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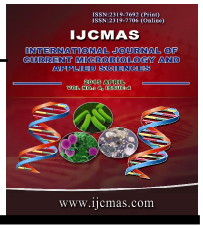

Review Article

Phytochemicals in obesity control

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A B S T R A C T

The escalating problem of obesity has become a cause of great concern in the world today as it leads to adverse effects on human health, including cardiovascular diseases, cancer etc. The major causes of obesity may be attributed to sedentary lifestyle and bad food habits. Conventional modalities to tackle obesity are not free from side-effects. Urgency of a novel, nontoxic means needs to be developed to control obesity. Various plant products have been found to be effective in controlling obesity. A good portion of fruits, vegetables, spices and herbs need to be included in the regular diet. Plant derived molecules or phytochemicals are blessed with strong anti-obesogenic, anti-carcinogenic and anti-inflammatory properties. Thus they may serve as a non toxic and cost-effective method to tackle obesity. These molecules target various pathways that are intricately linked to the process of adipogenesis. This review aims to elucidate the beneficial role of dietary food nutrients in control of obesogenicity.

Introduction

Obesity, a prime health issue is dependent on living, social and environmental factors. Obesity is the resultant of more calorie consumption than burning, hence energy imbalance is a key player (Verduin et al., 2005). Proper nutrition is vital to good health. However, optimization of nourishment is an important issue. Manifestation of nutrition related crisis is obesity, which results from accumulation of excess body fat (Haslam and James, 2005). According to WHO obesity is defined as a "phenotypic manifestation of abnormal or excessive fat accumulation that alters health and increases mortality" (World Health Organization, 1998). Obesity is quantitated in terms of Body Mass Index (BMI), which is defined as the ratio of the weight and the square of height (Heymsfield et al., 2009) and is a measure of body adiposity. Obesity is linked with various diseases including cancer. According to the International Task Force on Obesity and the World Health Organization (WHO), obesity is a 21st century epidemic. Although obesity is predominantly a disease of the developed

countries, developing countries like India are not lagging behind. Higher rates of obesity are directly linked to sedentary lifestyle (Unnikrishnan et al., 2012). Some other factors that might contribute to obesity are depression, monetary and social issues (Wyatt et al., 2006). Obesity, though considered to be a life-style related disorder, may run in families. Obesity, a disease with no single cause is also accredited to genetic and family link, health of an individual, certain medications, emotional factors, age, smoking, pregnancy, lack of sleep etc. Hormone treatment often prescribed for hypothyroidism, Cushing's syndrome, polycystic ovarian disease may lead to overweight. Corticosteroids, antidepressants, and seizure medicines also results in weight gain. Boredom, anger, anxiety and too much of stress also contribute to obesity. Nicotine level helps burning calories; therefore quitting smoking often leads to reduction in calorie burning, thereby causing obesity. Aging process results in muscle relaxation, particularly for those indulged in sedentary life style, which ultimately leads to weight gain due to inhibition of calorie burning. Adequate sleep is essential for maintaining a good body shape. Sleep maintains a balance between hormones like ghrelin, leptin that are responsible for hunger. Insufficient sleep disturbs the balance and thereby increases appetite, consequently leading to excess fat (Wright and Aronne, 2012). Excessive day sleepiness (EDS) and tiredness are common symptoms of obesity and are linked to an individual's health issues (Vgontzas et al., 2006).

