs, affecting one of the fundamental processes of the weight regulation in human body, have displayed serious side effects which outweigh their beneficial effects. Clinical and non-clinical researchers in this area are now facing a challenge to search for non-pharmacological alternatives for the prevention of obesity. Dietary interventions and life style changes with enhanced physical activity are two such options. Considering the importance of dietary interventions, the present review highlights the role, significance and potential of functional food ingredients for the management of obesity and associated co-morbidities.

* *Corresponding author.* Address: National Agri-Food Biotechnology Institute (NABI) (An Autonomous Institute of the Department of Biotechnology, Government of India) C-127, Industrial Area, Phase 8, S. A. S Nagar (Mohali), 160071 Punjab, India. Tel.: +91 172 2290128; fax: +91 172 4604888.
E-mail address: Kiran@nabi.res.in (K.K. Kondepudi).
URL: http://www.nabi.res.in (K.K. Kondepudi).

Abbreviations: ACC, acetyl-CoA carboxylase; ALT, alanine aminotransferase; AMPK, adenosine monophosphate-activated protein kinase; aP2, adipocyte protein 2; AST, aspartate aminotransferase; ANGPTL4, angiopoietin-related protein 4; C/EBPα, CCAAT-enhancer-binding protein alpha; CPT-1α, carnitine palmitoyltransferase-1alpha; FABP, fatty-acid-binding protein; FAS, fatty acid synthase; GLUT4, glucose transporter type 4; GPCRs, G-protein-coupled receptors; HDL-C, high-density lipoprotein-Cholesterol; JNK, c-Jun N-terminal kinases; KLF5, Krüppel-like transcription factor-5; LDL, low density lipoproteins; LDL-C, low density lipoprotein-cholesterol; LPS, lipopolysaccharide; MMP-2, matrix metalloproteinase-2; MAPK/ERK, mitogen-activated protein kinases/extracellular signal-regulated kinases; PPARγ, peroxisome proliferator-activated receptor gamma; SCFA, short chain fatty acid; SREBP-1c, sterol regulatory element-binding protein-1c; TC, total cholesterol; UCP2, uncoupling protein-2; TLR, toll like receptors; VEGF, vascular endothelial growth factor; TNFα, tumor necrosis factor-alpha.

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1. Introduction

Obesity is characterized by an increase in body mass index (BMI), defined as a person's weight in kilograms divided by square of the height in meters (kg/m^2). Obesity is classified as class I for BMI in-between 30–35, associated with moderate risk; class II in-between 35–39.9 at high risk and class III for a BMI $\geqslant$40 associated with a very high risk of mortality (González-Castejón & Rodriguez-Casado, 2011). Obesity is the fifth leading risk for global deaths and 2.8 million people die across the world every year due to obesity and its associated complications (WHO-World Health Statistics, 2012). In both developed and developing countries, obesity has become epidemic with rates being doubled (10% and 14% of men and women respectively in 2008 as compared to 5% and 8% men and women respectively in 1980) during the past three decades worldwide (WHO-World Health Statistics, 2012). It is staggering that 62% of the American population are overweight and 26% of them are obese as per WHO reports. As per Indian perspective 7.3% of Indian population is overweight and 1.2% is obese (Chatterjee, 2002). According to National Health Family Survey data, India, Punjab is the "heaviest" state with 30% of males and 38% of females being obese (National Survey, 2007). Development of adipose tissue, its secretome, types of adipose depots and their physiology have been reviewed elsewhere (Delzenne, Neyrinck, Bäckhed, & Cani, 2011).

Current anti-obesity medications are pharmacological agents which can reduce or control weight by altering appetite, metabolism or consumption of calories (Rodgers, Tschöp, & Wilding, 2012). They are not only difficult to develop but also pose undesirable side effects. Fen-phen (combination of fenfluramine and phentermine), an anti-obesity drug during 1990s, had an efficacy of up to 10% body weight loss, drew around 50,000 product liability lawsuits amounting to claims of 14 billion dollars. Side effects of the drug include pulmonary hypertension and heart valve problems (Mark, 2009). Fenfluramine (serotonin reuptake inhibitor) and Sibutramine (nor-adrenaline and serotonin reuptake inhibitor) were approved by FDA in 1973 and 1997, respectively, and were withdrawn in 1997 and 2010, respectively, due to their serious cardiovascular complications; pulmonary hypertension and increased risk of heart attack and stroke (Kang & Park, 2012). Rimonabant, a cannabinoid-1 receptor antagonist, approved by EMA in 2006, was withdrawn in 2009 due to increased suicidal tendency (Kang & Park, 2012). Orlistat, pancreatic lipase inhibitor, is also associated with multiple side effects (Adan, 2013; Dietrich & Horvath, 2012).

Recently, after 13 years, US-FDA approved two anti-obesity drugs, lorcaserin (serotonin receptor agonist, trade name Belviq, Arena pharmaceuticals, Nancy Ridge DriveSan Diego, CA, USA) and a combination of phentermine (increases the release of biogenic amines e.g. nor adrenaline, dopamine and serotonin) and topiramate, which acts on the brain receptor associated with satiety. The potential side effects (increased cardiovascular concerns, stroke, suicidality, depression, hyperoxaluria, and kidney stones) of these drugs outweigh their beneficial effects (Carter, Mouralidarane, Ray, Soeda, & Oben, 2012; Higgins et al., 2012). Companies like Merck stopped anti-obesity research due to persistent issues with side effects (Adan, 2013; Dietrich & Horvath, 2012).

