Strawberry polyphenols decrease oxidative stress in chronic diseases

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Abstract

Consumption of hypercaloric diets leads to increase of free fatty acids (FFA), pro-inflammatory cytokines and production of oxygen and nitrogen reactive species. These alterations induce oxidative and nitrosative stress causing dysfunction of tissues and consequently the development of chronic diseases. Therefore, it is important to decrease oxidative stress and thus preventing the development of these diseases. Strawberry has a lot of vitamin C and polyphenols, compounds with excellent antioxidant properties, which may be an option for reducing oxidative stress and therefore to prevent the development of some diseases. Studies conducted in vitro, in animal models and clinical studies support that this fruit can be a good alternative to reduce oxidative stress and thus reducing and/or preventing the development of diseases in humans.

KEY WORDS: *Hypercaloric diet. Obesity. Oxidative stress. Strawberry. Polyphenols.*

Introduction

The 2012 National Survey on Health and Nutrition in Mexico showed that the prevalence of overweight and obesity is 71.3% for both genders, with 73% in females and 69.4% in males. It also reported that the costs generated by obesity have been estimated in 67 thousand million pesos in 2008[1], and it is therefore urgent taking adequate measures in order to reduce obesity increase.

Mexican diet, in spite of its particularities, is very similar to the western diet; it is hypercaloric, with high fat and carbohydrate contents, and it is therefore one of the determining factors in the development of obesity. Evidences support that hypercaloric diet with high fat and carbohydrate contents significantly contributes to the development of obesity and metabolic syndrome in animals[2] and in humans[3]. Metabolic syndrome is a group of chronic metabolic conditions that include hypertension, dyslipidemias, insulin resistance, obesity and diabetes[4]. Thus, hypercaloric diets can induce an inflammatory state and higher production of free radicals (FR) (Fig. 1), which brings oxidative stress and the development of chronic metabolic diseases as a consequence, as it will be reviewed later.

Free radicals and antioxidant systems

FRs are chemical species with an unpaired electron in their most outer orbital, which confers them an unstable configuration and, therefore, a great capability to react with other molecules. FRs are divided into reactive nitrogen species (RNS) and reactive oxygen

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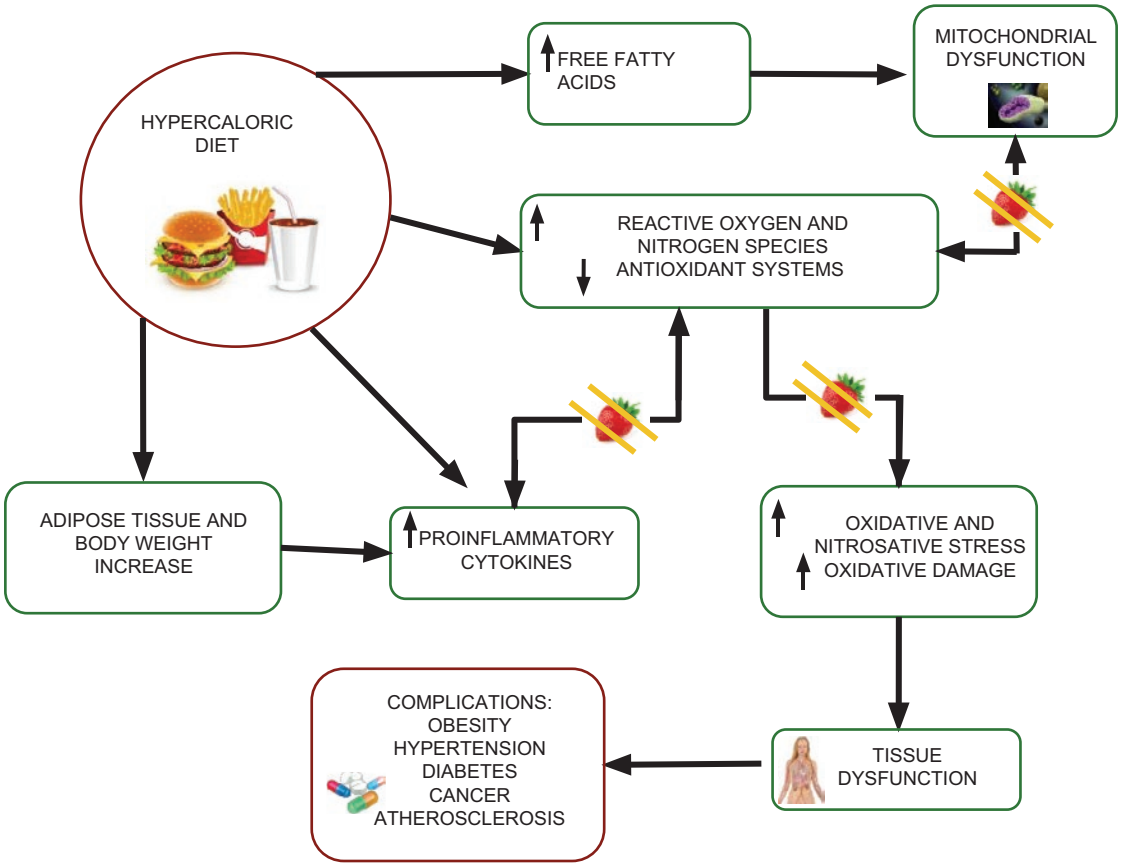