Adipose tissue may be considered to be an endocrine organ (Sikaris, 2004). An association between mutations in *LEP*, *LEPR*, *POMC*, *PCSK1* and *MC4R* genes and obesity has been observed (Choquet and Meyre, 2011). Susceptibility to weight gain is attributable to a gene named Bsx, which regulates hormones of the hypothalmous (Sakkou et al., 2007). Another important protein that facilitates uptake of Fatty Acid (FA) in adipose cells is Fatty Acid Transport Protein (FATP). An association exists between obesity and chronic inflammation through release of cytokines like interleukin (IL)-1β, IL-6, TNF-α, and monocyte chemo-attractant protein (MCP)-1 (Trayhurn and Wood, 2005). Adipokines leave an impact on appetite, metabolism of carbohydrate and lipid, regulation of blood pressure etc. The disruption of adipokine/cytokine network is a hallmark of obesity, resulting in inflammation and aberrant metabolism of adipocyte (Balistreri et al., 2010). Adipocytes secrete adipsin, a serine protease into the bloodstream. This encoded protein is highly expressed in fat cells, promotes transport of glucose for triglyceride accumulation in fats cells and results in inhibition of lipolysis (Rosen et al., 1989). Adipocytes produce leptin, which aids in reduction of appetite via signaling to the hypothalamus. Release of leptin is facilitated by insulin, glucocorticoids, tumor necrosis factor-alpha (TNF-α), and estrogens. Overexpression of leptin in obesity in turn renders the brain resistant to the feeling of satiety. Leptin signals through the janus kinase and signal transducer activator of transcription (JAK/STAT) pathway. Once secreted from adipocytes, leptin goes to the circulation and by traversing through the central nervous system, ultimately binds to the receptors in the hypothalamus. Production of pro-opiomelanocortin (POMC) thus results. Alpha-melanocyte stimulating hormone (alpha-MSH), a product of POMC hinders food intake through binding to melanocortin-4 receptors. Mutations in leptin, leptin receptor, POMC, alpha MSH receptor may result in obesity. Adiponectin, secreted from visceral adipose tissue, has a negative correlation with

adiposity. It exerts its effect through reduction of cytokine expression and mTOR signalling (Sikaris, 2004). Genes associated with the Peroxisome Proliferator Activated Peptide Receptor Gamma (PPAR-γ) and its coactivator-1 (PGC-1) are also linked with obesity (Sikaris, 2004). Visceral fat accumulation regulates expression of PAI-1 which inhibits activation of plasminogen in blood and contributes to cardiovascular diseases (Yamamoto et al., 2005). Very low density lipoprotein (VLDL) is high in obese condition due to more and more production of triglyceride rich lipoprotein and low rate of elimination of the same (Sikaris, 2004).

Adiposity is therefore synonymous with obesity. Adipose tissue, which is deposited subcutaneously or centrally is very important for the survival of an individual as it is the chief source of fatty acids for use of energy and production of heat. Centrally deposited fat is more active than peripheral subcutaneous fat (Donohoe et al., 2014). The two main types of adipose tissue present in mammals are white adipose tissue (WAT) and brown adipose tissue(BAT). WAT, the main constituent of adipose tissue is used as substrate of energy when required. Excessive accumulation of WAT results in obesity and its associated disorders. BAT is responsible for expenditure of energy for cold adaptation due to non-oxidative phosphorylation (Balistreri et al., 2010). Adipocytes arise due to differentiation of pre-adipocytes, which are induced by certain agents to undergo mitotic clonal expansion. In addition to this, CCAAT-enhancer-binding protein (C/EBP)-β and C/EBPd are induced and pre-adipocyte markers like pre-adipocyte factor-1 disappear. Enhanced expression of transcriptional regulators of adipogenesis namely C/EBPa and peroxisome proliferator-activated receptor (PPAR)-γ follows, resulting in adipocyte-specific expression of genes. Increased Glycerol-3-phosphate dehydrogenase (GPDH) activity, which serve as a catalyst in fatty acid generation and is an index for synthesis of fat (Andersen et al., 2010) also culminates in expression of adipocyte markers like acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), lipoprotein lipase (LPL), and fatty acid-binding protein (aP2). In addition to this, adipose cells have a direct and indirect impact on regulation of tumor growth. Adipogenesis results into an alteration in the morphology of the cell, vis-a-vis the type and expression of extracellular matrix and cytoskeletal proteins (Rayalam et al., 2011). Activation of AMP-activated protein kinase (AMPK) negatively controls differentiation of adipogenesis, and is thus a target for antiobesity molecules (Rayalam et al., 2011). Inhibition of signalling pathways leading to adipogenesis is therefore extremely vital for obesity control.