Epidemic of obesity has been increased due to both extrinsic factors such as control of ambient temperature, decreased physical activity, increased sedentariness, availability of cheap and high-calorie foods as well as intrinsic factors such as genetic, epigenetic and developmental factors (Harley & Karp, 2012; Schwartz, 2012). Obesity is associated with multiple co-morbidities like type 2 diabetes, cardiovascular complications such as hypertension, hyperlipidemia, arteriosclerosis, and cancer. It has recently been recognized that human and other animal's gastrointestinal tract microbes (gut microbes) also contribute towards obesity development (Delzenne et al., 2011). Trillions of bacteria containing thousands of species colonize the gut and perform vast number of functions such as fermentation of nutrients; secretes an array of bioactive compounds and act as an environmental factor that affects host's physiology and metabolism (Delzenne et al., 2011). Hence it can be considered as a separate organ of humans. Metagenomic analysis of human gut microbiota revealed an uneven existence of representatives of *Firmicutes* and *Bacteroidetes* (dominant phyla, >90% of total microbiota) and *Proteobacteria*, *Fusobacteria*, *Verrucomicrobia* and *Actinobacteria* (subdominant phyla) (Candela et al., 2010). More than 1800 genera and 16,000 phylotypes at species level have been identified and more species yet to be identified (Peterson, Frank, Pace, & Gordon, 2008). Fine balance between good and pathogenic bacteria within gut determines health of the colon of an individual. This, in turn, is dependent on age, gender, genetic background of host and environmental conditions such as stress, drugs, gastrointestinal

surgery, infectious and toxic agents. Specific food components such as fatty acids, carbohydrates, micronutrients, prebiotics and probiotics intake may bring significant changes not only in gut microflora composition but also gene expression in host tissues such as colon, small intestine, liver, adipose and muscle. Gut microbiota may also influence overall brain function and behaviour of an individual through central nervous system possibly by neural, endocrine and immune pathways (Cryan & Dinan, 2012). Gut microbial association in pathogenesis of obesity has recently become a major topic of research in biology (Sommer & Bäckhed, 2013). Gut microbiota increases energy harvest, secretes lipopolysaccharides (LPS) and increases intestinal permeability (Musso, Gambino, & Cassader, 2010; Ouchi, Parker, Lugus, & Walsh, 2011). A perturbation (dysbiosis) in gut microflora such as fewer *Bacteroidetes* and more *Firmicutes* and LPS secreting Gram negative pathogens were observed in gut of obese humans and animals (Ley, Turnbaugh, Klein, & Gordon, 2006; Ley et al., 2005; Ouchi et al., 2011). LPS activates pro-inflammatory pathway (more IL-6 and C-reactive protein) that leads to low-grade inflammation under obesity (Ouchi et al., 2011; Zhang et al., 2010; Zhang et al., 2012). *Escherichia coli* LPS induced obesity was manifested into metabolic endotoxemia with insulin resistance, type 2 diabetes and hyperlipidemia in mice fed with high-fat diet (HFD) (Cani et al., 2007).

An endotoxin-producing *Enterobacter cloaca* B29 that could induce obesity and insulin resistance in germ-free mice fed with HFD was isolated from an obese human's gut (Fei & Zhao, 2012). Intervention with a diet containing whole grains, traditional Chinese medicinal foods and prebiotics decreased *Enterobacter* load; hyperglycaemia and hypertension after 23 weeks (Fei & Zhao, 2012). This strengthened the argumentation of the role of certain gut bacterial groups in obesity development. More details on the association of gut microbiota and obesity have recently been reviewed (Harley & Karp, 2012).

The dismal history of anti-obesity medications is suggestive of their non-reliability and a need for alternative approaches. Genetic and epigenetic changes related to life style (over feeding, less exercise) alterations switches the balance towards fat accumulation. Over the years it has been seen that the best and most effective options for overweight and obese individuals remain to be diet and physical activity. Management through diets can be achieved by identifying bioactive functional food ingredients that could modulate molecular pathways and gene/protein expressions in a beneficial way along with calorie restriction and exercise (Bishnoi, Kondepudi, Baboota, Dubey, & Boparai, 2013; Bishnoi, Kondepudi, Gupta, Karmase, & Boparai, 2013; Bédard, Dodin, Corneau, & Lemieux, 2012; Ho et al., 2012; Sahagún, Márquez-Aguirre, Quintero-Fabián, López-Roa, & Rojas-Mayorquín, 2012). With increase in knowledge about the role of certain pathogenic gut microbial groups in influencing host metabolic processes, diets rich in functional food ingredients seems to play an important role as they could beneficially modulate the gut microbes. It is of utmost importance to have dietary regulations to prevent and modulate life style problems rather than searching for treatment. Here, the old saying "prevention is better than cure" is very true. The present review, therefore, underlines the role; significance and development of plant derived nutraceutical/functional food ingredients such as polyphenols, dietary fibres, proteins and prebiotics in alleviating obesity and associated complications. Further, intentional gut microbial manipulation using dietary fibres, prebiotics, probiotics and synbiotics and their impact on weight gain, gut hormones and inflammatory markers along with their significance to obesity will also be discussed. Modulation of brain, adipose tissue, gut hormones, gut microbes and production of anti-inflammatory molecules by functional food ingredients and their role in regulating obesity is shown in Fig. 1.

2. Role of phytochemicals, nutraceuticals in obesity and related complications

2.1. *Dietary polyphenols (DPs)*

DPs are plant secondary metabolites involved in defence mechanism and are synthesized via shikimate pathway (Tsao, 2010). Thousands of polyphenols have been identified in vegetables, fruits, whole grains, legumes, and other plant sources. DPs are classified as phenolic acids, flavonoids (include flavonols, flavones, isoflavones, flavanones, anthocyanidins, flavanols), lignans and stilbenes (Tsao, 2010). Conjugated and bound polyphenols are mostly glycosylated and are hydrolysed to aglycones through gut bacterial fermentation (Shahidi, 2012). DPs undergo biotransformation by gut microbial enzymes, which alter their bioavailability and beneficial effects (Laparra & Sanz, 2010).

There has been a renewed interest on the health potentials of DPs (Chandrasekara & Shahidi, 2010). DPs consumption imparts diverse health benefits such as antioxidant (Pandey & Rizvi, 2009); inhibiting free radicals and reactive oxygen species (ROS) (Chandrasekara & Shahidi, 2011a); anti-cancer (Link, Balaguer, & Goel, 2010); anti-inflammatory (Park et al., 2012); antibacterial (González-Lamothe et al., 2009); antiviral activities (Tang, Ling, Koh, Chye, & Voon, 2012); anti-proliferative activity and DNA scission inhibitory activity (Chandrasekara & Shahidi, 2011b) and beneficial against osteoporosis, neurodegenerative disease, cardiovascular disease, diabetes mellitus and other metabolic disorders (Vauzour, Rodriguez-Mateos, Corona, Oruna-Concha, & Spencer, 2010). Investigation on anti-obesity action of polyphenolic extracts and polyphenolic compounds using animal cell cultures (3T3-L1) of adipogenesis and HFD induced obese animals suggested that DPs may inhibit pre-adipocyte to adipocyte differentiation, cause adipocyte apoptosis (Moghe, Juma, Imrhan, & Vijayagopal, 2012), decrease fat absorption from gut, uptake of glucose by skeletal muscles, suppress lipid biosynthesis and promote catabolism in adipose, liver and other tissues. They may promote anti-inflammatory molecules in adipose tissue. Adipocytes generate ROS due to fatty acid oxidation in mitochondria and peroxisomes that may lead to oxidative stress under obesity (Fernández-Sánchez et al., 2011). This results in dysregulated expression of pro-inflammatory adipokines. Oxidative stress may also be generated by excess oxygen consumption that generates free