Figure 1. *Hypothetical model of tissue dysfunction and chronic diseases induced by hypercaloric diets. Hypercaloric diets induce the development of chronic diseases, while strawberry polyphenols can prevent the development of these diseases by reducing oxidative and nitrosative stress.*

species (ROS)[5]. FRs are physiologically produced in some reactions that take place as part of metabolism; for example in mammals' mitochondria at stage 4, 1 to 2% of consumed oxygen is converted into ROS[6-8]. It should be mentioned that FR controlled production enables the occurrence of different physiological processes, such as neurotransmission, vasorelaxation, ovule fertilization by spermatozoids, cell membrane genes and enzymes activation, collagen synthesis, bacterial lysis, etc., but FRs excessive production is deleterious for cell physiology.

ROS and RNS are broken down and/or neutralized by exogenous and endogenous antioxidants. Exogenous antioxidants are water-soluble (ascorbic acid), fat-soluble (tocopherols, carotenoids, xanthophylls) or have both properties (polyphenols, flavonoids, tannins, lignins, phenylpropanoids). In turn, enzymatic-type endogenous antioxidants are manganese-dependent superoxide dismutase (MnSOD) and coenzyme Q (CoQ), which are found in the mitochondrial intermembrane space, in addition to copper-dependent superoxide dismutase (CuSOD), zinc-dependent SOD (ZnSOD), glutathione peroxidase (GSH-Px), phospholipid-hydroperoxide glutathione peroxidase (PH-GPX) and catalases found in the cytosol[9-11].

Oxidative stress occurs when FR production exceeds exogenous and endogenous systems capacity[12-14]. Thus, FRs increase has toxic effects on cells and tissues because they can oxidize carbohydrates, DNA, lipids and proteins, with this being an important mechanism in the development of chronic metabolic diseases (Fig. 1), as later it will be reviewed.

Hypercaloric diet, oxidative stress and organ dysfunction

Using murine models, hypercaloric diets with fat and/or carbohydrates high contents were shown to induce an adipose tissue increase that body weight gain[2,15-17], while, in humans, hypercaloric diets were strongly associated with body weight increase[18-20] and, on the other hand, overweight and/or obesity were also strongly associated with pro-inflammatory cytokines increase[21-23]. In animal models, it is well documented

that hypercaloric diet causes weight increase and higher production of pro-inflammatory cytokines (Fig. 1). For example, hypercaloric diet increased the production of interleukin (IL) 1, IL-6 and tumor necrosis factor (TNF-); it also induced higher production of FRs and oxidative stress[15,17,24-26]. In addition, hypercaloric diet induced obesity and the development of hepatic steatosis in animal models[2,16]. In humans, hypercaloric diet has only been associated with obesity and liver fatty acids content, which were measured with ultrasonography[19].

Consumption of hypercaloric diets with high contents of free fatty acids (FFA) is worrying, since they increase the production of ROS (Fig 1). In rats, FFA plasma levels elevation increased the production of ROS[27]. FFA also increased the production of ROS in aortic endothelial cells and in human β-cells in vitro[28,29]. In neuronal cells in vitro, FFA increased ROS production and lipid peroxidation, which caused for the mitochondria to uncouple[29]. Similarly, in human hepatoma cells in vitro, FFA caused for the mitochondria to uncouple and increased nitrosative and oxidative stress, thus reducing oxidative phosphorylation[30]. FFA also induced IL-1a production and mitochondrial uncoupling in vitro[31]. In addition, sucrose increases ROS production and lipid peroxidation in rat isolated aorta[32]. All these studies show that lipid and/or carbohydrate-rich hypercaloric diets significantly contribute to the development of inflammatory state, FR production and obesity.