Obesity and cancer

The microenvironment around adipose tissue is associated with alterations in endocrines favouring the initiation and promotion stage of carcinogenesis (Park et al., 2014). Fat cells directly or indirectly controls mammalian target of rapamycin (mTOR) and protein kinases activated by AMP, thereby affecting tumor growth regulation (Hursting and Dunlap, 2012). Some of the major cancers that are strongly associated to obesity are breast; cervical; ovarian; colorectal; endometrial, esophageal; thyroid; gallbladder; kidney; and pancreatic cancer. For obese men there is 30-70% higher chance of colon cancer, whereas risk is much less in women (Bardou et al., 2013). Rise in levels of proinflammatory cytokines, estrogens, insulin-like growth factors (IGFs), hyperinsulinemia and alterations in adipokine levels may be considered as factors that lead to enhanced risk of this

cancer. Leptin, an adipokine is strongly associated with the development of colorectal cancer (Rodríguez et al., 2013). Higher level of estrogen is a probable cause of carcinoma of the breast and endometrium. In post menopausal women obesity has been found to be positively associated with risk of cancer, which is due to estrogenic status (Stephenson and Rose, 2003) and IGF mediated signaling. Endometrial cancer is attributed to the mitogenic effects of unopposed estrogens. Obesity is also a potent cause of ovarian cancer. It enhances androgen secretion, increases the conversion of androgen to estrogen; and diminishes the capacity of sex hormone-binding globulin, which leads to higher amounts of active estradiol (Monica et al., 2009). A diet that adds on to the weight may result in inflammation, thereby causing pancreatic cancer. Inadequate physical activity results in increased insulin resistance, which promotes carcinogenesis. High circulating levels of insulin, C-peptide and vascular endothelial growth factor (VEGF) in obesity may be linked to this type of cancer. These factors contribute to tumor promotion by affecting cellular proliferation, angiogenesis and apoptosis (Bracci, 2012). Another obesity and elevated BMI related cancer is oesophageal adenocarcinoma. Obese people suffer from gastroesophageal reflux disease (GERD), which leads to Barrett's esophagus and ultimately adenocarcinoma of the esophagus. Various studies have concluded that insulin like growth factor (IGF) pathway and adipokines also leads to development of oesophageal carcinoma (Chen et al., 2012). There are various mechanisms which probably increases chances of renal cancer in obese people. Chronic hypoxia of the tissues, insulin resistance and hyperinsulinemia, altered endocrine milieu and adipokine production, inflammatory response due to obesity, and lipid peroxidation and oxidative stress are some of them (Chow et al., 2010). Being overweight results in a pro-inflammatory state namely hypoadiponectinemia and insulin resistance, which, eventually causes high circulating levels of insulin and insulin-like growth factor-1, thus increasing the chances of occurrence of thyroid cancer. Insulin resistance in conjunction with other factors like adipocytokines/cytokines and thyroid-stimulating hormone also contributes to the higher risk (Pazaitou-Panayiotou et al., 2013).

Role of phytochemicals

Reducing portions and burning calories by physical activities are very important for obesity control. Foods rich in fat, sugar needs to be avoided, giving a space to dietary fibers. Anti-obesity drugs are available which not only brings down the appetite, but at the same time hinders absorption of fat. If diet, exercise and medication fail, insertion of a gastric balloon may be of help to reduce stomach volume. Bariatric surgery (weight loss surgery) is another alternative to control stomach volume and bowel length, which often results in satiety (O'Brien et al., 2013). Liposuction or liposculpture suction lipectomy, a cosmetic surgical procedure for fat removal from different parts of the body, though has become quite popular now a days, causes several complexities and side effects. The mechanisms of action of anti-obesity drugs include appetite suppression, increased rate of metabolism, reducing the capacity of the body to absorb certain food nutrients like lipids, triggering the process of thermogenesis and enhancing lysis of lipids (Chopra et al., 2014). Some of the anti-obesity drugs commercially available are Orlistat, Lorcaserin, Sibutramine, Rimonabant, Metformin, Exenatide, Pramlintide. These drugs have a wide variety of severe side-effects including

development of cardiovascular problems, restlessness, insomnia, faulty bowel movements, pain in stomach, psychiatric problems etc. Ideally anti-obesity agent would be such as to produce weight loss which can be retained, but with minimal side effects.