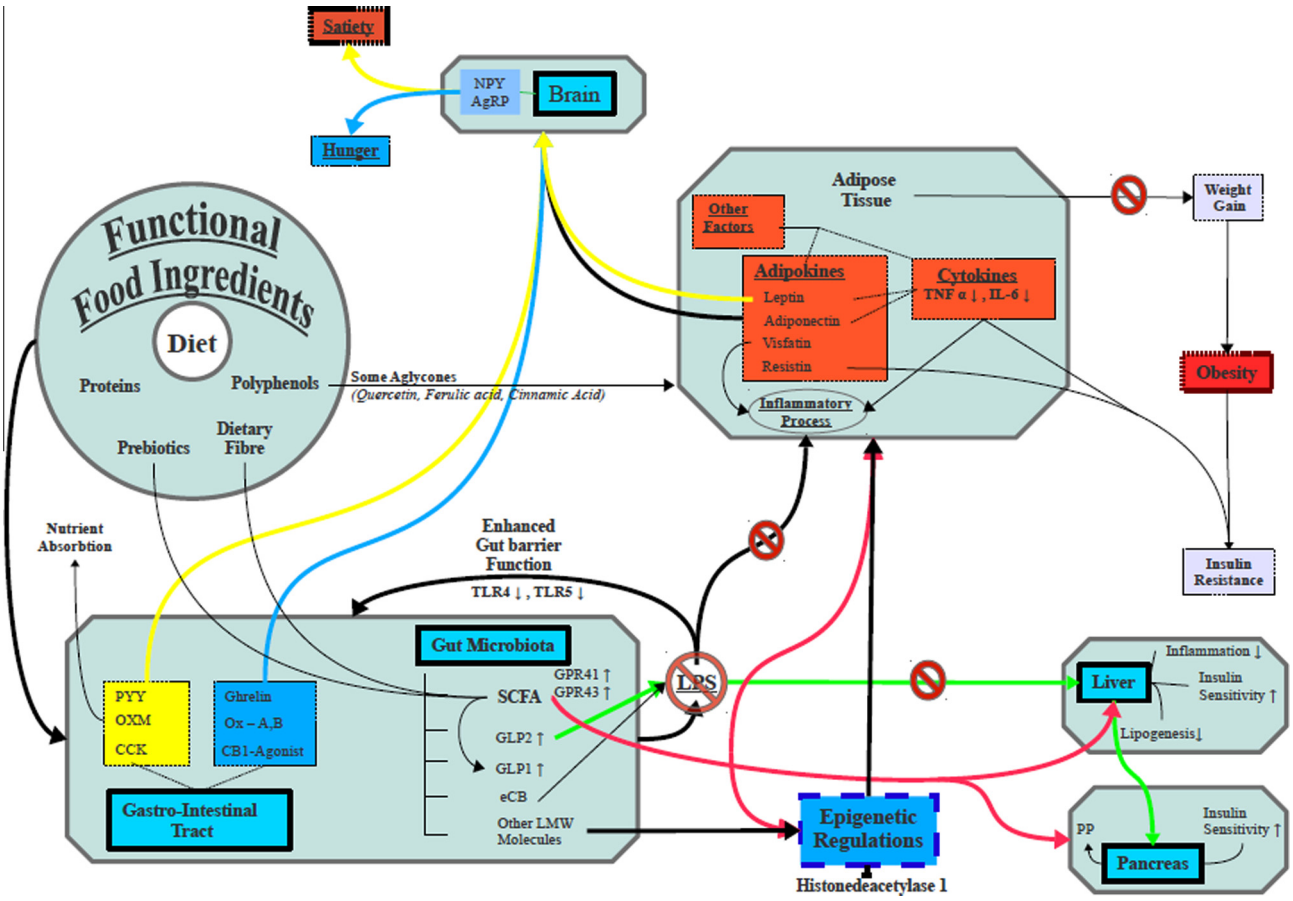

Fig. 1 – Interactions among functional food ingredients with brain; gut; gut microbiota; hormones/mediators; inflammatory molecules released by the adipose tissue. *Note*: Dietary polyphenols may prevent adipogenesis through inhibition of preadipocyte to adipocyte differentiation, preventing lipid accumulation, down regulation of transcription factors (C/EBPα, PPARγ and SREBP-1c), modulation of adipokine secretion, inhibition of lipogenic genes and/or through epigenetic regulation. Dietary proteins may inhibit adipogenesis and down regulate the associated transcription factors. DFs and prebiotics promote growth and numbers of beneficial gut microbes that produce SCFA. Certain SCFA transported to the adipose tissue, liver and pancreas helps in increasing insulin sensitivity, decreases lipogenesis and inflammation. They also stimulates the expression of GPR41 and GPR43 that in turn helps in the release of gut peptide hormones PPY, OXM, CCK and also leptin that influence the brain and causes satiety. Butyrate produced helps in epigenetic regulation of excess adipose tissue development through inhibition of histone deacetylase-1. Beneficial gut bacteria also helps in the secretion of gut hormones GLP2, eCB and others which in result suppress the activity of LPS and prevent its leakage into the circulation by enhancing intestinal barrier function and hence decreasing the obesity associated inflammation. Ghrelin, Ox-A, B, CB1 agonists on the other hand induces hunger.

radicals in mitochondrial respiratory chain coupled with oxidative phosphorylation (Fernández-Sánchez et al., 2011). Lipid-rich diets also cause production of ROS as they alter oxygen metabolism leading to a significant reduction in antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase (Fernández-Sánchez et al., 2011). This may in turn lead to obesity associated co-morbidities.