In humans, hypocaloric diets reduce body weight, leptin secretion, C-reactive protein, TNF-α, IL-6[33-35] and oxidized lipid markers[36], whereas body weight reduction decreases insulin resistance and oxidized low-density lipoprotein (LDL) levels[37]. These data reinforce data obtained in animal models, in the sense that hypercaloric diets induce pro-inflammatory cytokines expression and FR production, which contributes to the development of diseases such as diabetes.

Based on the above description, as shown in figure 1, it is highly likely for hypercaloric diets to induce oxidative stress and damage in two forms. First, hypercaloric diet increases the production of pro-inflammatory cytokines, which overstimulate cells to increase ROS and RNS generation. Second, hypercaloric diets induce mitochondrial uncoupling, which entails higher ROS production by the mitochondria itself. However, it is not clear whether hypercaloric diets first increase pro-inflammatory cytokines production or if they first cause for the mitochondria to uncouple, or if both processes are simultaneously produced. Regardless of which process takes place first, the result is the presence of oxidative stress, which entails increased oxidization of macromolecules that are important to cell physiology.

Macromolecule oxidization brings the development of complications such as diabetes as a consequence. For example, Carvalho-Filho et al. demonstrated in 2005 that a fat-rich diet in rats induces insulin receptor, insulin receptor substrate and protein kinase B/Akt nitration, which led to the development of insulin resistance[38]. Furthermore, in mice, a fat-rich diet impaired glucose uptake in muscular tissue, with this insulin resistance being accompanied by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 overexpression and a higher release of hydrogen peroxide. It also induced a decrease in the reduced/oxidized glutathione (GSH/GSSG) ratio[39], an antioxidant system that is highly important for the cell.

Strawberry use in clinical trials

Decreasing oxidative stress is clearly necessary in order to prevent and/or delay the development of chronic metabolic diseases. In that regard, antioxidant-rich foods can decrease oxidative stress, and it is therefore desirable for them to possess high reactivity to FRs; antioxidants also must be fat-soluble, in order for them to be able to cross biological membranes and neutralize FRs, and be able to neutralize the presence of secondary reactions; i.e., to neutralize secondary FRs[12,40].

In recent years, interest has been awakened by polyphenols owing to their high antioxidant capacity, which confers them great potential in the prevention and/or treatment of several diseases where oxidative stress has significant effect on disease pathophysiology (Fig. 1). Polyphenols are widely distributed in vegetable-origin foods such as turmeric, spinach, grapes, strawberries, apples, cranberries, grenade and cocoa beans, among others. In this review, we will focus on strawberry owing to its antioxidant properties and its potential in health.

Strawberry contains a large number of phenolic compounds such as anthocyanins (pelargonidin, etc.), flavonols (quercetin, etc.), proanthocyanidins (procyanidin, etc.), ellagitannins (agrimoniin, etc.), ellagic acid glucosides and cinnamic acid conjugates (coumaroyl-hexose and cinnamoyl-glucose)[41,42]. Strawberry also is of great interest due to its high contents of vitamin C, which together with phenols confer it great antioxidant power that can be beneficial for health, a

potential that has been demonstrated in different investigations, as we will next discuss.

In one study, healthy volunteers consumed 500 g strawberries/day. Strawberries significantly reduced total cholesterol, LDL and triglycerides; i.e., they improved plasma lipid profile. They also significantly decreased serum and urine malondialdehyde (MDA) levels, and improved antioxidant status biomarkers, anti-hemolytic defenses and platelet function[43]. In another study conducted in apparently healthy men and women, they consumed 500 g strawberries/day per each 70 kg body weight for 2 weeks. At treatment conclusion, a moderate vitamin C and fasting plasma antioxidant capacity increase was observed, in addition to a delay in plasma lipid oxidation and increased resistance to erythrocyte oxidative hemolysis[44]. Healthy adult females were assessed in order to find out how much does serum antioxidant capacity increase when any of the following antioxidants is consumed: 240 g of strawberries, 294 g of spinach, 300 mL of red wine, 125 mg of vitamin C or a control beverage. The results showed that total serum antioxidant capacity significantly increased from 7 to 25% during the 4-h period after the consumption of red wine, strawberries, vitamin C or spinach. Urinary antioxidant capacity also increased by 9.6, 27.5 and 44.9% in those who consumed strawberries, spinach and vitamin C, respectively, during the 24-h period after these treatments[45].