Diet low in fruits, fibres, vegetables and whole grains results in increased gain in weight (Vincent et al., 2010). Phytochemicals or active ingredients of plants, comprising of flavonoids, glucosinolates (isothiocyanates and indoles), phenolic acids, phytates, phytoestrogens (isoflavones and lignans) are capable of efficiently combating cancer (Surh, 2003). They possess anti-inflammatory, anti-obesity and anti-diabetic properties. Anti-inflammatory properties contribute to counteract the obesogenic state (Williams et al., 2013). Phytochemicals target key components of pathways related to obesity (Holubkováa et al., 2012). Dietary phytochemicals act on various stages of life cycle of adipocytes. Some probable mechanisms of action of these plant derived products are reduction in adipose tissue mass by inhibition of precursor cell proliferation, enhancing apoptosis of fat cells and hindering the absorption of triglyceride by reducing formation of pancreatic lipase. They are inhibitors of preadipocyte differentiation and stimulators of lipolysis (Williams et al., 2013). Anti-obesity mechanism of plant derived supplements is attributed to several effects they elicit; these are reduced lipid absorption, decreased intake of energy, more expenditure of energy and reduced lipogenesis (Chandrasekaran et al., 2012). A study was conducted to assess the relation between intake of phytochemicals rich foods and obesity by calculating the phytochemical index. Phytochemical index (PI) is the ratio of the energy obtained from diet rich in phytochemicals to the total energy consumed every day. PI is inversely associated with adiposity and oxidative stress (Vincent et al., 2010).

There are a plethora of phytochemicals which could tackle obesity. *In vitro* and *in vivo* studies show that the common phytochemicals which show effect on the process of adipogenesis include flavonoids, stilbenoids, phenolic acids and alkaloids. Natural compounds, such as epigallocatechin-3-gallate (EGCG), genistein, resveratrol, capsaicin, and procyanidins inhibit adipogenesis (Andersen et al., 2010). Various other plant derived products are reported in controlling obesity. Notable among these are fruits like watermelon, avocado, apples, blue berries, cucumbers, oranges, quinoa, grapefruit, pears, zizyphus (Indian plum) etc; vegetables like chillies and peeppers, curry leaves, cabbage, garlic, ginger, green leafy vegetables like spinach, beans, tomatoes, broccoli, spring vegetable like asparagus etc; pulses; millets such as jowar, bajra, ragi, oats etc; nuts like almonds, peanuts etc; spices like turmeric, cardamom, cinnamon, cloves etc. Some of the oils used in cooking also help in combating obesity; these are coconut oil, mustard oil, olive oil.

All these plant derived products have their own mechanism of action in obesity control. Spices are not only an integral part of gourmet, but at the same time they have a role in control of weight gain by virtue of their antioxidant and anti-inflammatory properties. No Indian recipe is complete without turmeric. Curcumin, the active ingredient of turmeric reduces low density lipoprotein (LDL) or the bad cholesterol and at the same time controls hypertension (Alappat and Awad, 2010). In addition to add taste, flavour and colour in cooking, spices have some beneficial effect on our

health. Cardamom, a herb increases the metabolism and therefore help to burn fat. Cinnamon (Sheng et al., 2008) and cloves (Aggarwal, 2010), extensively used in Indian cooking, are known to enhance insulin function, reduce glucose, total cholesterol, LDL and triglycerides which aid in obesity control.

Herbs may be very effective in the fight against obesity. They help in inhibition of lipase, down-regulation of adipogenesis, thermogenesis, metabolism of lipids and modulation of various signalling pathways leading to weight gain. Some examples of anti-obesogenic herbs include *Acacia arabica*, *Aconitum heterophyllum*, *Aloe vera*, *Azadirachta indica*, *Betula utilis*, *Calatropis gigantean*, *Cinnamomum zeylanicum*, *Emblica officinalis*, *Moringa oleifera* etc (Chandrasekaran et al., 2012). Use of curry leaves is common in many Indian recipes. Apart from its odour, curry leaves flush our fats and toxins, thereby reducing fat and bad cholesterol. Certain herbal plants of Malaysia, namely *Eleusine indica, Myristica fragrans, Melastoma candidum* and *Phyla nodiflora* possess anti-obesogenic properties because of their ability to inhibit pancreatic lipase activity. Inhibition of pancreatic lipase reduces fatty acid absorption and thus helps to reduce obesity (Ong et al., 2014).