DPs bind to electrophile responsive elements on the promoters sites and enhance gene expression of endogenous antioxidant enzymes (Stevenson & Hurst, 2007). They regulate cell signalling and cell cycle progression, gene expression through epigenetic changes (inhibiting DNA methyltranferase activity), reversal of hypermethylation and reactivation of genes (Link et al., 2010). Here we summarize the anti-obesity effects and mechanism of action of DP extracts and pure compounds based on *in vitro* and *in vivo* studies (Tables 1 and 2).

Existing evidences show that DPs are effective and promote health via multiple signalling pathways (such as lipid anabolism/catabolism pathways, apoptotic pathways) (Milenkovic et al., 2012). However, for food applications, assessment of DP extracts may be suitable due to synergistic action of bioactives and are relatively safe. A combined treatment with genestein, quercetin, and resveratrol was shown higher inhibition of adipogenesis in both primary human adipocytes and 3T3-L1 murine adipocyte than individual molecules (Park et al., 2008). Focused clinical studies and interaction of polyphenols with genes associated with adipose tissue development are required. This will allow

Table 1 – Anti-obesity effect of different polyphenol rich plant extracts.

Plant extracts	Active ingredients	*In vitro/in vivo* effects	Mechanism	References
White tea	Epigallocatechingallate (0.17%)	Inhibited adipogenesis and stimulated lipolysis in 3T3-L1 cells	Decreased PPARγ, C/EBPα and C/EBPδ and SREBP-1c mRNA	Söhle et al. (2009)
Lindera obtusiloba	Lignans and butanolides	Inhibited adipogenesis in 3T3-L1 cells and slightly induced apoptosis in preadipocytes.	Lowered expression of GLUT4 and VEGF, inhibited Wnt pathway and down-regulation of PPARγ expression and reduced secretion of MMP-2	Freise et al. (2010)
Anthocyanidins-enriched bilberry extracts	Delphinidin, cyanidin, petunidin, peonidin, or malvidin and one glucoside (glucopyranose, galactopyranose, or arabinopyranose)	Inhibited 3T3-L1 adipocyte differentiation	Decreased expression of PPARγ, C/EBPα and SREBP-1c and tyrosine phosphorylation of IRS1 (insulin pathway)	Suzuki et al. (2011)
Citrus depressa Hayata peel	Nobiletin and tangeretin	Decreased body and white adipose weight in mice	Decreased plasma triglyceride and leptin levels; mRNA levels of lipogenesis-related genes, such as ap2, stearoyl-CoA desaturase 1, ACC-1, fatty acid transport protein and diacylglycerol acyltransferase 1 in adipose tissue	Lee et al. (2011)
Coffee polyphenols	Mono- or di-caffeoyl quinic acids	Decreased body weight, abdominal and liver fat accumulation, and infiltration of macrophages into adipose tissues of HFD induced obese mice	mRNA levels of SREBP-1c, acetyl-CoA carboxylase-1 and -2, stearoyl-CoA desaturase-1, and pyruvate dehydrogenase kinase-4 in the liver were decreased	Murase et al. (2011)
Acacia polyphenols	Robinetinidol and fisetinidol	Body weight, plasma glucose and insulin were suppressed in obese diabetic KKAy mice.	Decreased expression of fatty acid synthesis related genes (SREBP-1c, ACC and FAS) in the liver and TNFα in adipose tissue.	Ikarashi et al. (2011)
Green tea polyphenols	Catechins, epicatechin, epigallocatechin gallate,epicatechin gallate, epigallocatechin gallate	Body weight regulation in HFD induced obese rats	Normalised expression of 3 orexegenic genes, 7 anorectic genes and 2 energy related genes	Lu, Zhu, Shen, & Gao, 2012
Alpinia officinarum	Galangin	Inhibited adipogenesis in 3T3-L1 cells Decreased body, liver and adipose tissue weights in HFD induced obese mice	Down-regulated C/EBPα, SREBP-1, PPARγ Suppressed protein expressions of C/EBPα, fatty acid synthase, SREBP-1 and PPARγ in the liver and adipose tissue and decreased serum insulin and leptin	Jung et al. (2012)

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Table 1 – Anti-obesity effect of different polyphenol rich plant extracts.

Plant extracts	Active ingredients	*In vitro/in vivo* effects	Mechanism	References
Vigna angularis	Water soluble fibre; 16% polyphenols (470 mg anthocyanidins, 20.7 mg catechins, 2.33 mg caffeic acid, 2.62 mg ferulic acid, 44.5 mg quercetin, and 102 mg protocatechuic acid).	Significant reduction in total hepatic lipid accumulation and secretion into the faeces in rats. Decreased triglyceride accumulation, glycerol phosphate dehydrogenase activity and inflammatory responses in human adipocytes		Kitano-Okada et al. (2012)
Glycyrrhiza glabra Linne (Licorice) supercritical carbon dioxide extract	Glabridin	Inhibited adipogenesis in 3T3-L1 cells. Reduced weight gain; hypertrophy of adipose tissue in HFD induced obese mice	Reduced hepatic steatosis through down-regulation of phosphoenolpyruvate carboxykinase and glucose 6-phosphatase and up-regulation of CPT-1.	Ahn, Lee, Jang, Kim, and Ha (2013)

Table 2 – Anti-obesity effects of pure polyphenol compounds.

Dietary Polyphenol	*In vitro* and *in vivo* effect	Mechanism	References
Apigenin	Suppressed lipid accumulation and adipogenesis in 3T3-L1	Down-regulated expression of PPARγ and its targets aP2 and SCD, via AMPK pathway	Ono and Fujimori (2011)
Capsaicin	Stimulated lipolytic activity and reduced intracellular lipid content in 3T3-L1 adipocytes	Up-regulated mRNA levels of hormone sensitive lipase, CPT-1α and UCP2	Lee, Kim, Kim, and Kim (2011)
(−)-Catechin	Adipocyte differentiation was promoted in human bone marrow-multipotent stromal cells	Enhanced PPARγ and adiponectin expression	Shin et al. (2009)
Curcumin	Inhibited adipocyte differentiation in 3T3-L1 cells	Inhibited mitotic clonal expansion process and mRNA levels of transcription factors KLF5, C/EBPα and PPARγ	Kim, Le, Chen, Cheng, and Kim (2011)
	Suppressed adipocyte differentiation in 3T3-L1 cells	Reduced expression C/EBPα, PPARγ, SREBP-1 and FAS Inhibited mitogen-activated protein kinase (MAPK) (ERK, JNK, and p38); activated Wnt/β-catenin signalling and enhanced expression of c-Myc and cyclin D1	Ahn, Lee, Kim, and Ha (2010)

identifying novel dietary polyphenol responsive genes and regulatory pathways during adipogenesis, which in turn allow for designing polyphenol enriched functional food products for the obesity management. As high doses of polyphenols

Table 2 – Anti-obesity effects of pure polyphenol compounds.