In a crossover study, adult men and women with overweight and regular consumption of foods with high carbohydrate content and moderate fat content ingested a beverage with 10 g of freeze-dried strawberry and placebo. The strawberry beverage increased postprandial plasma levels of anthocyanins and its metabolites, while decreasing inflammatory markers such as CRP and IL-6; it was also associated with an increase in insulin sensitivity[46]. In men and women with hyperlipidemia who consumed 10 g of freeze-dried strawberries in a beverage after a fat-rich meal, triglycerides and oxidized LDL levels significantly decreased after 6 weeks, in comparison with the group that consumed placebo[47]. In a double-blind study where 20 obese adults of both genders participated, they consumed freeze-dried strawberries (equivalent to 4 portions of frozen strawberries) for 3 weeks. At the end of treatment, cholesterol and high-density lipoprotein (HDL) small particle cholesterol plasma levels were decreased, and LDL particles were enlarged, with these changes being associated with a decrease in cardiovascular risk[48].

However, in men and women who consumed 20 or 50 g of strawberries/day for 12 weeks, no effect on adiposity, blood pressure and blood glucose measures was observed, and neither was there any effect on HDL, triglycerides and CRP serum concentrations. The group that consumed 50 g of strawberries only showed reductions in LDL cholesterol in comparison with the strawberry low dose. Both amounts of strawberry showed serum MDA decrease[49]. Similarly, obese men and women with a carbohydrate and fat-rich diet were administered 305 g of a strawberry beverage or placebo (10 g and 0 g of freeze-dried strawberries, respectively) for 6 weeks. The group that consumed the strawberry beverage showed a significant attenuation of plasminogen activator inhibitor-1 (PAI-1) postprandial concentrations and a non-significant decrease of IL-1β. No differences were found in platelet aggregation, high-sensitivity CRP test, TNF-α, insulin or glucose[50].

In a cohort study that included 16,010 nurse participants, with a 4-year follow-up, higher cranberry and strawberry consumption was found to be associated with a lower rate of cognitive impairment; in addition, it appears to delay cognitive aging up to 2.5 years[51]. These results clearly show that a diet rich in phenolic compounds has the potential to limit neurodegeneration and cognitive decline[52,53] and is associated with lower risk for myocardial infarction[54].

Strawberry use in animal models

More specifically, strawberry effectiveness to reduce oxidative stress has also been demonstrated in animal models. For example, in male rats that were fed strawberry or raspberry oil for 5 weeks, SOD and glutathione peroxidase (GSH-Px) activity was decreased, which suggests that the oils reduced or eliminated FRs, with activity of these antioxidant enzymes therefore being reduced. However, triglycerides, total cholesterol, LDL or HDL cholesterol levels were not affected[55]. In another research, strawberry supplementation to rats significantly reduced the production of ROS and doxorubicin (DOX)-induced DNA damage, and also improved oxidative stress markers, antioxidant enzymes activity and mitochondrial performance. This work confirmed that strawberry supplementation can counteract oxidative stress caused by DOX[56]. In albino rats with inflammatory bowel disease, strawberry ethanolic extract improved signs and symptoms of the condition, and this was considered to be owing to the antioxidant and anti-inflammatory properties of the extract[57]; furthermore,

a decrease in β-glucuronidase activity was observed in the cecum and feces, which indicates positive changes in the rats' microbiota[58]. On the other hand, Casto et al. demonstrated that freeze-dried strawberries can inhibit the formation of tumors in the hamster oral cavity[59]. Dudonné (2014) showed that there is synergistic activity of strawberry phenolic compounds with onion quercetin since, together, they improved bioavailability with possible UDP-glucuronosyltransferase intestinal induction. Three glucuronidated conjugates of strawberry and cranberry phenolic compounds (p-hydroxybenzoic acid glucuronide, catechins glucunoride and methyl-cathecins glucunoride) were found at higher quantities when ingested together with onion[60].

Interestingly, one study demonstrated that strawberry antioxidant capacity can also be observed in food preservation. One study added strawberry extract to chicken turnovers that were stored in refrigeration for 6 days. The strawberry extract decreased lipid oxidization, which demonstrates that the extract has good antioxidant power and prevents food oxidization[61].

Conclusions

Evidences addressed in this review support that hypercaloric diets can induce a pro-inflammatory state, characterized by FFA, pro-inflammatory cytokines and FR increase, contributing to the development of pathologies associated with cell redox state alteration. Evidence also supports that strawberries, owing to their elevated contents of antioxidant substances, can attenuate oxidative stress and/or prevent the development of diseases in the human.

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