Capsaicin present in chillies and capsicum works by increasing the metabolism and burn more calories, thereby controls obesity. Garlic is an age old healthy food, allicin present in garlic reduce cholesterol and unhealthy fats (Kim and Kim, 2011). Isothiocyanates are good anticancer agents present in cruciferous vegetables like cabbage, broccoli etc. (Sarkars et al., 2013) and they prevent conversion of sugar and carbohydrates into fat. Thus these vegetables are potential anti-obesity agents (Choi et al., 2012), anti-carcinogenic and anti-tumorigenic agents(Sarkars et al., 2013). Spinach, a green leafy vegetable is extremely low in calorie, but fibre rich, with vitamins and minerals. Spinach is famous for reducing water retention in our body, without causing any abdominal discomfort (Makris and Foster, 2011). Beans, which are low in calorie, also help to diminish fat in the body, keeping the stomach full, thereby reducing appetite (Hasani-Ranjbar et al., 2009). Asparagus is also effective in weight control. It works by flushing out toxins and other wastes from the body (Dhara et al., 2013). Tomatoes, a low calorie vegetable are consumed raw as well as cooked. Lycopene, the active constituent in tomato is famous for its anti-oxidant and anti-carcinogenic properties. Tomatoes are good for health as they also help to lose weight (Maruyama et al., 2013).

It is a known fact that fibres boost up the metabolism and brings down the hunger. Fibres present in millets have the capability to absorb cholesterol and increase bile secretion, thereby emulsifying fats which are very important step to weight reduction (Park et al., 2011). Oats, a popular breakfast item, is rich in antioxidants and other minerals. Fibre in oats brings down the cholesterol level (Chang et al., 2013).

Fruits like apples (Conceição de Oliveira et al., 2003), avocados are rich in fibre and other nutrients, consumption of which keeps one full for a longer time, decreasing appetite. Avocados are also rich in monounsaturated fatty acid (MUFA), and amongst other fruits are richest source of cholesterol-smashing beta-sitosterol (Devalaraja et al., 2011). Cucumber, watermelon, oranges, quinoa, grapefruit, pears are extremely low calorie food, which keeps the stomach full for a longer time. Berries are not only good to taste, but

normally they aid in weight reduction. Blueberries, rich in anthocyanins are responsible for breaking down fats and sugars and thus curtail extra fat from our body (Wu et al., 2013). *In vivo* studies also reveal that these compounds result in reduced body weight and accumulation of adipose tissues, therefore plays a vital role in obesity control. Resveratrol is abundant in grapes. Resveratrol causes a decrease in number of adipocytes by targeting various molecular targets. It was also found that this phytochemical in combination with genestein and quercetin causes a decrease in the process of adipogenesis. It was also found that resveratrol and vitamin D together prevented excess gain in weight. Thus resveratrol along with other phytochemicals may serve as potential candidates in therapy against obesity (Rayalam et al., 2008). Some of the beverages that we consume are of plant origin. The most popular beverage in the world next to water is tea. Green tea, obtained from the leaves of *Camellia sinensis* possesses a wide variety of disease fighting properties and may also aid in obesity control as it is hypocholesterolemic, hypoglycemic and antidiabetic (Hasani-Ranjbar et al., 2013).

Obesity has become an epidemic worldwide. Causative factors of obesity are predominantly lifestyle changes, including consumption of high-calorie fast food and sedentary lifestyle. Various health issues have come up, which are concomitant with obesity; one such vital disease is cancer. Different studies have reported that losing weight is directly linked to reduction in cancer incidence and mortality. Intense research needs to be done to establish the underlying mechanisms responsible for obesity in cancer. Conventional treatment modalities for obesity are often ineffective and pose various undesirable side effects. Commonly used anti-obesity drugs often show high morbidity and mortality. Few aspects thus need to be considered to develop agents to control obesity. These molecules should be efficacious, nontoxic and well tolerated. Phytochemicals or active ingredients of plants are blessed with strong obesogenic and anti-inflammatory properties. Studies show that these substances may be useful in obesity therapy. They affect signaling pathways that are associated with obesity. Thus inclusion of such molecules through daily diet may prove to be of enormous importance in fighting obesity and ultimately the occurrence of diseases like cancer.

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