Dietary Polyphenol	*In vitro* and *in vivo* effect	Mechanism	References
	Inhibited adipogenesis of 3T3-L1 cells and lipid accumulation	Decreased GPAT-1 mRNA expression and enhanced fatty acid oxidation through increased mRNA expression of CPT-1; activated AMPK pathway	Ejaz, Wu, Kwan, and Meydani (2009)
	Reduced body weight and adiposity in C57BL/6J mice	Increased fatty acid oxidation and reduced fatty acid esterification	
	Prevented differentiation of 3T3-L1 cells, and lipid accumulation	Down-regulated expression of FAS, PPARγ and CD36	Zhao, Sun, Ye, and Tian (2011)
(−)-Epigallocatechingallate	Inhibited 3T3-L1cell proliferation and suppressed adipose phenotype expression	Resulted in cell cycle arrest at G2/M and inhibited expression of C/EBPα and PPARγ	Chan, Wei, Castro-Muñozledo, and Koo (2011)
	Inhibited adipogenesis in 3T3-L1 cells	Down-regulated expression of PPARγ,C/EBPα, ap2 and FAS while up-regulated WNT/β-catenin pathway	Lee et al. (2013b)
Genistein	Inhibited lipid accumulation, decreased the non-esterified fatty acid(NEFA) content and attenuated the differentiation of 3T3-L1 cells	Inhibited the phosphorylation of p38 MAPK, inhibited the expression of FAS and phosphorylation of JAK2	Zhang et al. (2009)
Myricetin	Inhibited adipogenesis in human adipose tissue-derived mesenchymal stem cells	Decreased mRNA levels of C/EBPα, PPARγ, LPL, aP2 and adiponectin	Bin and Choi (2012)
Quercetin	Attenuated adipogenesis and induced apoptosis in mature adipocytes	Up-regulated AMPK pathway and activated apoptotic pathway	Ahn, Lee, Kim, Park, and Ha (2008)
Resveratrol	Lowered visceral adiposity and weight gain in HFD induced obese mice	Down-regulated adipogenic signalling molecules in adipose tissue. Suppressed expression of PPARγ2, C/EBPα, SREBP-1c, and LXR and their target genes FAS, LPL, aP2, and leptin in adipose tissues by down-regulating TLR2 and TLR4 expression	Kim, Jin, Choi, and Park (2011a)
	Attenuated cytokine production in adipose tissue and improved from inflammation		
	Inhibited preadipocyte proliferation, differentiation, and lipogenesis in human Simpson-Golabi-Behmel syndrome (SGBS) preadipocytes	Sirtuine1 is responsible for resveratrol-induced inhibition of proliferation. Down-regulated PPARγ expression. Down-regulated lipogenic genes, IL-6 and IL-8	Fischer-Posovszky et al. (2010)

(*continued on next page*)

Table 2 – Anti-obesity effects of pure polyphenol compounds.

Dietary Polyphenol	*In vitro* and *in vivo* effect	Mechanism	References
Rutin and o-Coumaric acid	Decreased body, liver organ, and adipose tissue weights of peritoneal and epididymal fat pads in Wistar rats	Decrease in serum lipids, insulin, leptin, hepatic triglycerides, cholesterol; reduced oxidative stress and glutathione disulphide, and enhanced glutathione, glutathione peroxidase, glutathione reductase, and glutathione S-transferase in liver	Hsu, Wu, Huang, and Yen (2009)
Silibinin	Suppressed adipogenesis in 3T3-L1	Down-regulated expression of C/EBPα, PPARγ, aP2, FAS, LPL and SREBP-1c	Ka, Kim, Kwon, Park, and Park (2009)
Vitexin and Orientin	Inhibited adipogenesis in 3T3-L1 cells	Decreased C/EBPα and PPARγ and their proteins	Kim et al. (2010)

Table 3 – Effect of probiotics on obesity.

Probiotic	Effect	References
Lactobacillus acidophilus NCFM	Preserved insulin sensitivity among type 2 diabetic humans in a randomized trial	Andreasen et al. (2010)
L. gasseri SBT2055	Abdominal visceral and subcutaneous fat decreased; body weight; BMI; waist and hip decreased; high-molecular weight adiponectin in serum increased in human adults with obese tendencies	Kadooka et al. (2010)
L. plantarum strain No. 14 (LP14)	Mean adipocyte size; white adipose tissue weight; serum total cholesterol and leptin concentrations were decreased in HFD induced obese mice	Takemura, Okubo, and Sonoyama (2010)
L. paracasei	Increased expression of ANGPTL4 in the colonic cells; decreased fat storage in HFD induced obese mice	Aronsson et al. (2010)
L. casei strain Shirota	Improved insulin resistance; glucose intolerance and reduced metabolic endotoxemia in HFD induced obese mice	Naito et al. (2011)
L. plantarum KY1032 cell extract	Decreased lipid accumulation in maturing 3T3-L1 preadipocytes; down-regulated mRNA and protein expression of PPARγ2, C/EBPα, fatty acid synthase, and FABP	Park, Ahn, Huh, Jeon, and Choi (2011a)
L. gasseri BNR17	Increased mRNA levels of fatty acid oxidation-related genes (ACO, CPT1, PPARα, PPARδ); and lowered fatty acid synthesis genes (SREBP-1c, ACC); reduced leptin and insulin in serum; enhanced glucose transporter-4	Kang et al. (2013)

Table 3 – Effect of probiotics on obesity.

Probiotic	Effect	References
Soy Milk fermented with *L. paracasei* subsp. paracasei NTU 101 and *L. plantarum* NTU 102	Inhibited differentiation of preadipocytes *in vitro*. *In vivo*, increased leptin expression and decreased body weight in HFD induced obese rats. LDL-Cholesterol, triacylglycerols and total cholesterol were decreased	Lee, Lo, and Pan, 2013
Bifidobacterium breve NCIMB 702258	Reduced TNFα and IFNγ levels in mice and weanling pigs	Wall et al. 2009
B. breve strain B-3	Suppressed body and epididymal fat weight gain; improved serum total cholesterol, fasting glucose and insulin levels; enhanced secretion of adiponectin in adipose tissue and proglucagon in large intestine of HFD induced obese mice	Kondo et al. (2010)
B. longum SPM 1205, and *B. longum* SPM 1207, *B. pseudocatenulatum* SPM 1204	Reduced body and fat weights, decreased levels of TC, HDL-C, LDL-C, triglyceride, glucose, leptin, AST, ALT, lipase, β-glucosidase, β-glucuronidase, and tryptophanase activities in HFD induced obese rats	An et al. (2011)
B. longum	Enhanced total bifidobacterial population; decreased body and fat weights; systolic blood pressure; fasting glucose; fasting triglycerides; LPS; IL-1β; intestinal myeloperoxidase levels and other intestinal inflammatory markers; improved insulin sensitivity; expression of intestinal Reg I (regenerating family proteins) mRNA and protein in the HFD fed rats	Chen et al. (2011)
B. adolescentis	Decreases body and fat pad weight and insulin resistance and alleviated complications associated with increased liver weight and steatosis in HFD fed rats	Chen, Wang, Li, and Wang (2012)
Kimchi fermented with *Weissella koreensis* OK1-6 (Korean fermented vegetable)	Decreased body and epididymal fat pad weight; serum and hepatic lipid profile; insulin; leptin concentration and expression level of PPARγ, stearoyl-CoA desaturase-1, liver × receptor α; SREBP2 in HFD induced obese mice	Park et al. (2012)
Fermented burdock diet with *Asperigillus awamori*	Faecal IgA and mucins were elevated; caecal *Bifidobacterium*; lactate, acetate, propionate, and butyrate were elevated and decreased perirenal adipose tissue weight in HFD fed rats	Okazaki et al. (2013)

may pose a risk from adverse effects, consumption in low quantities or in combination with other bioactives such as dietary fibres and prebiotics may be an added beneficial for the management of obesity (Meydani & Hasan, 2010).

2.2. *Plant derived proteins*

Dietary proteins may play an important role in regulating human metabolism (Keller, 2011). Recently stem bromelain, the

phytotherapeutic protein, and a tripeptide (Ile-Gln-Asn) isolated from black soyabean protein hydrolysates showed inhibitory effects on 3T3-L1 adipocyte differentiation (Dave et al., 2012). Expression levels of C/EBPα and PPARγ independent of C/EBPβ; fatty acid-binding protein, fatty acid synthase, lipoprotein lipase, CD36, and acetyl-CoA carboxylase were significantly down-regulated (Dave et al., 2012). Peptides from silk protein blocked the expression of adipocyte-specific genes such as PPARγ and its targets, including fatty acid-binding protein, CD36, C/EBPα and repressed the Notch target genes Hes-1 and Hey-1 (Jung et al., 2011). More research needs to be directed to identify bioactive peptides from plant sources that are active against metabolic disorders.

2.3. *Dietary fibres (DFs) and prebiotics*

Evidences suggest that gut microflora contributes towards obesity development (see above). Therefore intentional gut microbial manipulation is another potential strategy for obesity management that could be achieved by dietary fibres, prebiotic, probiotic or synbiotic food supplements (Gibson, 2008; Saulnier, Kolida, & Gibson, 2009). Several studies showed that DF consumption significantly enhances weight loss (Babio, Balanza, Basulto, Bulló, & Salas-Salvadó, 2010). DFs are non-digestible and non-starch polysaccharides and are widely distributed in plants and certain microbes. Pectin, β-glucan, xylan, arabinoxylan, inulin, resistant starch and guar gum are some of DFs. DFs are also rich in whole grain cereals and their intake significantly lowers the risk of coronary heart disease, stroke, hypertension, diabetes, obesity, gastrointestinal diseases and boosts the immune system and stimulates the growth of beneficial microbes in the colon (Anderson et al., 2009).

Prebiotics, on other hand, are oligosaccharide derivatives produced by enzymatic hydrolysis of polysaccharides or by transglycosylations. The most widely studied and European Union approved prebiotics are fructooligosaccharides; galactooligosaccharides and lactulose (Kolida & Gibson, 2011). Other prebiotic oligosaccharides are being studied more recently but their role in promoting human gut health is yet to be established (Kondepudi, Ambalam, Nilsson, Wadström, & Ljungh, 2012).

DFs and prebiotics are resistant to human digestion and are fermented to acetate; propionate and butyrate, short chain fatty acids, due to synergistic action of colonic microflora (Flint, 2012). Propionate stimulates expression of leptin and reduces the pro-inflammatory factor *resistin* in human adipose tissues (Al-Lahham et al., 2010). Arora et al. (2011) opined that propionate suppresses appetite and combats the obesity. Butyrate may epigenetically regulate genes in cholesterol biosynthesis by inhibiting histone deacetylase (Canani, Di Costanzo, & Leone, 2012). SCFAs may reduce risk of metabolic disorders via binding to G-protein-coupled receptors, GPR41 and GPR43 and alter their expression (Tremaroli & Bäckhed, 2012). In addition, SCFA are recognized as potential mediators of intestinal inflammatory response (Vinolo, Rodrigues, Nachbar, & Curi, 2011). Therefore a good SCFA profile in colon is crucial for colonic health. This could be achieved by incorporating 15–20 g of DF/prebiotic or their combinations (Brownawell et al., 2012). Effects of some important dietary fibres and prebiotics on obesity are summarized below.

Obesity prone and obesity resistant phenotypes of male Sprague–Dawley rats when fed with diets containing 0%, 4%, 8%, 12% and 16% high amylose maize resistant starch (RS) for 4 weeks in separate groups, obesity prone rats showed less weight with 4%, 12% and 16% RS compared to control whereas this effect in obesity resistant phenotype was significant with 16% RS. High levels of SCFA were detected in caecal contents of animals fed with RS. Glucagon-like peptide-1 and peptide YY levels were significantly high in the plasma whereas Gastric inhibitory polypeptide was decreased in animals fed with 8% or above RS. However, Insulin sensitivity was not affected by RS in any of the groups (Belobrajdic, King, Christophersen, & Bird, 2012). In overweight and obese subjects, RS supplementation (15–30 g/d of high-amylose maize type 2 resistant starch) improved inulin sensitivity (Maki et al., 2012). Therefore RS may help in alleviation of complications associated with insulin resistance. Feeding RS to rats showed alteration in the microbiota compositions due to blooms of *Bacteroidetes* and *Actinobacteria*, which was linked to the changes in SCFA and gene expression (Gsta2 and Ela1) in colon (Young et al., 2012). Type 2 RS feeding to mice, altered gut weight, proglucagon expression levels (Tachon, Zhou, Keenan, Martin, & Marco, 2013). Metabolism of RS by colonic bacteria produces butyrate that may play significant role in obesity.

Arabinoxylans are an emerging dietary fibre and are distributed in high quantities in whole grain cereals. Neyrinck et al. (2011) reported that dietary wheat arabinoxylan supplementation to HFD induced obese mice showed decreased adiposity, body weight gain, serum and hepatic cholesterol and insulin resistance. Adipocyte size was significantly decreased and high levels of rumenic acid were detected in the white adipose tissue by gut bacterial metabolism of arabinoxylan. Numbers of *Bacteroides-Prevotella* spp. and *Roseburia* spp. were restored; caecal bifidobacterial numbers were significantly enhanced with improved gut barrier function with lower circulating inflammatory markers (Neyrinck et al., 2011). Expression of genes associated with adipocyte differentiation, fatty acid uptake, fatty acid oxidation and inflammation; key lipogenic enzyme activity were significantly decreased in the subcutaneous adipose tissue.

Highly methoxylated apple pectin and β-glucan decreased the body weight; total cholesterol and triacylglycerols in Zucker fatty rats compared to those fed with standard diet (Sánchez et al., 2008).

Inulin-type fructans (ITF) are naturally distributed in onion, banana, chicory and artichokes and promotes gut health, ameliorate plasma lipid profiles and enhance mineral absorption. ITF enhance satiety; decrease energy intake and regulate body weight in human and animal studies (Welch, Kelly, Gallagher, Wallace, & Livingstone, 2008). Mohiti-Asli et al. (2012) observed that inulin supplementation in the diet reduced liver and abdominal fat weight; whereas cellulose supplementation decreased the feed intake, abdominal fat, and BW compared to control in hens. In a double blind placebo controlled study on obese women, ITF decreased the fat mass; plasma lactate and phosphatidylcholine levels (Dewulf et al., 2012). ITF also suppressed the numbers of *Bacteroi-*

des intestinalis, *Bacteroides vulgatus* and *Propionibacterium* and significantly increased the numbers of *Bifidobacterium* and *Faecalibacterium prausnitzii*. Serum LPS levels were decreased remarkably (Dewulf et al., 2012).

Fucoidans have been shown to exert various health benefits such as antioxidant, anti-inflammatory, anti-allergic, anti-tumor, anti-coagulant, anti-viral, anti-hepatopathy, anti-uropathy, and anti-renalpathy potentials (Vo & Kim, 2013). Fucoidans are acidic and sulfated polymers of L-fucose along with xylose, galactose and mannose, isolated from brown algae, *Fucus vesisulosus* and sporophyll of *Undaria pinnatifida*, showed anti-adipogenic effects *in vitro* (Kim, Chang, & Lee, 2009; Kim & Lee, 2012; Park, Jung, and Roh, 2011b). It inhibited adipocyte differentiation via fat accumulation and decreased aP2, ACC, and PPARγ gene expression (Kim et al., 2009; Kim et al., 2012). It increased the expression of hormone sensitive lipase; phosphorylated hormone sensitive lipase and decreased the glucose uptake into adipocytes leading to lipolysis and reduces lipid accumulation (Park et al., 2011b). Expression of PPARγ, C/EBPα, and ap2 were significantly decreased leading to decreased expression of inflammation-related genes. Lipid accumulation and reactive oxygen species production were significantly decreased in adipocytes (Kim & Lee, 2012).

In a study with HFD induced obese rats, Peng et al. (2013) found that oat supplementation did not show any effects on appetite control. However, it significantly reduced body weight, fat, food efficiency; lowered serum glucose, free fatty acids, triacylglycerols, cholesterol, and low density lipoprotein-cholesterol/high density lipoprotein-cholesterol which otherwise found elevated in control animals. Hepatic triacylglycerols and cholesterol were dose dependently reduced; fatty acid synthase, glycerol 3-phosphate acyltransferase and hydroxymethylglutaryl-CoA reductase activities were significantly reduced with 30% oat supplementation while expressions of oxidation markers PPARα, CPT-1 and phosphorylated-AMPK were stimulated upon supplementation with 15% and 30%. Further oat supplementation significantly increased the LDL receptor, which is beneficial for lowering serum lipid levels (Peng et al., 2013).

Among the prebiotics, oligofructose supplementation enhanced the levels of bifidobacteria in the intestine of HFD induced obese mice. Body weight and visceral adipose tissue mass in the oligofructose group were significantly decreased. Mucosal barrier function was improved with reduction in LPS levels (Cani et al., 2007). The mRNA levels of IL-1, TNFα, and plasminogen activator inhibitor type- 1and the levels of IL-1α and IL-6 were normalized in the adipose tissue (Cani et al., 2007).

In a double-blind, randomized, placebo controlled, cross-over study, on 45 overweight adults with ⩾3 risk factors associated with metabolic syndrome, Vulevic, Juric, Tzortzis, and Gibson (2013) observed a significant increase in total faecal bifidobacteria numbers; faecal calprotectin, plasma C-reactive protein, insulin, total cholesterol and triglycerides upon dietary intervention with galactooligosaccharides. The total cholesterol: high density lipids-cholesterol ratio was decreased significantly suggesting that galactooligosaccharides intervention improved gut microflora, immune function and significantly reduced the risk factors for metabolic syndrome (Vulevic et al., 2013).

Neyrinck et al. (2011) showed that wheat arabinoxylooligosaccharides supplementation significantly increased bifidobacterial content with a reduction in metabolic endotoxemia and macrophage infiltration in adipose tissue and IL-6 in plasma in HFD induced obese mice. Peptide YY and glucagon-like peptide-1 were enhanced, gain in body and fat mass was prevented, hyperinsulinemia and insulin resistance were decreased. Arabinoxylooligosaccharides supplementation improved gut barrier function through up regulation of *zonula occludens* 1 and claudin 3 (tight junction proteins) and levels of LPS and pro-inflammatory markers in plasma were significantly reduced and prevented from metabolic endotoxemia (Neyrinck et al., 2011).

Chitooligosaccharides exhibited anti-adipogenic activity against mouse 3T3-L1 cells by inhibiting lipid accumulation; free glycerol release and expression of adipogenic genes. Expression of IL-6 and prostaglandin-endoperoxide synthase 2 genes was up-regulated by chitooligosaccharides (Bahar, O'Doherty, & Sweeney, 2011). Dietary supplementation of chitooligosaccharides (1% or 3%) along with HFD for 5 months reduced the body weight by 15% in mice (Choi, Yahg, & Chun, 2012). Smaller adipocytes and marked improvement in serum and hepatic lipid profiles were noticed. Adipogenesis-related matrix metallopeptidases 3, 12, 13, and 14; tissue inhibitor of metalloproteinase 1, and cathepsin k in adipose tissue were significantly modulated. Influenced 25% of genes involved in inflammatory response and cytokine production. These results suggest that chitooligosaccharides supplementation may positively modulate obesity and associated inflammation.

Above observations indicated that DFs and prebiotics not only lower fat and body weight, that are prerequisite for obesity management but also, brought about prebiotic changes in gut microflora. Further, DFs and prebiotics significantly improve immune functions (more anti-inflammatory markers and less pro-inflammatory markers), gut barrier function, regulation of gut hormones (increases satiety) and alteration of gene expression in liver and adipose tissues. Modified or partially broken carbohydrates may signal at specific receptors to alter whole-body energy and glucose metabolism (Ryan & Randy, 2013). Short chain fatty acids (SCFA) formed in gut helps in maintaining host's health especially butyrate generation is more important as it regulate gene expression through epigenetic regulation (Canani et al., 2012). DFs and prebiotics also regulate release of gut hormones that signals brain of satiety. Therefore careful dietary manipulation of gut associated microflora should be a top priority for prevention or management of obesity and co-morbidities. Hence there is a scope for the identification and evaluation of novel DFs and prebiotics for their assessment on metabolic disorders.

2.4. *Probiotics and synbiotics*

FAO/WHO defined probiotics as "live microorganisms which when administered in adequate amount confer health benefits to the host". Colonized in the gut of humans and certain

animals, probiotics promote gastrointestinal health. They are also recognized for many health promoting effects such as modulation of the host immune system, improving bioavailability of nutrients, decreasing lactose intolerance. Recently they are being recognized for their remarkable role in regulating the host metabolic processes, weight gain and obesity (Thomas & Versalovic, 2010). Most widely studied and generally regarded as safe (GRAS) probiotic strains include species from the genera *Lactobacillus* and *Bifidobacteria*. The numbers of these beneficial microbes can be enhanced by various dietary fibres and prebiotics as mentioned in the previous section. More information on the selection criteria, the role and function of probiotics for maintaining the healthy gut are mentioned elsewhere (Ambalam, Kondepudi, Nilsson, Wadström, & Ljungh, 2012; Ganguly et al., 2011; Raman et al., 2013; Thomas & Versalovic, 2010).

Ambiguity exists concerning the role of probiotic bacteria especially *Lactobacillus* spp. in regulating obesity as certain *Lactobacilli* are reported to promote growth and body weight in farm animals (Million et al. 2012). A comparative meta-analysis showed *Lactobacillus acidophilus*, *Lactobacillus ingluviei* and *Lactobacillus fermentum* promoted weight gain (Million et al., 2012). Similarly Arora et al., (2012) reported that supplementation of *L. acidophilus* NCDC 13 enriched yoghurt did not bring changes in adiposity markers in HFD induced obese mice (C57BL/6). However, it is not all *Lactobacilli* in the human gut, a vast microbial diversity comprising bacterial groups such as those belonging to *Bifidobacteria* spp., *Roseburia*, *Akkermansia*, and *Bacteroidetes* spp., etc., which may also play a role in obesity prevention also exist. In Table 3 we have summarized the potential of specific probiotic strains that ameliorate the progression of obesity.

Indigenous gut microbes also secrete low molecular weight bioactive metabolites such as short chain fatty acids, peptides, endotoxins, vitamins, enzymes and co-enzymes that may influence epigenetic reprogramming and post-translational modifications. Thus gut microbes may regulate host metabolism (Shenderov, 2012). However, the mechanism remains unclear.

Based on above discussions a light of hope arises for probiotic-mediated modulation of gut flora as a potential approach for obesity and other metabolic diseases management provided next-generation human probiotic species for obesity should contain well studied *Lactobacilli*, *Bifidobacteria* and other non-lactic acid bacterial strains that must be inversely associated with weight gain in humans. Their combination with a non-digestible carbohydrate source (dietary fibre or prebiotic) may be a better choice. As such a "*synbiotic combination*" would render double benefits of both the ingredients that may take a lead in the future management of this major health problem. However, well directed animal and human based intervention studies are required to understand the mechanism of action of such formulations.

3. Conclusion

Apart from major surgery, there seems to be no efficient treatment for obesity with therapeutic drugs as they are associated with potential side effects. Existing data shows that functional food ingredients hold promise for management of obesity and associated co-morbidities. However, there remains a lot to research and understand about the interaction of functional food ingredients with brain; gut; gut microbiota; genes and pathways involved in adipose tissue development and function. Combined nutrigenomic, metagenomic and metabolomics approach should be taken up to elucidate the interrelation of host's brain-gut axis on energy metabolism. This will allow for identification of novel molecular targets that could be relevant for future development of innovative therapies, preventive measures and customized dietary regimen and functional food/nutraceutical supplements with reference to obesity and associated co-metabolic disorders.

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